

Food allergy and food intolerance: diagnosis and treatment

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Abstract Food allergy is a matter of concern because it affects about 0.5–3.8% of the paediatric population and 0.1–1% of adults, and as well may cause life-threatening reactions. Skin prick testing with food extracts and with fresh foods, the measurement of food-specific IgE, elimination diets and a double-blind, placebo-controlled food challenge are the main diagnostic procedures; many non-validated procedures are available, creating confusion among patients and physicians. The treatment of food allergy is still a matter of debate. Antihistamines, corticosteroids and, if necessary (in case of anaphylaxis), epinephrine, are the drugs of choice for the treatment of symptoms of food allergy. Sodium cromolyn may be used prophylactically even though there are no controlled studies certifying its efficacy. The only etiologic treatment of food allergy is specific desensitization. Sublingual-oral-specific desensitization has been used by our group for the treatment of food-allergic patients with a high percentage of success.

Keywords Food allergy · Food intolerance · Skin prick test · Double-blind placebo-controlled food challenge · Oral specific desensitization

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Introduction

Adverse food reactions (AFRs) can be divided into toxic and hypersensitivity reactions (HRs). When an immunologic mechanism has been demonstrated, hypersensitivity food reactions should be referred to as food allergy; if the role of IgE is highlighted, the exact term is IgE-mediated food allergy. All other reactions, previously referred to as food intolerance, should be called non allergic food hypersensitivity (pharmacologic, enzymatic, undefined) (Fig. 1) [1].

About 20% of people report an AFR, but food allergy has a lower prevalence: 0.5–3.8% in children and 0.1–1% in adults [2].

Symptoms of food allergy

Food allergy can involve several organs and systems: it may cause cutaneous, gastrointestinal respiratory and systemic symptoms [3].

Acute urticaria (pruritus, hives, swelling) and angioedema are the most frequent cutaneous manifestations of food allergy; on the contrary, chronic urticaria (symptoms lasting more than 6 weeks) is rarely caused by food allergy.

Gastrointestinal anaphylaxis usually presents as nausea, colicky abdominal pain, vomiting, or diarrhoea; it generally occurs with allergic manifestations in other target organs. Allergic eosinophilic esophagitis and allergic eosinophilic gastroenteritis are characterized by infiltration of the oesophagus, the stomach, or the intestinal wall with infiltration of eosinophils and peripheral eosinophilia. They are characterized by nausea, vomiting, dysphagia, epigastric and abdominal pains. Food protein-induced proctocolitis is a non IgE-mediated disorder that typically

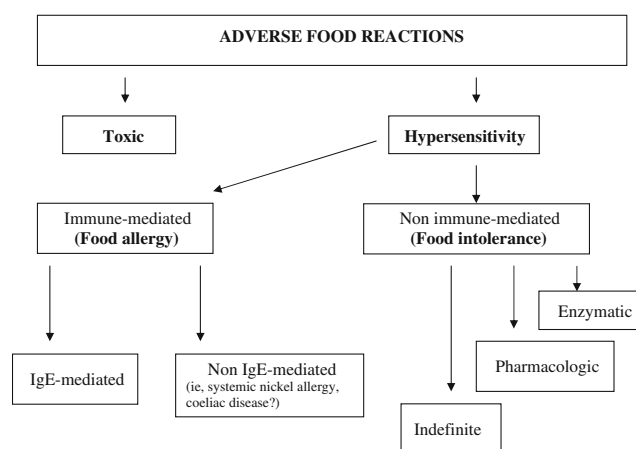


Fig. 1 Classification of AFRs (1, modified)

affects infants in the first months of life; it is caused by food proteins contained in maternal breast milk or by milk- or soy-based formulas. It is characterized by the presence of blood in the stool, and the infiltration of eosinophils in the distal large bowel. Food protein-induced enterocolitis is another non IgE-mediated disorder usually seen in infants. It is caused by milk or soy proteins. The patients usually present with prolonged vomiting appearing about 1–3 h after allergen ingestion. Dietary protein-induced enteropathy presents with diarrhoea and poor weight gain. It is characterized by villous atrophy and a mononuclear cell infiltrate of the mucosa with a few eosinophils.

Food allergy can also induce a number of disorders in the respiratory tract. Isolated rhinoconjunctivitis (periocular pruritus, tearing and conjunctival erythema, nasal congestion, sneezing and rhinorrhea) or asthma (wheezing, cough, dyspnea) is frequently associated with other allergic manifestations.

Food allergy is responsible for at least one-third to one half of anaphylaxis cases seen in hospital emergency departments (ED). In addition to the above-mentioned symptoms, patients may also have cardiovascular symptoms (hypotension, vascular collapse and cardiac dysrhythmias). Food-dependent exercise-induced anaphylaxis occurs only when the patient exercises within 2–4 h of ingesting a food. In the absence of physical exercise the patient can ingest the food without any clinical reaction.

Atopic dermatitis is frequently associated with airborne or food allergen sensitisation, but food allergens are rarely responsible for the onset of symptoms.

The pollen-food allergy syndrome (oral allergy syndrome) is caused by some plant proteins that cross-react with airborne allergens, especially birch, ragweed and mugwort. It is characterized by the onset of mild pruritus, tingling or angioedema of the lips, palate, tongue or oropharynx; systemic symptoms are rare.

Medical history and clinical examination

The diagnostic approach to suspected food HRs begins with the medical history and the clinical examination. The medical history should investigate: (1) the responsible food of the HR and the amount ingested; (2) the length of time between food ingestion and the development of symptoms; (3) whether ingesting the suspected food produced similar symptoms on other occasions; (4) whether other factors (e.g. exercise, alcohol or drug ingestion) are necessary to provoke symptoms; (5) the time interval from last HR; (6) the symptoms provoked by the responsible food, and if the patient took any medication (such as antihistamines, corticosteroids or epinephrine), and (7) whether the patients are suffering from other allergies [4].

Moreover, when taking the clinical history, the physician should keep in mind that foods may be contaminated (for example during packaging) and may contain hidden allergens (for example, milk and soy proteins are often added to increase protein content or enhance flavour).

During the physical examination, the physician should pay attention to the cutaneous, gastrointestinal and respiratory systems since they are mostly involved in food allergy.

First step diagnostic procedures

Skin prick tests

Skin prick testing (SPT) provides a rapid method to screen patients with suspected food allergy. Glycerinated food (when available) extracts are applied by the prick or puncture technique. A wheal at least 3 mm larger than the negative control is considered positive. In case of negative SPTs with food extracts, SPTs with fresh foods (prick by prick method) should be performed (Table 1).

SPT has a high sensitivity and negative predictive value (>95%), but low specificity and positive predictive value (50–80%) [5, 6]. Negative SPT responses (together with the absence of food-specific IgE) virtually exclude IgE-mediated reactions (but do not rule out the diagnosis of food intolerance), while a positive SPT, if it is not confirmed by the measurement of specific IgE and by a double-blind, placebo-controlled food challenge (DBPCFC), does not let the physician establish the diagnosis of clinical food allergy. However, a positive SPT response may be considered diagnostic in patients who experienced life-threatening reactions after ingestion of an isolated food. Niggemann et al. evaluated the diagnostic capacity of SPT in predicting the outcome of food challenges. They have established some decision points for the wheal size to render DBPCFCs unnecessary. Calculation of 95% predicted probabilities reveal predictive

Table 1 Diagnostic procedures for food allergy

1st step diagnostic procedures	1. Skin tests (prick tests and prick by prick) 2. Measurement of specific IgE
2nd step diagnostic procedures	1. Elimination diets 2. Double-blind, placebo-controlled food challenge
Diagnostic procedures for research purposes	1. Proteomic microarray 2. Basophil activation test 3. RAST-inhibition 4. Immunoblotting
Diagnostic procedures with non unanimous consent	1. Atopy patch test 2. Measurement of specific IgG
Non validated diagnostic procedures	1. Cytotoxic test 2. Kinesiology (DRIA test) 3. Electrodermic test (VEGA test) 4. Provocation/neutralization test 5. Iridology 6. Hair analysis

decision points of 13.0 mm for hen's egg and 12.5 mm for cow milk, respectively. No decision points could be calculated for wheat and soy [6]. Unfortunately, there is no unanimous consent about this topic and larger multicentric studies are necessary to determine decision points for all foods.

Measurement of specific IgE

Detection in serum of a specific IgE is the second step after SPTs for the diagnosis of food allergy. It should be considered as a first-line test in patients with significant dermatographism, with severe skin disease (e.g. atopic dermatitis or psoriasis), or in those patients who have difficulty in discontinuing antihistamines.

Detection of specific IgE takes more time than SPTs, and it is more expensive; it gives way to quantitative measurements of food-specific IgE antibodies.

Some authors determine food-specific IgE levels with a 95% positive predictive value and show there is a direct correlation between the food-specific IgE level and the probability that a patient will react to a food if ingested. Sampson determined the 95% positive predictive value of specific IgE for the four major food allergens: 6 kU_A/L for hen's egg, 32 kU_A/L for milk, 15 kU_A/L for peanut and 20 kU_A/L for fish [7].

Celik-Bilgili et al. find different decision points from those obtained by Sampson: they could not calculate the 95% decision point for milk while they find a 95% decision point of 12.6 kU_A/L for hen's egg [8]. These discrepancies may be due to the fact that these authors studied different

populations. Therefore more studies are needed worldwide to obtain standardized results.

Moreover, patients with food-specific IgE levels less than 0.35 kU_A/L may still experience an allergic reaction. In these cases, if there is any suspicion of food allergy, a food challenge may be necessary to confirm the absence of clinical food allergy.

Second step diagnostic procedures

Elimination diets

Once some specific foods are suspected to be responsible for an allergic disorder, the aim of elimination diets is to eliminate the patient's symptoms and confirm the diagnostic hypothesis. A detailed clinical history often gives the physician highly probable targets.

When symptoms, such as chronic urticaria or gastrointestinal disorders unrelated to enzymatic deficiencies or to bacterial contamination, do not seem to be related to a single food, the physician should take into consideration the possibility of a delayed-type allergy to nickel [9], chrome, cobalt or a latex-fruit syndrome [10].

In case of a positive patch test to nickel, chrome or cobalt, patients should avoid foods containing these metals; a positive response is usually seen at least after 4 weeks of the elimination diet (Table 2). In case of a latex-fruit syndrome, the elimination from the diet of cross-reacting foods (Table 2) should promptly relieve symptoms [10].

Elimination diets should be given on the basis of allergy testing results. In case of allergy to a single food or to a few foods, diets are based on the elimination of the offending food(s), with a prompt resolution of symptoms in a few days. When after allergy testing it is not possible to identify a responsible food, the patient should undergo an elemental diet, containing foods that very seldom cause sensitization (Table 3). These diets should be followed for at least 4 weeks, and, in case of resolution of symptoms, the patient can introduce a single food every 4 days till the responsible food is identified.

Foods may naturally contain substances (such as tiramine, histamine, phenyl-ethylamine, sodium nitrate), or may provoke the release of histamine from mast cells (e.g. strawberries). Elimination diets usually cause a resolution of these food-related disorders, but should be followed for several weeks.

Intolerance to food additives (mainly sulphites, glutamate, benzoates and p-oxybenzoates) may mimic food allergy. In this case, a diet without additives is recommended, but it is very difficult to obtain (Table 4).

Table 2 Foods with high nickel content and cross-reacting with latex

Foods with high nickel content		Foods cross-reacting with latex	
Apricot	Lettuce	Apricot	Melon
Canned foods	Lentil	Citrus fruits	Hazelnut
Foods cooked in metal pots	Baking powder	Pineapple	Walnut
Asparagus	Liquorice	Peanut	Oregano
Peanut	Corn	Avocado	Papaya
Lobster	Almond	Banana	Potato
Oats	Margarine	Carrot	Bell pepper
Avocado	Mussel	Chestnut	Pear
Broccoli	Walnut and hazelnut	Water melon	Peach
Cocoa and chocolate	Oyster	Fig	Tomato
Carrot	Potato	Buckwheat	Turnip-beetroot
Cauliflower	Pear	Kiwi	Sage
Onion	Pea	Lettuce	Celery
Bean	Tomato	Mango	Spices
Wholewheat flour	Spinach	Apple	Spinach
Fig	Tea	Aubergine	Grapefruit
	Mushroom		
	Buckwheat		

Table 3 Oligo-allergenic diets

Diet 1	Diet 2
Bread, pasta, brown rice	Rice, oat flour
Oats, pure corn flour	Turkey meat, horse meat
Beef, lamb meat, dried beef	Green salad, potato
Olive or corn oil	Olive oil, margarine
Spinach, carrot, artichoke, fennel	Pear (peeled)
Green salad, potato	Salt
Apple, pear, banana, pineapple	Brown sugar
Chamomile, barley coffee	Tea (not tea bags)
Salt	Mineral or natural water
Brown sugar	
Mineral or natural water	

Elimination diets are often an unrealistic therapeutic approach for various reasons [11]:

- the responsible food may be an essential component of the diet (such as milk or egg), or it may be contained in various foods;
- some diets may be expensive;
- children and younger adults are at higher risk from the responsible food ingestion;
- foods can be contaminated by hidden allergens during the process of production and cooking.

It is important to read the list of ingredients of a food since they can be called by synonyms and consequently they may be not recognized.

Oral provocation tests

The double-blind, placebo-controlled, food challenge (DBPCFC) is considered the gold standard for the diagnosis of food hypersensitivity [12].

It must not be performed in the following instances: in case of a clinical history of anaphylaxis to a well-known food; if the patient is suffering from a systemic acute illness; if the patient is taking drugs that may diminish (antihistamines, corticosteroids) or amplify (ACE-inhibitors, etc.) the reaction or diminish the efficacy of epinephrine (β -blockers).

The DBPCFCs should be conducted in a clinic or hospital setting, and with trained personnel and equipment immediately available for the treatment of anaphylaxis.

We currently perform DBPCFCs, giving the patient the placebo or the allergenic food usually diluted in vanillin. Each dose, which is different for each food, is given every 30 min, till the onset of symptoms or till the highest dose is reached [13, 14].

Although DBPCFCs are considered the gold-standard in the diagnosis of food-related symptoms, false negative and false positive results are possible. False negative results may be obtained because of inadvertent drug use during oral challenges. Augmentation factors such as physical exercise, drugs (e.g. aspirin), alcohol, hormonal factors (e.g. menstruation), respiratory or gastrointestinal infections, systemic mastocytosis or psychogenic factors may render scarcely reproducible the DBPCFC where these factors are missing. Augmentation factors may also be

Table 4 Foods containing sodium benzoate, methyl paraoxybenzoate, sodium glutamate and sulphites

Foods containing sodium benzoate and methyl paraoxybenzoate	Foods containing sodium glutamate	Foods containing sulphites
Non alcoholic beverages (sparkling and with no gas)	Bouillon cubes	Vinegar and pickles
Vegetable preserves	Canned meat	Brandy (eau de vie), maraschino
Meat preserves	Vegetable preserves	Avocado and other tropical fruits
Fish preserves	Meat preserves	Citrus fruit beverages
Frozen dairy products	Fish preserves	Beer, wine
Syrups, jellies e fruit juices		Fresh red meat and packaged codfish fillets
		Some parboiled foods, potato chips
		Fresh and dehydrated fruit if packaged
		Shrimps and other seafood and sometimes fish
		Salads (especially in restaurants or if packaged)
		Green stuff (especially if cleaned and packaged)
		Fruit juices

responsible for positive reactions during a challenge that was negative in the past.

Despite the pitfall in performing a DBPCFC, this procedure must still be considered, if not the gold-standard, the “silver-standard” for the diagnosis of food-related symptoms [15].

Diagnostic procedures for research purposes

These tests are not routinely available and are performed for research purposes in a few centres (Table 1). Proteomic microarray and the basophil activation tests still need standardization, but preliminary results are promising.

Proteomic microarray

It is now possible to map allergenic epitopes of many food allergens and determine where patients' IgE bind to these proteins.

It has been shown that individuals who have IgE antibodies to sequential epitopes react to the food in any form. Those with IgE antibodies to conformational epitopes appear to tolerate small amounts of the food after extensive heating or partial hydrolysis because the tertiary structure of the protein is altered, and conformational epitopes are destroyed. Patients with IgE binding to many epitopes are at risk of more severe reactions than those who have IgE antibodies to few epitopes.

For these reasons, protein and peptide microarrays may in the future let the physician know if the patient will react to a certain food, or will outgrow the hypersensitivity, as well as being able to predict the severity of a reaction [16].

Basophil activation test (BAT)

The BAT is based on the detection by means of flow cytometry of plasma proteins that are expressed by activated basophils. At present, CD63 (tetraspanin), a secretory granule-associated protein, and CD203c, an ectonucleotide pyrophosphatase/phosphodiesterase 3, are considered as markers of basophil activation [17].

There are a few studies [17, 18] evaluating the use of the BAT for the diagnosis of food allergy. A BAT may be useful when a DBPCFC is contraindicated (e.g. history of anaphylactic shock), or when it is not practicable for other reasons (e.g. underlying illness, use of β -blockers etc.). However, further studies are needed to obtain standardized results and to establish the usefulness of the BAT in the diagnostic protocol of food allergy.

Diagnostic procedures with non-unanimous consent

Atopy patch testing

Atopy patch testing (APT) is the means for the diagnosis of delayed-type (cell-mediated) allergy.

APT has been proposed as a diagnostic procedure for a better diagnosis of food allergy and atopic dermatitis [19]. It is performed in the same way of patch testing with contact allergens; food allergens, which are usually responsible of IgE-mediated responses, are used.

This procedure is not very well standardized even if APT with fresh foods seems to have a higher sensitivity in comparison to APT with food extracts.

Actually, APT seems useful for the diagnosis of gastrointestinal disorders related to food allergy; more studies

are necessary to clearly elucidate the way of execution, the field of application and their real usefulness [20].

Measurement of specific IgG4

Testing for blood IgG4 against several foods can be performed by enzyme-linked immunosorbent assays and radioallergosorbent assays. Since many patients believe that their symptoms are related to food ingestion, test for specific IgG4 is a growing market. However, many individuals show positive results without any clinical symptom, and there is no convincing evidence that IgG4 have histamine-releasing properties. The presence of IgG4 against foods indicates exposure to the food itself, and should be considered an indicator of immunological tolerance [21].

Detection of specific IgG4 have been used by our group for the follow up of patients undergoing food oral desensitization; in fact, we observed a reduction of specific IgE and an increase of specific IgG4 in patients successfully desensitized [13, 14].

Non-validated diagnostic procedures

Cytotoxic testing: it is based on the assumption that the addition of a specific allergen in vitro to whole blood or to serum will reduce white blood cells or kill the leucocytes. However, several controlled studies have shown that this test does not correlate with IgE-mediated reactions to foods and lacks reproducibility. Moreover, positive cytotoxic effects are frequently obtained with foods that produce no clinical symptoms while negative results are obtained with foods that do produce clinical symptoms.

Applied kinesiology: allergens for testing are placed in a sealed glass bottle that the patient holds in one hand while the investigator estimates muscle strength on the other arm. A decrease in muscle power while the food is held indicates a positive test. This procedure is completely without any scientific support.

Electrodermal testing: it is performed with a galvanometer to measure conductivity of the skin. The patient holds two electrodes and food extracts in closed glass vials come in contact with an aluminium plate within the circuit. A drop in electrical conductivity of the skin leads to the diagnosis of food allergy/intolerance. No studies have explained its usefulness in food allergy.

Provocation/neutralization test: it consists in placing three drops of an aqueous food extract under the tongue and waiting 10 min for symptoms to appear. If symptoms occur, a neutralizing dose (usually three drops of a more diluted solution of the same extract) is placed under the

tongue. Symptoms are expected to disappear in about the same temporal sequence in which they appeared. The neutralizing dose can also be used to prevent symptoms before food ingestion. A multicenter double-blinded study by the American College of Asthma, Allergy and Immunology and the American Academy of Asthma, Allergy and Immunology have failed to demonstrate the usefulness of this test in food allergy.

DRIA test: it consists in placing a food extract under the tongue and measuring muscle strength. A decrease in muscle power leads to the diagnosis of food allergy. The test has no scientific support, and has not been validated by any study.

Particular cases of food allergy

Diagnosis of systemic nickel allergy

Patients with allergic contact dermatitis to nickel show, in about 20% of cases, systemic cutaneous disorders (chronic urticaria, eczema) or gastrointestinal symptoms (abdominal pain, diarrhoea, etc.) after the ingestion of food containing high amounts of nickel (Table 2).

The diagnosis of nickel allergy is made by means of patch testing [22]. Once the diagnosis has been made, the patient should follow a nickel-free diet for at least 4 weeks. If symptom score shows an improvement of at least 70%, a DBPCFC test with nickel is advisable. The starting dose is 2.5 mg, and it is increased by 2.5 mg every 96 h until a final dose of 10 mg is reached. The test is scored as positive at the onset of cutaneous or gastrointestinal disorders [23].

Cross-reactivity between foods and pollens

According to various studies, about 20–40% of patients suffering from pollinosis develop AFR after ingestion of some vegetable foods. Symptoms are usually limited to the mouth, the so-called oral allergy syndrome (OAS); in some cases (for example, in case of the Compositae-celery-spice syndrome) severe anaphylaxis may occur [24].

OAS is caused by the sensitizations to structurally similar cross-reacting proteins that are shared by all vegetables and are called panallergens (pathogenesis related proteins, chitinases, lipid transfer proteins, profilins, etc.) (Table 5).

Latex allergy, latex-fruit syndrome

After the discovery of the so called panallergens, some authors [25] put in evidence the cross-reactivity between latex and some vegetable foods (latex-fruit syndrome).

Table 5 Food panallergens

Profilins	Lipid transfer proteins
<i>Umbelliferae</i> : anise, carrot, cucumber, fennel, parsley, celery	<i>Rosaceae</i> : apricot, black cherry, kaki, cherry, quince, strawberry, raspberry, almond, apple, blackberry, medlar, nut, pear, peach, plum, dogrose
<i>Rosaceae</i> : apricot, black cherry, cherry, kaki, quince, strawberry, raspberry, almond, apple, blackberry, medlar, walnut, pear, peach, plum, dogrose	Others: peanut, orange, asparagus, pineapple, banana, cauliflower, broccoli, carrot, chestnut, wheat, kiwi, lettuce, lemon, corn, melon, pomegranate, nut, walnut, barley, tomato rice, sunflower seeds, sesame, celery, soybean, grapefruit, mustard
Others: pineapple, watermelon, peanut, orange, asparagus, avocado, banana, chestnut, onion, fig, kiwi, mango, melon, nut, potato, pepper, pea, tomato, rice, celery, saffron, sesame, soybean, grapefruit, zucchini, pumpkin, sunflower seeds	

Therefore the search for a concomitant latex allergy in patients with vegetable food allergy has become necessary. Moreover, patients with latex allergy may show sensitization to pollens of Graminae and ragweed and to the sap of leaves and of stems of Euphorbiaceae, such as Christmas flower (*Euphorbia pulcherrima*) and *Ficus benjamina* (latex-pollen syndrome and latex-pollen-fruit syndrome) (Table 2) [26].

The diagnosis of latex allergy is made on the basis of the medical history and the clinical examination, skin prick and patch testing with latex extract and latex gloves, detection of specific IgE and organ-specific provocation tests (percutaneous, mucous, bronchial, sublingual, conjunctival, vaginal) [27].

Celiac disease

Celiac disease is an autoimmune disorder (non IgE-mediated) characterized by malabsorption and mucosal damage of the small bowel. It is caused by the ingestion of gluten, the major storage protein of wheat and similar grains. The diagnosis of celiac disease is based, first of all, on the medical history and the medical examination (the physician should always keep in mind that clinical manifestations may be extremely variable). Then the patient should undergo some serological testing such as detection of antibodies of the IgA and the IgG classes (IgA are the most sensitive) against gliadin, reticulín, endomysium and tissue

transglutaminase and the HLA assessment (the absence of HLA-DQ2 and HLA-DQ8 have a high negative predictive value).

A biopsy of the small bowel remains the standard for diagnosing celiac disease. The histological examination of the specimens may put in evidence villous atrophy and other pathologic changes [28].

Diagnosis of food intolerance (Table 6)

Treatment of food allergy

Pharmacological treatment

Anti-H₁ antihistamines are useful for the treatment of the OAS, of skin symptoms and upper airway symptoms while they have less efficacy on lower respiratory airways (such as asthma) and gastrointestinal symptoms and anaphylaxis.

Oral corticosteroids can be used for the treatment of chronic IgE-mediated disorders, but unfortunately, often with unacceptable side-effects.

Even if there are no controlled studies of its efficacy, sodium cromolyn can be used for the treatment of food IgE-mediated disorders, and, according to our personal experience, may prevent (or reduce the severity of) adverse reactions during oral-specific desensitization with foods [13, 14].

Table 6 Diagnosis of food intolerance

Syndrome	Symptoms	Diagnosis
Favism (glucose-6-phosphate dehydrogenase deficiency)	Hemolysis provoked by oxydant agents (broad beans, drugs)	1. Clinical history 2. Measurement of glucose-6-phosphate dehydrogenase activity
Carbohydrate intolerance (lactose, fructose, sorbitol)	Meteorism, flatulence, nausea	Breath tests (lactose, fructose, glucose, etc.)
Food additive intolerance (methyl-paraoxybenzoate, sodium benzoate, sulphites, etc.)	Respiratory, cutaneous and gastrointestinal symptoms	Oral provocation test

Table 7 First aid kit

ZONE	SYMPTOMS	WHAT TO DO	
GREEN	NO SYMPTOMS	Drug	Dose
In case of: ☐ Accidental ingestion of forbidden foods		☐ Bethamethasone 0.5 mg ☐ Levocetirizine	1-2 tablets to be put under the tongue 1 tablet
YELLOW: ATTENTION	OR	☐ Lyophilized ebastine ☐ Levocetirizine	1 tablet 10-20 drops
In case of: ☐ Itching or erythema ☐ Paresthesia of the mouth	MILD SYMPTOMS		
RED: ALARM!	WORSENING OF YELLOW ZONE SYMPTOMS	☐ Self-injectable epinephrine (Fastjekt® 330)* ☐ Self-injectable epinephrine (Fastjekt® 165)* for children < 30 kg * <u>It can be repeated after 5-10 minutes</u>	1 vial im 1 vial im
☐ Generalized urticaria, angioedema of the face, of the lips and the tongue ☐ Vomiting or abdominal pain ☐ Dysphonia or throat constriction ☐ Dyspnoea ☐ Paleness, sweating or cyanosis ☐ Hypotension, tachycardia ☐ Feeling of impending disaster ☐ Loss of consciousness	OR	☐ Bethamethasone ☐ Clorpheniramine ☐ Salbutamole	4-8 mg im 10 mg im 1-2 puffs
	SEVERE SYMPTOMS		



Always go to the nearest Emergency Department!

Intramuscular epinephrine, at the dose of 0.3–1 mg for adults and 0.1–0.5 mg for children, is the treatment of choice for anaphylaxis, while antihistamines and parenteral corticosteroids are second choice drugs.

Moreover, the patient should carry a “first aid kit”: it should include self-injectable epinephrine, oral and parenteral corticosteroids, oral and parenteral antihistamines. The allergist should train the patient, and clearly explain when to use each single drug (Table 7).

Omalizumab, a monoclonal antibody against IgE, has been used for the treatment of food allergy [29]. Omalizumab inhibits binding of IgE to mast cells and basophils, down-regulates the expression of FcεRI on basophils, and may inhibit allergen-specific activation of T cells.

Even if without relevant side-effects, omalizumab therapy has shown some weakness: (1) 75% of patients show a significant increase in the threshold dose, and

Table 8 Protocol for oral desensitization with cows' milk [22]

Dilution: 1 drop of milk in 100 ml of water		Pure milk			
Days	Drops	Days	Dose	Days	Dose (ml)
From 1 to 3	1	From 37 to 39	1 drop	From 133 to 135	35
From 4 to 6	3	From 40 to 42	2 drops	From 136 to 138	40
From 7 to 9	6	From 43 to 45	3 drops	From 139 to 141	45
From 10 to 12	10	From 46 to 48	4 drops	From 142 to 144	50
From 13 to 15	15	From 49 to 51	5 drops	From 145 to 147	55
From 16 to 18	20	From 52 to 54	6 drops	From 148 to 150	60
		From 55 to 57	7 drops	From 151 to 153	65
		From 58 to 60	8 drops	From 154 to 156	70
		From 61 to 63	9 drops	From 157 to 159	75
		From 64 to 66	11 drops	From 160 to 162	80
		From 67 to 69	13 drops	From 163 to 165	90
		From 70 to 72	16 drops	From 166 to 168	100
		From 73 to 75	20 drops	From 169 to 171	110
		From 76 to 78	24 drops	From 172 to 174	120
		From 79 to 81	30 drops	From 175 to 177	130
		From 82 to 84	36 drops		
		From 85 to 87	42 drops		
		From 88 to 90	48 drops		
		From 91 to 93	54 drops		
		From 94 to 96	62 drops		
		From 97 to 99	70 drops		
		From 100 to 102	80 drops		
		From 103 to 105	3 ml		
		From 106 to 108	4 ml		
		From 109 to 111	5 ml		
		From 112 to 114	6 ml		
		From 115 to 117	8 ml		
		From 118 to 120	11 ml		
		From 121 to 123	15 ml		
		From 124 to 126	20 ml		
		From 127 to 129	25 ml		
		From 130 to 132	30 ml		
		Maintenance dose:			
		130 ml of milk (about 1 glass) at least 2–3 times a week			

patients did not obtain a real desensitisation but only a partial tolerance. About 25% of patients treated with 450 mg/week (at the highest dose tested) did not show any improvement of the threshold dose, before and after the treatment; (2) it is a life-lasting treatment since IgE increase after treatment interruption; (3) it is a very expensive treatment, for the patient or the National Health System, and (4) on rare occasions, it can cause an anaphylactic reaction itself [30].

The role of antileukotrienes in the treatment of food allergy should be better defined. Some reports report a

certain efficacy for the treatment of atopic dermatitis [31] and of chronic urticaria related to food additive intolerance [32], and, according to our experience, may prevent (or reduce the severity of) adverse reactions during oral-specific desensitization with foods.

Oral-specific desensitization

At present, the only aetiologic treatment of food allergy is specific desensitization. This treatment should be taken into consideration when [13, 14]:

Table 9 Protocol for oral desensitization with egg [22]

Dilution: 1 drop of raw shaken egg (albumen + yolk) in 100 ml of water		Pure raw shaken egg	
Days	Drops	Days	Dose
From 1 to 3	1	From 61 to 63	1 drop
From 4 to 6	2	From 64 to 66	2 drops
From 7 to 9	3	From 67 to 69	3 drops
From 10 to 12	4	From 70 to 72	4 drops
From 13 to 15	5	From 73 to 75	6 drops
From 16 to 18	6	From 76 to 78	8 drops
From 19 to 21	8	From 79 to 81	10 drops
From 22 to 24	10	From 82 to 84	12 drops
Dilution: 10 drop of raw shaken egg (albumen + yolk) in 100 ml of water		From 85 to 87	15 drops
		From 88 to 90	20 drops
From 25 to 27	1	From 91 to 93	27 drops
		From 94 to 96	37 drops
From 28 to 30	2	From 97 to 100	50 drops
From 31 to 33	3	From 101 to 104	2 ml
From 34 to 36	4	From 105 to 109	3 ml
From 37 to 39	5	From 110 to 113	4 ml
From 40 to 42	6	From 114 to 117	5 ml
From 43 to 45	8	From 118 to 121	6 ml
From 46 to 48	11	From 122 to 125	7 ml
From 49 to 51	15	From 126 to 129	8 ml
From 52 to 54	20	From 130 to 133	10 ml
From 55 to 57	25	From 134 to 137	12 ml
From 58 to 60	30	From 138 to 141	15 ml
Maintenance dose: 1 egg 2–3 times a week		From 142 to 145	20 ml
		From 146 to 149	25 ml
		From 150 to 153	30 ml*
		From 154 to 157	35 ml
		From 158 to 161	40 ml
		From 162 to 165	45 ml
		From 166 to 168	50 ml

* As regards albumen allergy, we used the same doses and we shook the albumen only; desensitization was interrupted at this point since albumen is about 30 ml

- it is impossible to avoid food exposure in the environment (for example a cook);
- it is impossible for multiple food allergic patients to maintain an adequate diet regimen;
- it is impossible to maintain a diet regimen that may be expensive or socially discriminating;
- when patients do not outgrow their food hypersensitivity after a strict elimination diet.

As regards children, a spontaneous desensitization may occur (but only during infancy) after 2–3 years of a strict elimination diet: it is more frequent for milk, egg and soy allergy, while it is more difficult for peanut, hazelnut and fish allergies to be outgrown [33].

Literature data about this topic are not unanimous: Bock in 1982 reported that a spontaneous desensitization occurs

in 44% of children under 3 years and in 19% of children over 3 years [34]. Other authors find that 30% of patients under 3 years, 40% under 6 years and 50% under 9 years spontaneously lose their food hypersensitivity [35]. Finally, Host and Halken find that 87% of children with food hypersensitivity reach a spontaneous recovery at the age of 3, and that patients with milk allergy outgrow their food hypersensitivity: 56% at the age of 3, and up to 97% at the age of 15 [36, 37]. Bishop et al. report a spontaneous desensitization of 28% at the age of 2, of 56% at the age of 4 and of 78% at the age of 6 [38].

Children with peanut allergy reach a spontaneous desensitization in just 20% of cases [39].

As regards egg allergy, a spontaneous desensitization may occur later, but 34% of children over 5 years do not outgrow their egg hypersensitivity [40].

Table 10 Results of oral-specific desensitization in food allergic patients

Foods	Cases	Success	Partial tolerance	Failure	Interruptions (lack of compliance)
Milk	36	25	—	6	5
Sheep milk	1	1	—	—	—
Mixed milk (50% cow + 50% sheep)	5	4	—	1	—
Whole egg	29	19	1	4	5
Albumen	3	2	1	—	—
Codfish	12	9	—	1	2
Mixed fish (50% codfish + 50% soil)	2	2	—	—	—
Soil	1	1	—	—	—
Wheat	3	2	—	1	—
Corn	3	2	—	1	—
Apple	2	2	—	—	—
Bean	1	—	—	—	1
Orange	2	2	—	—	—
Peanut	2	1	—	—	1
Peach	1	1	—	—	—
Lettuce	1	—	—	—	1
Total	104	73 (82%)	2 (2,2%)	14 (15,8%)	15

Specific desensitizations have been attempted by the subcutaneous and the oral routes.

Subcutaneous desensitization has been used for the treatment of peanut allergy, but with unacceptable side-effects (the authors used epinephrine, both during the induction and the maintenance phases, to treat anaphylaxis) and with no modifications of immunologic parameters (IgE and IgG4) [41].

Sublingual-oral specific desensitization should be given more attention; in fact, it has been used for the treatment of food-allergic patients with a high percentage of success [13, 14, 42–45].

As regards our group's experience, we performed 104 desensitizing treatments in 90 patients (some patients were allergic to more than 1 food) according to standardized protocols (Tables 8, 9). In 15 cases, the patients abandoned the treatment. In the remaining 89 cases, the treatment was successfully completed in 73 (82%), and in 2 cases (2.2%) patients achieved a partial tolerance and in 14 (15.8%) the treatment failed because of the occurrence of side-effects, not controlled with symptomatic or prophylactic therapy (Table 10).

It can be hypothesized that oral desensitization with food allergens could be mediated by the same mechanisms occurring during desensitization with respiratory allergens or Hymenoptera venoms. In our patients we find a significant increase of specific IgG₄ and a significant decrease of specific IgE (Fig. 2). In a patient with milk allergy who successfully completed the oral desensitizing treatment, we also found a decrease in IL-4 (able to induce specific IgE synthesis) and an increase in IFN- γ production (able to

inhibit specific IgE synthesis) by T lymphocytes, both spontaneously and after induction by allergen or mitogen [43].

Recently, by means of peptidic microarray [46], we studied the modifications of specific IgE and IgG₄ in 13 patients who underwent oral desensitization with milk: Eight patients completed the treatment successfully, while in five cases it was interrupted because of the impossibility to increase the dosages of the protocol. All patients were able to produce epitope-specific IgE binding to the region 171–180 of α S2-casein, which has been considered as a reliable marker of persistence of allergy. By means of peptidic microarray we found a signal reduction in patients who completed the treatment while, in case of failure, there

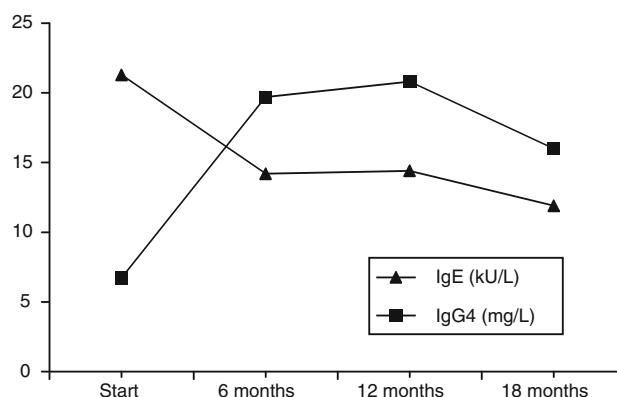
**Fig. 2** Modifications of specific IgE and IgG₄ values in patients who successfully completed the treatment

Table 11 Results of oral-specific desensitization in patients with non-allergic food hypersensitivity

Food	Method	Cases	Length	Success	Failure	Interruption
Tomato	Rush	1	6 days	1	–	–
Wheat	Rush	1	13 days	1	–	–
Codfish + soil	Traditional	2	160 days	1	–	1 (lack of compliance)
Egg yolk	Traditional	1	13 months	1	–	–
Milk	Traditional	1		–	1	–
Total		6		4	1	1

is an increase of the signal itself. Specific IgG₄ were increased in both groups [unpublished data].

Gastrointestinal mucosa is rich in immune system cells (dendritic cells, T and B lymphocytes) that can recognize and process food allergens; and also the WHO confirmed the efficacy of sublingual specific immunotherapy of respiratory allergies [47].

Our data about oral desensitization with foods have been confirmed by the works of other authors [48, 49].

Oral desensitization has been also attempted with a rush method, with a shorter induction phase. It is riskier than a traditional treatment, and can be performed in a recovery regimen only [50, 51].

Specific immunotherapy with pollen allergens in patients with allergy to cross-reacting foods has been attempted in patients with birch and apple allergy, with interesting results [52].

We used oral food desensitization also for some cases of food intolerance (non allergic food hypersensitivity); the treatment, performed by traditional or rush method, let some patients introduce in their diets the foods that they were not able to tolerate (Table 11). The exact mechanism of tolerance induction is unclear since there are no changes of immunologic parameters as happens in patients with IgE-mediated allergy [53].

Latex-fruit syndrome

Thirty patients with latex allergy and latex-fruit syndrome (patients experienced adverse reactions to cross-reacting foods in 66 cases) underwent an oral specific desensitizing treatment with latex [54]; at the end of the treatment, patients could reintroduce in the diet the cross-reacting foods in 62 cases out of 66 (93.9%) (unpublished data).

Oral specific desensitization with nickel

For some time, our group has been using oral-specific desensitization in patients suffering from systemic nickel allergy. By administering increasing doses of nickel via the oral route, 94 out of 136 patients (69.1%) showed a complete (47%) or partial (22.1%) improvement of symptoms;

so, they could introduce again in the diet foods containing nickel [9, 23].

An attempt of specific desensitization of celiac disease

The only treatment for celiac disease is a strict elimination diet of all foods containing gluten. Since celiac disease is an immune-mediated disorder, we tried an oral desensitizing protocol with gluten in four patients with celiac disease. The treatment was not successful since two patients had a relapse of the disease after 12 and 4 months of a free diet, and the remaining two showed a relapse during the treatment [55].

Novel therapeutic approaches in the management of food allergy

The newest and theoretical approaches to food allergy are:

- plasmid DNA (pDNA) immunization [56];
- the use of probiotics such as *Lactobacillus rhamnosus* [57];
- allergen immunotherapy with heat-killed *Listeria monocytogenes* as adjuvant, which induce IFN- γ production [58];
- traditional chinese medicine [59].

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