Ten to 20% of adults in the population report food intolerances—mostly they refer to these as "food allergies." But only a small proportion of these are genuine, immunologically mediated allergies (1, 2). Food intolerances are therefore overrated on the one hand, but on the other hand, potentially dangerous food allergies are often not diagnosed at all or only with delays.

The term food intolerance or food hypersensitivity is a classification and means that objective, reproducible symptoms occur after food has been ingested that a normal person can tolerate (figure 1) (3, 4).

This study focused on the diagnosis of immunoglobulin E (IgE) mediated food allergy (type I allergy). Any mention of food allergy therefore always refers to IgE mediated food allergy. Symptoms after a meal, after inhalation, after skin or mucosa contact with a food allergen can range from local contact reactions—e.g., oral allergy syndrome, baker's asthma, gastrointestinal symptoms, and contact urticaria—to systemic, potentially life-threatening, anaphylactic reactions (box 1) (5, 6). Differential diagnoses include disorders such as intolerance reactions, gastrointestinal disorders, or psychovegetative reactions; these can often be distinguished not on the basis of their symptoms but only after extensive diagnostic tests.

Methods
From January 2000 to December 2007, all persons in whom food allergies were suspected were examined in a standardized fashion with stepwise allergological diagnostics. The tests were intended to provide answers to two questions:

- Were the symptoms caused by food?
- If yes, which foods were responsible?

The selection and interpretation of the diagnostic methods depend on the symptoms (anaphylaxis or oral allergy syndrome) and the food under suspicion (known or rare allergen). Further, sensitivity and specificity of the tests have to be taken into consideration (box 2). The tests were intended to provide answers to two questions:

- Were the symptoms caused by food?
- If yes, which foods were responsible?

As in all diagnostic tests for allergies, and especially before the provocation tests, patients were informed about risks and benefits; all gave written consent.

Medical history
The clinical symptoms ranged from oral allergy syndrome to gastrointestinal complaints to urticaria with or without angioedema and anaphylaxis (box 1). The degree of severity of anaphylaxis was classified as in the table (7, 8). Accompanying circumstances—such as physical exertion, alcohol intake, medication (nonsteroidal anti-
inflammatory drugs), or infectious diseases—were also captured. Since symptoms of food allergies usually develop very soon after food intake, finding out the latency period was important (5).

To identify a suspected food, the type, amount, preparation, and individual ingredients of a meal were investigated, as were the packet declarations of ready meals. Mere assumptions were made about so-called hidden allergens—e.g., cow's milk or egg in sausages or ready meals; seasonings, soya, or nuts in baked products or sweets. Particularly indicative of an allergy were reproducible symptoms—i.e., similar symptoms after an earlier or subsequent repeated exposure. The history was completed with questions about known allergies and the manifestations of atopy.

**Laboratory tests**

Food specific IgE in the serum was measured with a commercially available immunoassay. The test method binds IgE antibodies in the serum to solid phase bound food allergens. A positive test shows values up to 100 kU/L. Food specific IgE was measured only in a targeted way and not used as a search test. In patients with positive skin reactions to common and known food allergens and in oral allergy syndrome, no IgE measurements were taken.

In patients with a history of an anaphylactic reaction, serum tryptase was measured using a quantitative assay (9). Values <10 ng/mL are normal, 10–20 ng/mL is a grey area, whose importance and prognosis are unclear, and values >20 ng/mL are pathological.

**Skin tests**

Conducting and reading skin prick tests on the volar lower arm after 20 minutes was done in accordance with international guidelines (10). In the prick-to-prick test with native foods, the prick test lancet was first pricked into the food and then into the skin. Grain flours, nut flours, or seasonings were floated with physiological saline and then pricked through the drop. In many patients, suspected foods, such as types of meat/innards or seeds, were tested in addition to the standard series.

**Provocation tests**

Neither a positive skin prick test nor a finding of food specific IgE is always clinically relevant; they only indicate sensitization. In individual cases, food allergies were ruled out by using oral, open food provocation tests. The average daily intake dose—e.g., 150 mL cow's milk or 1 egg—were increased. These tests were conducted and evaluated in accordance with international guidelines (11).

**Results**

419 patients aged 10 to 85 years (median 40 years) were studied, 270 (64.4%) were female and 149 (35.6%) male.

**Medical history**

35.3% of patients had isolated skin symptoms—pruritus, erythemaflushing, urticaria, angioedema, contact urticaria (3, 4). Symptoms of anaphylaxis (table) were reported in 35.8%—with or without skin symptoms, the airways were affected (dysphonia, cough, inspiratory or expiratory stridor, bronchospasm), and/or the cardiovascular system (hypotension, tachycardia, loss of consciousness). Higher grade anaphylaxis (grade 2 and 3) was documented in 21 (5.0%) and 14 (3.3%) patients.

The most common individual symptom after urticaria and anaphylaxis was the oral allergy syndrome (box 3); 8.8% of participants reported exclusively gastrointestinal complaints, such as nausea and vomiting, stomach ache, or diarrhea.

In 69.0% the latency period between food ingestion and symptoms was less than 2 hours, in 28.6% between 2 and 4 hours (figure 2b).

Foods were suspected in 260 patients (62.1%), most often vegetables/fruit, tree nuts, and grains (figure 2c).
In 159, however, no particular food was suspected of triggering the reaction. 189 patients (45.1%) had atopic disorders; 18 (4.3%) were known to have an allergy to natural latex.

Laboratory tests
176 patients (42.0%) had at least slightly raised IgE values (>0.70 kU/L) against suspected foods; in 206 patients measurement of food specific IgE was not done (figure 3a). Of the patients with anaphylactic symptoms, 3 had serum tryptase values >20 ng/mL (figure 3a) because of systemic mastocytosis. Diagnosis: shrimp allergy (family Penaeidae); because of the risk of cross-reactivity, avoidance of all crustacean families was recommended (crustacean: crayfish/Astacidae, rock lobsters/Palinuridae, decapod crabs/Brachyura).

Skin tests
The test results of the standard series are shown in figure 3b. General reactions triggered by prick tests with native foods are rare but cannot be excluded (12).

Provocation tests
To exclude a food allergy, 66 provocations were conducted, with negative results, among others using
- Cow’s milk (4×)
- Egg (6×)
- Shrimp (4×)
- Cod (4×)
- Tree nuts (7×)
- Soya (10×)
- Other foods, such as strawberries, asparagus, pear, rice.

<table>
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<th>TABLE</th>
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<tbody>
<tr>
<td>Grades of severity of anaphylaxis symptoms (7)</td>
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<td>Grade 1 (slight)</td>
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<tr>
<td>Skin</td>
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<tr>
<td>Airways</td>
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<td>Cardiovascular system</td>
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<td>Gastrointestinal tract</td>
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<td>Nervous system</td>
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Diagnosis
In 214 patients (51.1%), IgE mediated food allergies were diagnosed, supported by unequivocal findings; however, stepwise allergological diagnostic tests ruled out food allergies in 205 patients (48.9%) (figure 4).

Discussion
To differentiate questionable diagnostic methods—e.g., the pointless measurement and interpretation of food specific IgG—from genuine ones, national and international institutions have for many years attempted to optimize the diagnostics of food allergies on the basis of guidelines.

The authors identified food allergens in their own patients by using standardized diagnostic tests and thereby enabled beneficial allergen avoidance. In many cases, however, it was of equal importance to rule out food allergies and therefore prevent unnecessary diets and imposing limitations on people’s everyday lives.

Discussing the results of 419 patients with suspected food allergy has to consider the selected patient cohort at a specialist outpatient center at a university hospital. The distribution of the observed symptoms and allergens thus cannot correspond to a random sample from the general population. Original data and a meta-analysis of the prevalence of food allergies in the general population have recently been published (2, 13).

Tests for food specific IgE do not always have sufficient sensitivity and specificity. Evaluable results can be expected for common allergens such as cow’s milk, chicken egg, crustaceans, peanut, soya, pollen- and latex-associated foods (14). However, for rarer food allergens, IgE testing is often not sufficiently validated.

For skin tests, not only the foods suspected by the patients themselves should be tested but additionally a standard series should be tested that includes the most common food allergens. The prick test has higher sensitivity with native, i.e. fresh, foods than with commercially available food extract solutions (15).

A prick-to-prick test with fresh foods has a negative predictive value of >95%. This means that if the test is negative then the probability of an allergy against the tested food is <5% (16). The positive predictive value is only <50%; this means that the clinical relevance of a positive skin test may have to be investigated (17–20).

**Data from the medical histories of patients with suspected food allergies. a) Symptom (categorization of anaphylaxis into severity grades 1–3, see table; OAS=oral allergy syndrome, see box 3). b) Latency period between exposure and symptoms. c) Foods that were suspected as the cause in 260 patients.**

**BOX 3**

**Oral allergy syndrome (e9)**

**Definition**
Contact urticaria within a few minutes after or even during chewing of raw (heat labile) types of fruit and vegetables with only mild oropharyngeal symptoms.

**Causes**
Pollen associated food allergy; cross-allergy with pollen allergens, either pollen allergy with seasonal allergic rhinoconjunctivitis or clinically nonrelevant pollen sensitization.

**Allergens**
- Cross-allergy with birch, alder, or hazel pollen: apple (50% to 60%), hazelnut (40% to 60%), peach (20% to 30%), cherry (10% to 20%), carrot (10%), soya (10%).
- Cross-allergy with mugwort pollen: celery (40%), seasonings (10%)

**Symptoms**
Oropharyngeal pruritus, paresthesias (tickling, burning, scratching sensation), erythema, edema of the lips, tongue, and/or oral mucosa; symptoms increase during pollen flight season.
An intracutaneous test with food extracts is not advisable—or will have to be closely monitored—because of the high likelihood of false positive test results (21). The question of whether a positive skin test and/or the detection of food-specific IgE antibodies are clinically relevant or merely show sensitization can be answered with a food provocation test (20).

Food allergies are a common cause of anaphylaxis; the published allergens are mostly crustaceans, fish, peanuts, and tree nuts; in the authors’ own study cohort, types of meat/in-mards, grains, and types of vegetable/fruit were also identified (figure 4 a, b) (22, 23).

An allergy to cow’s milk or eggs is common in children but rare in adults. Anaphylaxis is the maximum variant of an IgE-mediated allergy, and affected patients will have to be educated about hidden allergens (soya, nuts), label descriptions/declaration, and cross contamination (24). Recurrent anaphylaxis often occurs when people eat in restaurants or at fast food venues, because the ingredients are unknown or not fully declared (25). Most patients who died as a result of anaphylaxis knew about their food allergy and had identified the causative allergen (e1).

Patients with food independent, exercise induced anaphylaxis develop symptoms only after food intake with subsequent physical exertion. They tolerate all foods if eating is not followed by exertion and do not register any complaints after exertion if no food was ingested beforehand (e2). Food allergens often mentioned in this context include wheat, celery, cow’s milk, tomatoes, or poultry meat. The authors identified in 21 patients wheat allergy 11 times, celery allergy 3 times, egg allergy twice, peanut allergy twice, and once each for soya, hazelnut, and banana. The activities that triggered the reaction were mostly movement intensive types of sports—such as jogging, tennis, dancing, aerobics, or cycling; more rarely, less strenuous exertions such as hiking or walking caused the reaction (e3). With respect to the pathogenesis of this unusual manifestation of a food allergy, only hypotheses exist. One of these postulates a disrupted temperature regulation (sometimes cholinergic urticaria occurs concomitantly), another postulates an increase in allergen resorption (e4). A safe prophylactic measure consists of food or allergen avoidance for 3 hours before exercise.

Acute generalized urticaria with or without angioedema may be an early or partial symptom of anaphylaxis (e5). In a different classification of anaphylaxis, four degrees of severity are differentiated (grades 1 to 4); acute urticaria is equivalent to grade 1 anaphylaxis (e6). In contrast to urticaria, which is caused by intensively itching, transient edema of the upper dermis, angioedema (synonym: Quincke’s edema) is an edema of the subcutaneous tissues and can persist for 2 days; it is accompanied by a feeling of tension (e7). It is assumed that acute urticaria is one of the more common manifestations of food allergies, although no exact prevalence data have been published (5). In the authors’ own investigations, 28 of 214 patients (13.1%) had urticaria or angioedema as the presenting symptom of a food allergy; 10 of these patients had contact urticaria (figure 4 a, b). Direct skin contact with food allergens such as potatoes, fish, meats, fruit, or vegetables causes urticaria that is limited to the area of contact (e8). In 10 patients, the authors identified wheat or rye as so-called protein contact allergens in 3 cases, pork in 1 case, raw potato in 3 cases, fish in 2 cases, and kiwi fruit in 1 case. The cause of the sensitization and clinical manifestation was mostly work related contact in people with a damaged skin barrier, e.g., chronic eczema on the hands or irritation related fissures. A combined reaction of urticaria and eczema is often observed in such a scenario—20 to 30 minutes after exposure, contact urticaria develops, followed by protein contact eczema over the following 1 to 3 days (e8).

Pollen associated food allergies will develop within a few minutes after the oral mucosa has been in contact with raw fruit or vegetables. It is mostly characterized by the oral allergy syndrome—a sudden oropharyngeal pruritus that can lead to edema of the lip (e9). The cause is inhalational sensitization to pollen: People with an allergy to birch pollen may react to apples, hazelnuts, cherries, peaches, and other types of stone fruit, as well as to raw carrots, celery, and soya, whereas an allergy to grass pollen can be associated with an allergy to tomatoes (e10). The food allergens that cross-react with pollen are heat labile, so that the foods are usually tolerated after being heated up. Depending on the sensitivity to proteases, pollen associated allergies usually cause only an oral allergy syndrome, but they can cause generalized urticaria or symptoms of anaphylaxis. Pollen associated...
Results from allergological diagnostics in 419 patients with suspected food allergies.
a) 214 patients with diagnosed food allergies that manifested as grade 1–3 anaphylaxis, oral allergic syndrome, or acute urticaria (categorization of anaphylaxis by severity grades 1–3, see table; OAS=oral allergy syndrome, see box 3).
b) Food allergens and symptoms.
c) In 205 patients, food allergies were mostly excluded (GI=gastrointestinal)
**Box 4**

**Differential diagnoses**

**Psychovisual reactions**
- Heterogeneous group: somatoform disorders are more common, depression, anxiety disorders, and vegetative function impairments
- Typical characteristics include chronic symptoms, a long history of illness, "doctor-hopping" phenomena, and a strong subjective illness experience (e15, e16)

**Functional gastrointestinal disorders**
- Manifestations and causes are manifold and include genetic predisposition, motility disorders, intestinal hyperreactivity, and psychosocial factors
- Irritable bowel syndrome is an exclusion diagnosis; in addition to food allergies, organic gastrointestinal disorders (for example, celiac disease, inflammatory bowel disorders, cancers) need to be ruled out (e17, e18)

**Intolerance to additives**
- Additives are added to foods to give them a particular effect and/or change or influence the food’s attributes
- Symptoms after different foods, after ready meals, and an absence of problems after eating freshly prepared foods should raise the suspicion of an intolerance to additives, for example glutamate, salicylate, or sulfite (e19, e20).

**Intolerance to histamine**
- The reason for histamine intolerance is a low individual threshold for histamine containing food
- Proteolysis and degradation of the free amino acid histidine to histamine cause the histamine content of individual foods to rise with the maturation process and depending on the duration of storage
- Hard cheeses, ham/bacon, canned fish, and red wine contain large quantities of histamine, whereas fresh foods contain very little (e21, e22).

**Idiopathic anaphylaxis**
- Careful exclusion of immunological and nonimmunological trigger factors is necessary
- Anaphylaxis sometimes occurs only after simultaneous exposure to several trigger factors: summation anaphylaxis
- In recurrent "idiopathic" anaphylaxis and normal serum tryptase measurements, bone marrow biopsy should be undertaken to exclude systemic mastocytosis (e23, e24)

**Mastocytoses**
- Clinically heterogeneous spectrum of disorders with increased mast cells in skin, gastrointestinal tract, bone marrow, bone, lymph nodes, spleen, liver
- Symptoms resembling those of IgE allergy result from spontaneous or triggered release of mastocyte mediators
- The particular importance of mastocytosis in diagnosing allergies is the fact that it can cause or aggravate symptoms of anaphylaxis (e24–e27)

**Lactose intolerance**
- Primary or secondary lactase deficiency: after exposure to lactose (cow’s milk, dairy products) dose dependent stomach pains, flatulence, and diarrhea (e28, e29)

**Inflammatory bowel disorders**
- Crohn's disease, ulcerative colitis: food intake can provoke gastrointestinal symptoms (e30)

**Celiac disease (gluten sensitive enteropathy)**
- In patients with genetic predisposition, this is an autoimmune disease caused by gluten: stomach ache, diarrhea, constipation, flatulence, nausea (e31)
It is of great importance to rule out food allergies because this helps to avoid unnecessary and potentially dangerous diets.

Key messages

- IgE mediated (type I) food allergy is characterized by a close temporal relation between exposure to the allergen and occurrence of symptoms. They range from localized (oral allergy syndrome) or generalized (urticaria, angioedema) to life-threatening (anaphylaxis) symptoms with sudden onset.
- In typical symptoms of a food allergy and positive IgE tests (food-specific serum IgE, skin prick test), no further diagnostic test (provocation) is required.
- The negative predictive value of the IgE tests is >95%, oral provocation of foods that tested negative on prick test is usually tolerated.
- Guideline oriented diagnostics can identify the causal food allergen and enables targeted allergen avoidance (caution: hidden allergens, cross-allergies); in anaphylaxis, emergency medication will have to be prescribed.
- It is of great importance to rule out food allergies because this helps to avoid unnecessary and potentially dangerous diets.

Conclusion

Guideline oriented allergological diagnostics (e32) can prevent patients from overrating or underrating food allergies.

Stepwise allergological diagnostics are safe in the hands of experienced allergologists. Food allergies can usually be diagnosed by looking at the medical history, skin tests, and specific IgE in combination.

The patient cohort presented in this study came from a university hospital. In 50% of patients who reported a corresponding medical history, a food allergy was detected. Targeted allergen avoidance and if required emergency medication for self-treatment should protect patients from recurrences. In the other 50%, food allergies were mostly ruled out and exclusion diets therefore became unnecessary.

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

REFERENCES


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Food Allergy in Adults: An Over- or Underrated Problem?

Cornelia S. Seitz, Petra Pfeuffer, Petra Raith, Eva-B. Bröcker, Axel Trautmann

E-REFERENCES

e32. The guidelines of the German Society for Allergology and Clinical Immunology are available at www.dgaki.de/Leitlinien/Leitlinien.html or at www.awmf-online.de under the navigation item “Leitlinien-Datenbank” [guide line database] and the key word “Allergologie” [allergology].