

## ARTICLE

# Diagnosis of food allergy: History, examination and *in vivo* and *in vitro* tests

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One cannot depend on one single test to diagnose food allergy. A detailed history is an essential initial step in cases of suspected food allergy. Aspects of the history should be gathered separately for each food being considered, as a patient may experience different types of reactions with various foods, each of which requires individual diagnostic and management strategies. History alone is not diagnostic and additional measures of sensitisation or food challenges are often required.

In suspected immunoglobulin E (IgE)-mediated allergy, skin-prick tests (SPTs) and/or measurement of serum specific IgE antibodies (ImmunoCAP) to suspected foods is used to prove sensitisation. Sensitisation does not, however, confirm clinical food allergy as these tests indicate an immunological response to the specific allergen, but the diagnosis requires a clear correlation between the test result and clinical reaction (by positive history or food challenge). The magnitude of the test result (SPT mean wheal size or ImmunoCAP level in kU/L) correlates with the likelihood of clinical allergy, but not the severity of a reaction.

Choice of the allergens tested should be guided by the history, but limited to the lowest necessary number to avoid false-positive results. Tests for sensitisation to foods should not be performed when the history indicates that such foods are tolerated. Ninety-five per cent positive predictive values (where a clinical reaction can be predicted in 95% of cases) have been described for immediate reactions, but may be population specific.

There are no validated tests to confirm non-IgE- or mixed IgE- and non-IgE-mediated food allergies. Diagnosis of this group of allergies depends on elimination of the suspected food, clearance of symptoms, and recurrence of symptoms on re-introduction of the food.

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## History

A detailed history is an essential initial step when a food allergy is suspected.<sup>[1]</sup> This will help to determine the likelihood of and type of food-induced allergy and potential causative food/s. History alone is not diagnostic. In combination with the results of the specific immunoglobulin E (IgE) tests or skin-prick tests (SPTs), the likelihood of clinical food allergy can be identified.<sup>[2]</sup> Aspects of the history should be gathered separately for each food being considered, as a patient may experience different types of reactions with various foods, each of which will require individual diagnostic and management strategies.

Information gathered during the history should include an allergy-focused family history,<sup>[2-4]</sup> clinical history,<sup>[3,5,6]</sup> and dietary history.<sup>[3]</sup> Table 1 outlines the specific information required from the history.

## Examination

The physical examination focuses on the signs of acute allergy, should the patient be examined during an acute reaction, or the stigmata of chronic allergic disease when the patient presents with chronic symptoms. Acute signs may include urticaria and angio-oedema, wheeze, cough, rhinorrhoea, diarrhoea, vomiting, and cardiovascular signs such as hypotension and tachycardia.

A general examination may reveal allergic facies, allergic salute and pallor. Nutritional status should be assessed by plotting height, weight and weight-for-height. Signs of nutritional deficiencies, such as iron deficiency or rickets, should be sought.

The skin is examined for signs of atopic eczema and urticaria. Mouth breathing, allergic mannerisms, nasal congestion, dental

abnormalities and post-nasal drip are looked for in the upper airways, while the chest is examined for hyperinflation and wheeze.

## Diagnostic tests

One cannot depend on one single test to diagnose food allergy.<sup>[5]</sup> A history aids in identifying potentially involved food when differentiating between potential IgE- and non-IgE-mediated disease and assessing the severity of reactions. In suspected IgE-mediated allergy, SPTs and/or measurement of serum specific IgE antibodies (ImmunoCAP) to suspected foods is used to prove sensitisation. Sensitisation does not, however, confirm clinical food allergy, as these tests indicate an immunological response to the specific allergen, but the diagnosis requires a clear correlation between the test result and clinical reaction (by positive history or food challenge).<sup>[12]</sup> Blind testing without suspicion of a reaction to a specific allergen is not advocated – findings are often misleading as they indicate asymptomatic sensitisation alone.<sup>[13]</sup> Tests for sensitisation to foods should not be performed when history indicates that those foods are tolerated.

There are no validated tests to confirm non-IgE- or mixed IgE- and non-IgE-mediated food allergies. Diagnosis of this group of allergies depends on elimination of the suspected food, clearance of symptoms, and a re-introduction of the food as an oral food challenge (OFC). In certain cases endoscopy with biopsy is indicated to evaluate the response to dietary changes.

## Diagnostic tests to identify sensitisation in IgE-mediated food allergy

### Skin-prick tests

An SPT is a useful and scientifically valid tool to confirm IgE-mediated sensitisation to a specific allergen. Skin-testing directly

**Table 1. Information gathering in history-taking**

<b>Family history</b>	Presence of first-degree relatives with any atopic disease (asthma, eczema or allergic rhinitis) or food allergy
<b>Clinical history</b>	
Personal history	History of atopic disease Relationship of person who raised the concern of food allergy
Age	Age at first exposure to the food, any subsequent exposures and timing and type of all reactions
Occupation- and environmental-associated risks	Possible exposures at work/crèche/school/home
Symptom type	Symptoms associated with IgE-mediated reactions (may differ according to severity of reaction) <ul style="list-style-type: none"> <li>• Urticaria, angio-oedema</li> <li>• Oral itching</li> <li>• Abdominal pain, nausea, vomiting</li> <li>• Nasal symptoms: congestion, sneezing, rhinorrhoea</li> <li>• Respiratory symptoms, e.g. difficulty breathing, wheezing, persistent coughing, voice change</li> <li>• Floppiness, change in level of consciousness, anxiety, sleepiness</li> <li>• Cyanosis, loss of consciousness, hypotension</li> </ul> Symptoms associated with non-IgE-mediated reactions (may differ according to type and severity of reaction) <ul style="list-style-type: none"> <li>• Lower gastrointestinal symptoms: diarrhoea, failure to thrive, malabsorption, protein-losing enteropathy, abdominal pain, bloody stools, constipation, cramps or colic</li> <li>• Gastro-oesophageal reflux disease, dysphagia, odynophagia, vomiting</li> <li>• Atopic dermatitis not responding to maximal appropriate topical therapy</li> <li>• Pallor, signs of macro- and micronutrient deficiencies</li> </ul>
Timing of reaction	Timing of symptoms after exposure to the food, which could indicate possible immunological reaction <ul style="list-style-type: none"> <li>• Immediate: minutes up to 2 hours (usually IgE mediated)</li> <li>• Delayed or late onset: &gt;2 hours (non-IgE mediated)</li> <li>• Both immediate and delayed reactions</li> </ul>
Reaction details	Duration Severity <ul style="list-style-type: none"> <li>• Mild to life-threatening</li> <li>• Reaction severity compared with previous reaction</li> </ul> Frequency and whether the reactions have occurred previously
Causative food allergen	Suspected food/s causing the reaction and simultaneous ingestion of other food/s or ingredients
Dose of allergen	Level of food allergen exposure causing a reaction
Form of food	Processed/canned and/or raw/cooked/heat-treated/dried food
Setting	Details where the reaction occurred
Reproducibility	Reaction repeatability and consistency each time the offending food is given
Route of allergen exposure	Route of exposure <ul style="list-style-type: none"> <li>• Oral, via breastmilk or other food/feed</li> <li>• Inhalation</li> <li>• Skin contact</li> </ul>
Concomitant diseases	Presence of other medical conditions, including asthma or atopic diseases
Co-factors	Exercise or ingestion of alcohol, coffee or drugs before or after eating the offending food
Co- and cross-reactivity	Tolerance of or reaction to related food allergens Cross-reactivity between inhalant allergens and food allergens <sup>[5,7]</sup> Common examples <ul style="list-style-type: none"> <li>• Peanuts, with cross-reactive allergy to one or more tree nuts<sup>[8]</sup> and/or sesame,<sup>[10]</sup> or co-reactivity between peanut and egg<sup>[9]</sup></li> <li>• Pollen-food syndrome, with reactions to many different fruits and vegetables<sup>[7]</sup></li> <li>• Latex allergens can cross-react with kiwi, avocado, banana and others<sup>[11]</sup></li> </ul>
Treatment	Details on how the symptoms were treated, medication used and time to symptom resolution
<b>Dietary history</b>	
Growth and development	Check growth records of the infant/child Identify cause of poor growth, whether related to food allergy or other cause

Continued ...

**Table 1. (continued) Information gathering in history-taking**

Referral to other healthcare providers	Identify the need for referral to other healthcare professionals for assessment, e.g. a dietician to ensure nutritional adequacy; speech and language therapist and/or occupational therapist with expertise in sensory or behavioural issues related to poor food intake
Feeding history	Feeding history, duration of breastfeeding, type of infant formula given, age of solid food introduction, food aversion/refusal, which may indicate food allergy related to pain or discomfort on exposure
Dietary intake	Dietary intake should be assessed with a detailed dietary history, a 3-day food record, a 24-hour recall or a typical day's intake
Cultural and religious factors	Assess cultural and religious factors that affect the patient's diet
Incidental or accidental ingestion	Ensure awareness of hidden sources of the offending food
Other foods	Ability of the patient to eat a full age-appropriate portion of ... (name specific commonly allergenic foods as well as cross-reactive foods)
Elimination diets	Foods avoided and reasons for avoidance Results of previous elimination diets in alleviating symptoms and/or identifying the offending food
Supplements	Dosage, type and manufacturer of supplements taken to cover for missing nutrients

**Table 2. Food allergy skin prick test decision points<sup>[14]</sup>**

Food allergen	100% PPV <2 y (wheal diameter)	100% PPV >2 y (wheal diameter)
Cow's milk	6 mm	>8 mm
Egg	5 mm	>7 mm
Peanut	4 mm	>8 mm

PPV = positive predictive value.

assesses the presence of mast-cell-bound allergen-specific IgE. Allergen extracts, prepared commercially or directly from the suspected food, are introduced into the skin. A reactive SPT is a sign of sensitisation only, and cannot be considered diagnostic without clear clinical correlation and/or confirmation with an OFC. This test is simple, with rapid results, good performance, low cost and high sensitivity.<sup>[12]</sup> The allergens tested for should be guided by the history, but also need to be limited to the lowest necessary number to avoid false-positive results. Antihistamines should be discontinued 3 - 5 days before the test. SPTs should be performed in a setting where equipment and medication are available to treat rare, severe reactions, including anaphylaxis.

The mean wheal diameter correlates with the likelihood of clinical allergy, but must be interpreted in light of the clinical history. In itself it is not diagnostic and cannot predict the severity of reactions. Individuals with a clear history of a severe reaction to a particular food should not undergo skin-testing to that food to prove sensitisation, because where there is uncertainty and an increased risk of a severe reaction, such risks may exceed the benefit. In individuals with atopic dermatitis, positive predictive values (cut-off values for the mean wheal diameter in the common food allergens where a clinical reaction can be predicted in the specified proportion of cases) have been described for immediate reactions (Table 2), but may be population specific.

**Allergen-specific serum IgE**

Serum IgE specific to a particular allergen can be determined by immunoassays (ImmunoCAP). These assays are validated, reliable and reproducible, but costly. Cut-off values for the 95% positive predictive values of a clinical reaction to common food allergens are given in Table 3, but may be population specific.<sup>[13]</sup>

**Table 3. Food allergy ImmunoCAP decision points**

Food allergen	Decision point (kUA/L)	PPV, %
Cow's milk		
<1 y <sup>[15]</sup>	5	95
>2 y <sup>[16]</sup>	15	95
Egg		
<2 y <sup>[17]</sup>	2	95
>2 y <sup>[16]</sup>	7	98
Peanut <sup>[16]</sup>	14	100
Fish <sup>[16]</sup>	20	100
Wheat <sup>[16]</sup>	26	74
Soya <sup>[16]</sup>	30	73
Tree nuts <sup>[16]</sup>	15	95

PPV = positive predictive value.

Purified recombinant allergen-specific IgE tests against individual major allergen components in food may improve the diagnosis of clinical allergy and differentiate true food allergy from cross-reactivity. Certain component allergens are correlated with persistence of food allergy (e.g. ovomucoid in egg and casein in cow's milk protein allergy), severity of reactions (e.g. Ara h 2 in peanut allergy)<sup>[5]</sup> and whether heat-degraded protein will be tolerated (e.g ovomucoid and casein).

The assessment of co- and cross-sensitisation to related food or aeroallergens should be considered. Cross-reactive food allergies such as pollen food syndrome and latex food allergy are common. Only food and aeroallergens related to the specific patient's presentation should be tested to prevent mislabelling of asymptomatic sensitisation alone as clinically relevant food allergy.

**Total serum IgE**

Total serum IgE is not recommended in the diagnosis of food allergy and should not be done.<sup>[3]</sup>

**Atopy patch test**

The atopy patch test has been developed to aid diagnosis in delayed reactions in patients with atopic dermatitis and eosinophilic

oesophagitis. This test has, however, not been validated or standardised and is not recommended for the routine diagnosis of food allergy.<sup>[2]</sup>

## Intradermal tests

Intradermal skin tests have a low specificity and high risk for systemic and irritant reactions. They are not recommended for food allergy testing.<sup>[2,3]</sup>

## Non-standardised and unproven procedures

Unconventional tests for allergy diagnosis used by complementary and alternative health professionals include IgG and IgG4 testing, kinesiology or applied kinesiology, iridology, cytotoxic (antigen leukocyte cellular antibody test (ALCAT)/Bryan's) testing, Vega (electrodermal) testing, and hair analysis. These tests are unvalidated, poorly reproducible, have poor predictive value for allergies and cannot diagnose sensitisation. Practices that claim to affect a cure by removing the patient's blood, processing it and then re-infusing it into the patient (autohaemotherapy) are strongly discouraged.

Such tests may be harmful to patients by leading to under- or over-diagnosis of food allergy. False-negative results from unconventional tests may prompt patients with clinically important food allergy to continue to ingest foods that are harmful to them, and conversely false-positive results may prompt multiple dietary exclusions and cause significant nutritional impairment.<sup>[18]</sup> In addition, such tests are often extremely expensive.

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