

## Guideline

# Skin testing with food allergens

## Guideline of the German Society of Allergology and Clinical Immunology (DGAKI), the Physicians' Association of German Allergologists (ÄDA) and the Society of Pediatric Allergology (GPA) together with the Swiss Society of Allergology

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### Summary

Skin testing has a central role in the diagnosis of food allergy. Prick testing is well-established as a routine diagnostic tool. Nonetheless, unstable allergens and the lack of standardized extracts create difficulties in the identification of sensitization to foods in patients with suspected food allergy. Therefore prick-to-prick tests with native (raw, fresh) foods are still recommended. The indications and contraindications are the same as those of routine skin testing in clinical allergology. We recommend a careful and restricted application of skin tests in patients with a history of severe anaphylaxis to foods.

### Keywords

food – allergy – skin test – diagnostics

### Introduction

To diagnose food allergy, a sensitization towards food allergens must be demonstrated. Along with a careful history, the prick test with elicitation of a locally limited allergic skin reaction is the mainstay. The problem lies in the fact that in contrast to the most important inhalation allergens, no standardized extracts of food are available. This means that a comparable quality of extracts from different batches or manufacturers cannot be guaranteed. Further, for plant food extracts the simple extraction with a buffer solution and a phenol additive might destroy allergenic determinants resulting in false-negative prick test results. Nevertheless, skin tests cannot be waived.

The goal of this article is to depict the peculiarities of testing with food allergens and to make recommendations for achieving results with the highest possible validity.

### Methods for skin tests and test materials to be used

#### *Comparison of the various test methods*

The general test methods are only briefly summarized and evaluated here as detailed guidelines are available on the European level [5] and are being developed on the national level (Rueff et al., Guideline of the DGAKI).

The *prick test* is the standard test for food allergy that should be performed according to the general recommendations

with commercial extracts or native (raw, fresh) food together with control reactions [1, 8, 12, 16] and documented exactly. For stable food allergens (see test materials to be used) high sensitivity and specificity can be expected. Performance is simple and of little burden to the patient. The risk of a systemic allergic reaction is relatively low, but cannot be ignored when a high-grade sensitization, i. e. severe clinical signs and symptoms despite intake of only a small amount of allergens, is suspected.

The *prick-to-prick* test [2, 12, 16] is a special variant especially to test food stuffs in their original form. Here the prick lancet is first stuck into the food to be tested and then into the skin of the test person. This approach is often more sensitive than using commercial extracts (see above).

The *scratch (scarification) test* [16] due to traumatization of the skin with false-positive results and the *rub test* due to lack of clinical reproducibility play a secondary role in the diagnosis of food allergy. Only when *in vitro* tests are not available, should an *open patch test* and then perhaps rub tests perhaps be performed in highly sensitized patients with anaphylactic reactions (grade III or IV) be considered. The tests are positive when local urticarial reactions are observed after 20 minutes.

Due to the higher risk of allergic reactions and the small number of

**Table 1:** Suitability of various skin tests in food allergy.

|                                                        | <i>Prick test</i> | <i>Prick-to-prick test</i> | <i>Scratch test</i> | <i>Rub test</i> | <i>Intracutaneous test</i> |
|--------------------------------------------------------|-------------------|----------------------------|---------------------|-----------------|----------------------------|
| <b><i>Simplicity of the test</i></b>                   | +++               | ++                         | +                   | ++              | (+)                        |
| <b><i>Suitability for commercial food extracts</i></b> | +++               | 0                          | 0                   | 0               | ++                         |
| <b><i>Suitability for native foods</i></b>             | 0                 | ++                         | +                   | ++              | 0                          |
| Unspecific reaction (depending on the food)            | 0*                | +                          | ++                  | +               | +++                        |
| <b><i>Sensitivity</i></b>                              | +                 | ++                         | +                   | +               | +++                        |
| Risk of systemic reaction                              | +                 | +                          | ++                  | +               | +++                        |

\*In individual cases unspecific reactions can even occur depending on the food and the manufacturer of the extract

commercial extracts available and the frequent non-specific reaction, the *intracutaneous test* is only exceptionally performed, e. g. with flour.

The suitability of the various test methods, their advantages and disadvantages are summarized in Table 1. Their actual limitations are determined by the availability of test materials.

The *atopy patch test* can be used to assess a relevant deterioration of the skin condition in atopic dermatitis. The test does not play a significant role in day-to-day clinical practice [19]. In case of positive results, further diagnostic approaches (e. g. targeted elimination diet, oral challenge) are always recommended before initiating a diet [24].

#### *Test materials to be used*

As previously mentioned, there are two main sources of test allergens:

- *Commercially available food extracts* (prick and intracutaneous test) which, in contrast to the most important inhalation allergens, are unfortunately not standardized biologically,
- *Native foods can be tested raw or cooked* (prick-to-prick test, open patch test, scratch and rub test).

Which test materials are to be used depends on the stability of the food allergens. It has long been known that commercially produced food extracts of fruits and vegetables are of inadequate quality [21]. The difficulties in the extraction of these food allergens are

- the small and highly variable protein content depending on degree of ripeness, storage and variety and
- the lability of the allergens caused by the presence of inactivating enzymes, interfering phenols and temperature

elevations acting on the proteins during processing.

These factors are not adequately taken into consideration during *commercial* extract production. In addition, the phenol content of the prick test solution leads to further allergen instability.

Special extraction processes developed at the start of the 1980s [3, 14, 15, 21, 22] using various inhibitors and solvent extraction at low temperatures demonstrated that it was possible to produce fruit and vegetable extracts of good quality, but to date these have only been employed in scientific studies by various working groups.

For these reasons, the *prick-to-prick test* with native material from fresh fruits and vegetables has been established, with differences in the allergenic raw material depending on ripeness and storage placing limits on the comparability of the tests. For apples detailed investigations of the differing allergen content depending on variety exist. Thus “*Granny Smith*”, “*Golden Delicious*” and “*Jona-gold*” have a high and “*Gloster*” a low allergen content [23]. Subsequent analyses confirmed the results [4]. Similar variations must be suspected for other fruits. As *heat-labile* and *heat-stable* allergens in foods are differentiated, it might be sensible to test with native and cooked material in individual cases.

Due to the large number of allergens to be tested, the limited availability in the practice and the trouble and expense of procuring the natural products, a new method was developed where fruit and vegetable juices were portioned and frozen at – 20 °C to be thawed shortly before the test [18]. The authors claim to have developed an alternative to the

*prick-to-prick test* with native foods. Because freshly harvested fruit has lower allergen content than stored, ripened fruit and because heating during grinding with phenols cause rapid inactivation, this method cannot be recommended.

A high content of biogenic amines in foods and non-specific histamine release by foods such as tomatoes, strawberries, citrus fruits and shellfish can be responsible for “false-positive” results in testing with native foods [9]. In testing spices non-specific skin irritation also often plays a role and should not be misinterpreted as “allergy” when control persons also react positively.

*Food allergens of animal origin* are usually more stable, so that testing with commercial extracts is sufficient. But even here there are exceptions. In individual cases when a specific food allergy is suspected and the prick test with commercial extracts is negative, a test with native material should follow. When there is a history of reactions only after the ingestion of certain organs (e. g. pork kidneys) a test with native material should be performed due to the possibility of an organ-specific sensitization [7].

Considering the aspects mentioned above, Table 2 outlines recommendations for testing various foods.

When food allergy is suspected in adults, where 60 % are based on cross-reactions with inhalation allergens, prick testing with the respective inhalation allergen is indicated [6].

#### *Choice of foods to be tested*

When history provides specific indications, foods suspected of having induced the allergic reactions are to be tested. When there are no concrete clues, the skin

**Table 2:** Recommendations and suitability for testing selected foods.

|                                     | <i>Commercial extract</i> | <i>Native test suitable*</i> | <i>Native test partly suitable**</i> |
|-------------------------------------|---------------------------|------------------------------|--------------------------------------|
| <b>Food of animal origin</b>        |                           |                              |                                      |
| Fish                                | +                         | +                            |                                      |
| Meat                                | (+)                       | +                            |                                      |
| Hen's egg                           | +                         | +                            |                                      |
| Non-vertebrate seafood and snails   | +                         | +                            |                                      |
| Milk                                | +                         | +                            |                                      |
| <b>Food of plant origin</b>         |                           |                              |                                      |
| Pineapple                           |                           |                              | +                                    |
| Apple                               |                           | +                            |                                      |
| Cereals                             | (+)                       | +                            |                                      |
| Strawberries                        |                           |                              | +                                    |
| Peanuts                             | +                         | +                            |                                      |
| Spices                              |                           |                              | +                                    |
| Hazelnuts                           | +                         | +                            |                                      |
| Carrot                              |                           | +                            |                                      |
| Kiwi fruit                          |                           |                              | +                                    |
| Lychee                              |                           | +                            |                                      |
| Mango                               |                           | +                            |                                      |
| Oilseeds (e. g. poppy seed, sesame) |                           | +                            |                                      |
| Peach                               |                           | +                            |                                      |
| Celery                              | (+)                       | +                            |                                      |
| Mustard                             |                           |                              | +                                    |
| Soy                                 | (+)                       | +                            |                                      |
| Tomato                              |                           |                              | +                                    |
| Grape                               |                           | +                            |                                      |
| Snow pea                            |                           | +                            |                                      |

\*Test control persons because of possible irritative components in or on the food

\*\*Because of irritative potential

test must fulfill the function of a search test and should include the regionally most common foods (Table 3) taking the individual case into consideration.

#### Indications and contraindications for skin tests

Indications for skin tests are the necessity of the identification or exclusion of a sensitization in the form of a *confirmation test* when a specific food is suspected by history or as a *search test* when a targeted indication of an allergen is lacking. *Contraindications* for skin tests with food generally do not differ from those with

other allergens [1, 8]. *Absolute contraindications* include skin infections at the test site and acute allergy symptoms at the time of testing, i. e. the test should be performed in the symptom-free interval. Skin disease at the test site such as e. g. acute or chronic eczema, inflammatory skin lesions or urticaria limit the validity of the test considerably and represent *relative contraindications*. The same holds true for pregnancy, major systemic diseases, intercurrent infections, vaccinations and acute inflammatory diseases. These usually require a delay in testing. Also, clinically very severe reactions with

anaphylactic shock are a *relative contraindication* for skin tests. Here, primarily *in vitro* tests should be employed. If these are negative, a titrated test under continual observation of the test reaction, perhaps with an established venous line, should be performed.

Since there is inadequate evidence that *ACE inhibitors* increase the risk of immunotherapy as reflected in the recommendations of the ÅDA 2002 [17] and the current guidelines of the DGAKI of 2006 [10], which also applicable to skin tests, universal discontinuation of ACE inhibitors before the prick test is not

**Table 3:** Important allergenic foods (Prick test block when no targeted indication for a possible sensitization exists in case of suspicion of food allergy).

|                        |
|------------------------|
| Apple                  |
| Tree nuts              |
| Peanut                 |
| Fish (cod)             |
| Hen's egg              |
| Carrot                 |
| Crustaceans* (shrimps) |
| Milk                   |
| Celery                 |
| Sesame                 |
| Soy                    |
| Wheat                  |

\*Only recommended for adults

**Table 4:** Effects of drugs on immediate-type reactions. According to Bergmann and Müsken 2000, Malling 1993, Van Metre et al. 1990, Ring 1992 [16].

| Drug                                                                                        | Required interval<br>between discontinuation and test |
|---------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Cromolyn                                                                                    | 0                                                     |
| Short-acting antihistamines                                                                 | > 3 days                                              |
| Longer-acting antihistamines                                                                | > 5 days                                              |
|                                                                                             |                                                       |
| Tricyclic antidepressants                                                                   | > 2 weeks                                             |
|                                                                                             |                                                       |
| Topical corticosteroids (at the test site)                                                  | > 1 week*                                             |
| Systemic corticosteroids                                                                    |                                                       |
| a) Long-term                                                                                |                                                       |
| - up to 10 mg prednisolone equivalent daily                                                 | 0                                                     |
| - higher dose                                                                               | > 3 weeks                                             |
| b) Short-term                                                                               |                                                       |
| - < 50 mg prednisolone equivalent daily                                                     | > 3 days                                              |
| - higher dose                                                                               | > 1 weeks                                             |
| * Depending on the potency of the applied product and treatment duration of up to > 3 weeks |                                                       |

required. While in the past *beta-blockers* were also discontinued prior to testing, the increased usage of the agents and the fact that even their short-term discontinuation can result in cardiovascular complications have led to a reconsideration of the issue. *Targeted* prick testing

with selected allergens with close observation of the test reaction can be performed while patients are taking *beta-blockers*. Inpatient admission for testing is only occasionally required. It might be considered when *contraindications* for the administration of epinephrine (e. g

arrhythmia, hypertension) exist and prick testing is required. It is essential to recognize the drug intake in the drug history and to react to initial allergic reactions in order to prevent cardiovascular side effects.

**Confounding factors in skin tests**

A prerequisite for any skin test is the ability of the skin to react normally; this can be affected by medications, especially antihistamines and sedatives including antidepressants. These drugs must be discontinued at the proper interval (Table 4). If this is not possible for clinical reasons, the validity of the test, especially in the case of negative reactions, is significantly limited. The use of skin care products on the day of test also disturbs testing. Systemic corticosteroids appear to have no effect on the prick test even at higher doses [11].

**Evaluation and interpretation of the test results**

Besides correct performance of the test and the exact assessment of the test reaction by measurement and documentation on the test sheet, the interpretation of the test results is crucial and requires the consideration of all factors mentioned up to now especially for food allergy. First, the test reaction must be scored as positive or as negative taking the reactivity of the skin into consideration, and then it must be determined if the results are clinically relevant. For the *first step*, certain rules apply, while an exact standardization is not possible. The skin test can be false-negative especially for unstable non-standardized food allergens. Other possibilities for error include too small distance between test sites with confluent reactions, not changing the prick lancet or the use of unsuitable test materials (Table 5). For the *second step*, the evaluation of the clinical relevance of the skin test as a confirmation test can be simple. One must remember that a food allergy is much more frequently suspected by the patient than can actually be confirmed [13, 25]. It is difficult from the start when the skin test is used as a search test. Here, all diagnostic parameters including cross-sensitization, *in vitro* test and perhaps oral challenge must be considered in evaluating the clinical relevance. It must be remembered that the skin test as well as the *in vitro* test depend on the quality of the extract.

**Table 5:** Possibilities for error in testing.

| False-positive                                           | False-negative                                   |
|----------------------------------------------------------|--------------------------------------------------|
| Unspecific reaction of test material                     | Unsuitable test material (inactivated allergens) |
| Hyperreactivity of the skin (urticarial dermatographism) | <i>Intake of medications</i>                     |
| Test site too small                                      | Lack of reactivity of the skin                   |
| Not changing prick lancet                                |                                                  |

No conclusion on the clinical relevance can be drawn from the size of the wheal of the skin test reaction in adults. Double-blind, placebo-controlled challenge studies in children exist, that show, similar to specific IgE measurements, that wheal size and skin index (wheal size of allergen/ histamine wheal) for cow's milk and hen's egg white possess a positive predictive value for clinical reactions [20].

#### Conclusions:

1. Depending on the food the prick test with commercial extracts or the prick-to-prick test with native foods constitute the diagnostic standard when food allergy is suspected.
2. The test reaction is measured and documented on the test sheet.
3. In performing and evaluating the test the instability of certain foods and the lack of standardization of the extracts must be taken into consideration.
4. After a severe anaphylactic reaction, specific IgE should first be measured and then a decision made about prick testing.
5. The clinical relevance of an identified sensitization must always be evaluated.

#### Procedure in creating consensus

Guideline of the German Society of Allergy and Clinical Immunology (DGAKI), the Physicians' Association of German Allergologists (ÄDA) and the Society of Pediatric Allergology (GPA) together with the Swiss Society of Allergology

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