ORIGINAL ARTICLE

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

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

SUMMARY

Background: 10% to 20% of the population sees itself as suffering from food allergy, yet genuine, immune-mediated food allergy is suspected by patients and their physicians far more often than it is actually shown to be present. The unfounded suspicion of an IgE-mediated food allergy can substantially impair a patient's quality of life through needless dietary restriction and the accompanying anxiety. On the other hand, an IgE-mediated food allergy that has gone undiagnosed or that has not been taken seriously can manifest suddenly with anaphylaxis, which may be life-threatening. The present study, carried out on a large cohort of patients, underscores the importance of differentiating IgE-mediated food allergy from other, non-allergic types of food reaction.

Methods: 419 patients that had been referred to our outpatient allergy clinic for suspected food allergies underwent a standardized allergological diagnostic evaluation, including thorough allergologic history-taking, IgE serology, and challenge tests when indicated.

Results: 214 patients (51.1%) were found to have an IgE-mediated food allergy. Almost half of these patients (24.3% of the overall group) had previously experienced food-induced anaphylaxis. In 205 patients (48.9%), however, an IgE-mediated food allergy was ruled out as far as possible.

Conclusion: Only a comprehensive allergological evaluation performed by an experienced allergologist in accordance with current guidelines can protect patients from the negative consequences of excessive concern about a non-existent food allergy (e.g., needless dietary restriction) or, on the other hand, the negative consequences of inadequate attention to a genuine food allergy (anaphylaxis). A proper evaluation consists of detailed allergologic history-taking, skin tests, and challenge tests when indicated.

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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*).

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-

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FIGURE 1

Classification of food hypersensitivity (e14)

BOX 1

Symptoms (3, 4)

Skin

- Pruritus, erythema/flushing, urticaria, angioedema, contact urticaria

Gastrointestinal tract

- Oral allergy syndrome: see box 3
- Gastrointestinal allergy (mostly as a partial symptom of anaphylaxis, rarely isolated): nausea, vomiting, stomach ache, diarrhea

Airways

- Mostly partial symptoms of anaphylaxis, rarely isolated and often work-related: rhinitis, pharyngeal or laryngeal edema, bronchial asthma

Systemic reaction

- Anaphylaxis: see table

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, erythema/flushing, and generalized urticaria with or without accompanying angioedema (figure 2a). 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).

BOX 2

Case reports: Targeted diagnostics in suspected food allergies

- A 20-year-old patient noticed an oral allergy syndrome when chewing apples (*box 3*). If the apples were peeled the problems were less pronounced; no complaints occurred if she ate foods containing heated or cooked apple, such as apple cake or apple sauce. Between March and May—the months of her allergic rhinoconjunctivitis due to birch pollen allergy—she cannot eat apples at all, but she can tolerate certain types during the rest of the year. On a skin prick test using apple (*malus domestica*), a weal of 8 mm diameter developed after 20 minutes. Diagnosis: birch pollen associated allergy to apples.
- A 33-year-old male patient described grade 1 anaphylaxis (*table*), onset 30 minutes after eating shrimp salad. An emergency doctor was called; the patient improved after i.v. application of H1 antihistamines, volume substitution, and administration of glucocorticoids. A skin prick test with shrimp (*Penaeus* species) resulted in a weal of 12 mm diameter after 20 minutes; shrimp-specific serum IgE is 19.2 kU/L, tryptase was 4.1 ng/mL (no indication of 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/Decapoda).
- A 40-year-old patient has had urticaria several times a year for the past three years, which usually improves when treated with oral H1 antihistamines. Before the latest episode, the patient had had a glass of soya milk 3 hours before the weal developed. Physical exertion, medication, and symptoms of infection were excluded. The skin prick test with soya bean (*Glycine max*) and soya milk was negative, soya-specific IgE was not detected. The patient tolerated subsequent open oral provocation with 150 mL soya milk without developing symptoms. Diagnosis: chronic intermittent urticaria.

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.

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).

A patient in whom an allergy to fish was suspected developed low grade general symptoms with erythema, flushing, and generalized urticaria 10 minutes after the test was started, in addition to the positive test reaction.

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

Grades of severity of anaphylaxis symptoms (7)

	Grade 1 (slight)	Grade 2 (moderate)	Grade 3 (severe)
Skin	Pruritus, erythema/flushing, urticaria, angioedema	Grade 1 symptoms possible	Grade 1 symptoms possible
Airways	Rhinitis: sneezing, rhinorrhea, obstruction, pharyngeal pruritus, sensation of pharyngeal obstruction	Dysphonia (hoarse voice), cough, difficulty swallowing, stridor (laryngeal edema), dyspnea, asthma symptoms (wheezing)	Asthma exacerbation, cyanosis, hypoxemia, respiratory arrest
Cardiovascular system	Tachycardia (increase >15/min)	Tachycardia (increase >15/min)	Hypotension, shock, arrhythmias (bradycardia), cardiovascular arrest
Gastrointestinal tract	Oral pruritus, edema of the lips, nausea, slight stomach ache	Crampy stomach pains, vomiting	Incontinence (defecation)
Nervous system	Restlessness, anxiety	Drowsiness, impaired vision, sensation of pressure in the ears	Confusion, loss of consciousness

FIGURE 2

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.

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).

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/innards, 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 posits a disrupted temperature regulation (sometimes cholinergic urticaria occurs concomitantly), another posits 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

Proof of IgE sensitization against food in vitro and in vivo.

a) Measurements of food-specific serum IgE and serum tryptase (n.d. = not done).

Skin test results of the standard series. Grains: rye flour, wheat flour; fruit and vegetables: celery, tomato, carrot, apple, banana; tree nuts: hazelnut, walnut, almond; seasonings: paprika, pepper, mustard, curry mixture.

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)

FIGURE 4

BOX 4

Differential diagnoses

Psychovegetative 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)

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.

food allergies have caused symptoms of anaphylaxis in 1% to 2% of cases, according to the literature; of the authors' own 96 patients, only 8 (8.3%) had generalized urticaria, 4 (4.2%) developed low grade symptoms of anaphylaxis.

The allergy to natural latex is caused by protein contamination in natural latex rubber (e11). Sensitization develops either through intensive skin/mucosa contact—e.g., through medical rubber gloves and catheters—or via the airways. In these cases, powder from the gloves is being inhaled, which, owing to natural latex proteins binding to the powder material, is a potentially sensitizing biological aerosol. Through cross-reactions with certain foods (in 15% to 20% of cases banana, 10% to 15% avocado, 5% to 20% kiwi fruit), latex associated food allergy may develop (e12). Usually, systemic symptoms develop after intake of certain foods, ranging from (mostly) urticaria with or without angioedema to life-threatening anaphylaxis. Of the authors' 17 patients, 10 developed urticaria or angioedema and 7 anaphylaxis symptoms.

In the authors' allergy clinic, many patients present with chronic intermittent urticaria, an episodic form of urticaria with symptom-free intervals lasting weeks to months, in whom a food allergy is suspected. Asking three questions will rule in or rule out a food allergy as the cause of the urticaria (e13):

- Does urticaria develop (reproducibly) within 2 hours (mostly within 30 minutes to 1 hour) after certain foods have been eaten?
- Does urticaria develop after eating and subsequent physical exertion?
- Does contact with certain foods result in urticaria?

If the answer to all three questions is "no," a food allergy as the cause of the urticaria is unlikely. 91 patients (21.7%) of the study cohort had chronic urticaria without any finding of a food allergy (*figure 4c*) (e5). *Box 4* gives an overview of other differential diagnoses to food allergy, some of which require an interdisciplinary approach.

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.

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