

## R E V I E W

# Food allergy: an updated review on pathogenesis, diagnosis, prevention and management

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**Abstract.** Food allergy (FA) is an adverse immunologic response triggered by normally innocuous food protein antigens. FA can be broadly classified into those that are IgE mediated, those that are mediated by both IgE-dependent and IgE-independent pathways (mixed), and those that are not IgE mediated Immunoglobulin E. (IgE)-mediated reaction is characterized by rapid onset of symptoms involving respiratory, gastrointestinal, dermatologic and cardiovascular systems; mixed and non-IgE-mediated has a longer onset and manifests primary in the gastrointestinal tract and skin. The diagnosis of food allergy is based on clinical history, diagnostic testing (skin prick test and allergen-specific IgE levels in the serum), elimination diet and, oral food challenge. In recent years the diagnosis and treatment of pediatric FA have notably improved. In the diagnostic pathway of FA an important recent innovation is the CRD introduction. This resulted in the possibility of improving diagnostic accuracy through FA prediction severity and prognosis and thereby decreasing the OCF necessity. Recent studies emphasize the possibility of preventing FA through early introduction of food (peanuts and egg) to high-risk infants. FA management is based on avoidance of offending food and prompt treatment of allergic reaction. Currently under study are recently developed treatment approaches for FA management including specific OIT. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** food allergy, pathogenesis, diagnosis, prevention, management, children

## Introduction

FA is an adverse immunologic response occurring reproducibly on exposure to a given food. It has to be distinguished from food intolerance, that is a non-immune reaction involving metabolic, toxic, pharma-

cologic and undefined mechanisms (1). Nowadays FA is a major health issue. Its prevalence has significantly increased in the last 20 years worldwide, particularly in westernized developed countries (3-5). Developing countries are showing similar trends as their economies grow, moreover, their population is embracing a

more westernized lifestyle. (6). Overall FA prevalence is estimated to be 5% in adults and 8% in children (3). The present narrative review aims at providing updated review on pathogenesis, diagnosis, prevention and management of FA in children.

## Pathogenesis

The breakdown of immunologic and clinical tolerance to an ingested food is the trigger for FA; this results in IgE-, non-IgE- or mixed IgE- and non-IgE-mediated reactions (3). IgE-mediated FA is characterized by immediate clinical manifestations, due to the release of mediators triggered by the bonding of IgE antibodies, mast cells and basophils. Non IgE-mediated FA, is due to T-cell driven inflammatory responses (7).

Oral tolerance consists in the systemic suppression of cellular and humoral immune response to an antigen first encountered in the gastrointestinal (GI) tract (8), although immune tolerance can be induced by other routes such as airways and intact skin (9). Physical barriers, digestive processes, specific immune cells and immune modulation determine gastrointestinal tract's ability to develop oral tolerance. Specialized GI cells (microfold, intestinal epithelial, and dendritic cells) play an essential role in antigen presentation and oral tolerance development, process food proteins outliving the digestive process. Dendritic cells play a central role in induction and maintenance of tolerance to food antigens. After antigen uptake they migrate into the mesenteric lymph nodes where they determine activation and differentiation of effector T cells. DCs determine active generation of food-antigen-specific regulatory cells (Tregs), which are probably influenced by the local microbiome (10, 11). Treg cells determine a regulatory, tolerant immune response by the production of transforming factor beta (TGF- $\beta$ ) and inhibitory cytokines (IL-10) through a retinoic acid-dependent mechanism (12). The subsequent actions of both T and B cells are suppressed by TGF-beta and the latter also aids the production of secretory IgA (13); T-cell anergy is induced by IL-10 which also sustains Treg populations. The switching of B-cell class to produce secretory IgA is also partially provided by IL-10 (14).

Sensitization is a condition of having detectable food antigen specific IgE which can precede (or sometimes follows if clinical tolerance develops) the development of clinical FA. Immunologic mechanisms leading to the sensitization start with the first contact when the allergen occurs. Disruption of food tolerance is a consequence of epithelial barrier damage following the exposure to many factors such as pathogen-associated molecular patterns (PAMPs). In response to injury, epithelial cells produce pro-inflammatory cytokines such as IL-25, IL-23 and thymic stromal lymphopoietin (TSLP) and DCs activation (15). This induces danger signals, inflammatory cytokines release and dendritic cells activation. The activated dendritic cells in turn activate naive T cells into acquiring a T helper cells 2 (Th2) phenotype, which promotes inflammatory signals, inducing food Ag-specific B cells to class switch and produce food antigen-specific IgE. Skin antigen exposure has also been associated with sensitization. Factors breaking immune tolerance through the skin include skin barrier defects consequent to filaggrin's mutations, a protein essential for skin integrity (16, 17), damage to the skin, microbial adjuvants such as staphylococcus enterotoxin B. All these factors induce an innate inflammatory skin response causing sensitization (9). The respiratory route is also responsible for triggering sensitization: inhaled aeroallergens can cross-react with food antigens, resulting in an oral allergy syndrome. Once sensitization has been established, re-exposure to the antigen can lead to local or systemic manifestations. Once produced, IgE bind to its high-affinity receptor Fc $\epsilon$ RI on the surface of mast cells and basophils, therefore arming these cells for activation on re-exposure to the antigen. The second contact with the antigen activates and makes these cells degranulate, resulting in performed mediators release (histamine, tryptase, platelet activating factor, prostaglandin and leukotrienes) and can lead to local and systemic manifestations (18). Several hypotheses have been formulated to explain the increase of FA.

- *The hygiene hypothesis.* A lack of microbes and infections exposure in early childhood might increase susceptibility to allergic disease by altering the development of the immune system through an imbalance of the immune responses in favor of the Th2 lymphocyte profile rather than Th1 (19). Observational

studies suggest that factors associated with increased microbial exposure, such as exposure to pets, childcare attendance, vaginal delivery and presence of older siblings, might have protective effects against developing food allergy (20-22).

-*The dual-allergen hypothesis.* Several studies conducted in animals and humans suggest that disrupted skin barrier function in infant eczema might cause allergen sensitization through environmental exposure via the skin rather than oral route (23). This hypothesis also supposed food antigens skin exposure is more likely to lead to allergy compared to early oral consumption, which is more likely to lead to tolerance (24). FA is likely a combination of both skin and gut exposure to a food antigen, with a higher tendency towards sensitization if the first exposure is through the skin.

-*The Vitamin D hypothesis.* Vitamin D has well-recognized immunoregulatory and tolerogenic functions, and its deficiency is considered a possible risk factors for FA development (25). Vitamin D was first related to the prevention of FA by demonstrating that infants with vitamin D level <50 nmol/L at 1 year of age had an 11-fold higher risk of peanut allergy, confirmed by oral food challenge, compared to infants with vitamin D levels >50 nmol/L (26). Some evidence suggests that vitamin D is important in the regulation of Th cells differentiation and the induction of T-reg cells (27) and Th2 immune responses have been shown to be favored under low vitamin D or vitamin D-deficient conditions (28-30). The Western diet along with fruit and vegetable low intake and low sun exposure may represent a risk of vitamin D deficiency, which could potentially enhance.

-*The microbiota hypothesis.* The presence of specific bacterial strains as well as dietary substrate and their metabolites, could influence FA development (31,32).

-*The "false alarm hypothesis".* Smith et al. (33) very recently proposed a different theory to explain FA increase. The Western diet is high in advanced glycation end-products (AGEs) deriving from cooked meat, oil and cheese, and high concentration of sugar. They suggest AGEs, that are present or formed from the food in our diet and are alarmins, prime innate signaling, leading to development of FA (34).

## Clinical presentation

FA has been nicknamed the great transformer. In fact, it is not a single disease, nor is it caused by a single pathophysiologic disturbance (35). The type and severity of symptoms changes from one subject to another, and in the same subject from one reaction to another, in accordance with food and with the same food depending on the sensitizing molecule. In both IgE and non IgE mediated FA, symptoms most frequently affect the skin, GI, respiratory and cardiovascular system, in either isolation or in association. The short period of time (usually < 2 hours) between ingesting a food and the appearance of symptoms leads to a suspicion of a mediated IgE reaction, except for food dependent exercise anaphylaxis (FDEIA) and of delayed anaphylaxis to red meat (36). Cow's milk allergy (CMA), for example, can occur with several different immune mechanisms that induce rather different clinical frameworks. In IgE mediated CMA, clinical history is often characteristic and repetitive. Symptoms often arise within two hours of the first exposure to cow's milk and include cutaneous symptoms (such as flushing, urticaria, angioedema, pruritus) and/or GI symptoms (such as nausea, regurgitation, vomiting, and sometimes diarrhoea) and/or sometimes other symptoms such as crying or lethargy, etc. Clinical manifestations are extremely evident and in most cases regress within a few hours and reappear following further exposure to cow's milk protein (37). On the contrary, in non-IgE mediated CMA, clinical history is less suggestive and characteristic, because they may have gastrointestinal symptoms, more often occurring several hours later or even several days after milk exposure. Usually present at a young age and often whilst the infant is being breastfed. More, symptoms such as crying, abdominal pain, nausea, regurgitation, vomiting, diarrhoea or sometimes hard stools are less specific because their presence in other diseases such as gastroesophageal reflux, infantile colic, and functional gastrointestinal disorders (3, 38). In other disorders, such as atopic dermatitis, eosinophilic gastrointestinal disorders and asthma, FA seem sometimes to have a role through a mixed IgE and cell mediated immune mechanism. Also, in these disorders the relationship between food ingestion and symptoms onset is not al-

ways obvious especially if symptoms are chronic and/or relapsing (39). Anaphylaxis is the most severe of allergic reactions. Anaphylaxis involves at least 2 body systems and is defined as “a serious, life-threatening generalized or systemic hypersensitivity reaction” and “a serious allergic reaction that is rapid in onset and might cause death” (40). To facilitate prompt diagnosis of anaphylaxis validated clinical criteria are available (41) (Table 1). Patients with anaphylaxis commonly present symptoms involving skin or mucous membranes, followed by respiratory and gastrointestinal and cardiovascular symptoms. A large international study involving 1970 patients referred to tertiary allergy centers in ten European countries, showed the percentage of anaphylaxis symptoms in children (42, 43) and are listed in Table 2.

## Diagnosis

The diagnosis of FA is not simple because of its multiple clinical manifestations and because diagnostic tests are not always enough to offer diagnostic certainty. The combination of history and diagnostic tests in some cases (e.g anaphylaxis or in children with a clinical

history suggestive of allergy and positive results in skin tests or specific IgE), can provide enough diagnostic reliability to make the diagnosis of a FA without conducting an oral food challenge (OFC) (44-46). In all other cases, or if the certainty of diagnosis is sought, an OFC is required. Since severe reactions might occur, the OFC should be carried out by experienced physicians in a proper environment, equipped for emergencies (47). The diagnosis of IgE-mediated FA relies on a compatible clinical history and on the results of skin prick tests (SPTs) and/or the determination of serum-specific immunoglobulins E (sIgEs). An accurate collection of clinical history is essential to define when further diagnostic investigations are needed, how to implement them, and interpret their results. Clinical history aims to identify food allergy cases by investigating symptoms, possible allergens, relationships between food ingestion and the onset of symptoms, ingested dose, intercurrent diseases, potential cofactors or cross-reactivity, other allergies, the role of the suspected allergen in the diet, and possible effects of previous diets (37). The goal of clinical history is also to identify the possible immunological mechanism underlying the FA. Some conditions may point to IgE-mediated allergic reactions such as signs of skin involvement (urticaria,

**Table 1.** Criteria for anaphylaxis diagnosis

The presence of any 1 of these 3 criteria indicates that anaphylaxis is highly likely:	
A	Acute and rapid progressive onset with involvement of skin, mucosal tissue, or both and one of the following: <ol style="list-style-type: none"> <li>1. Respiratory symptoms</li> <li>2. Hypotension or end-organ dysfunction</li> </ol>
B	Two or more of the following occurring suddenly after exposure to a likely allergen <ol style="list-style-type: none"> <li>1. Mucocutaneous involvement</li> <li>2. Respiratory symptoms</li> <li>3. Hypotension*</li> <li>4. Persistent gastrointestinal symptoms</li> </ol>
C	Hypotension after exposure to a known allergen

\*Hypotension in infant and children: Systolic BP <70 (1-12 months)  
> (70+2x age) (1-10 years)  
> 90 (11-17 years)

Da Simons WAO J 2014, modified

**Table 2.** Signs and symptoms and of anaphylaxis

Organ system		Presentation	Symptoms
<b>Skin</b>	92%	Urticaria 62% Pruritus 37% Erythema/flush 29%	Itching, flushing, hives, swelling, redness, rash
<b>Oral and nasal mucosa</b>		Angioedema 53%	Redness, swelling lips/tongue/uvula, itching tingling, periorbital edema, conjunctival erythema, rhinorrhea, nasal congestion, sneezing
<b>Respiratory</b>	80%	Dyspnea 55% Wheezing 25%	Hoarseness, throat itching, throat tightness, stridor, cough, difficulty breathing, chest tightness, wheeze, cyanosis
<b>Cardiovascular</b>	41%	Myocardial depression Myocardial vasoconstriction Vasodilation	Tachycardia, bradycardia, chest pain, hypotension, collapse shock, weak pulse, heart palpitations
<b>Gastrointestinal</b>	45%	Vomiting 27% Nausea 15% Abdominal pain 16% Diarrhea 5%	
<b>Central nervous system</b>	26%		Sudden behavioral changes, irritability, headache, altered mental status, confusion, anxiety, tunnel vision, sense of doom

LoVerde D (42) and Grabenhenrich LB (43) modified

angioedema, erythematous rash), respiratory features (rhino conjunctivitis, cough, dyspnoea, or asthma) or GI ones (oral itching, nausea, vomit, abdominal pain, and diarrhoea), or even malaise and hypotension that occur within 2 h after ingestion of a probable allergen. FDEIA is an exception as it arises after a greater temporal latency. The longest intervals between eating and onset of the symptoms were 3.5 h, while between the start of exercise and the onset of symptoms it was 50

min. Subjects affected by FDEIA are sensitized to the food responsible for anaphylaxis, even if specific IgE blood levels are lower than in other food allergies. Ingestion of the suspected food provokes clinical manifestations only when followed by physical exercise. At the same time, physical activity does not induce adverse reactions if not preceded by food ingestion. In allergen-specific FDEIA, the role of exercise (or other co-factors such as aspirin, alcohol, etc.) is crucial, because

it prompts the development of clinical reactions to a food that is commonly eaten by the patient, without any clinical manifestation. Delayed symptoms, however, especially those affecting the GI tract, lead towards a non-IgE-mediated reaction or to a mixed IgE- and non-IgE-mediated reaction (Table 3). Both tests have good sensitivity but low specificity, which means that they are often positive in non-allergic subjects. Several authors, guidelines, and international consensus have suggested the use of cutoff values to reach a diagnosis of FA without performing an OFC. The Food Allergy Committee of Italian Society of Pediatric Allergy and Immunology (SIAIP) recently published two systematic reviews on the predictive value of SPTs and specific IgEs for egg (48) and milk (49). The methodological quality of the included studies was evaluated according to the design of the study (prospective vs. retrospective) and the type of OFC (open vs. DBPCFC) and assessed according to the QUADAS-2 tool 12. Cutoffs periods proposed for milk and egg allergy by the methodologically best studies (50–61) are shown in Table 4. However, these predictive values are dependent on the population prevalence and other variables such as background history, age, sex, geographic location, ethnicity, and concomitant allergies the food allergen in question, the degree of cooking of food used for the oral food challenge, the type of allergen used to perform SPTs (e.g. commercial extract or raw food), etc. It is therefore not possible to easily apply predictive values across different populations and in different settings.

### Novel Diagnostic Approach

Allergen component-resolved diagnostic testing (CRD) is a method able to dose purified or recombinant allergens for the identification of specific molecules causing sensitization or clinical allergy. CRD can be performed either in single test formats (Singleplex® – ImmunoCap Phadia® – Thermo-Scientific®) or in a microarray (Multiplex-ImmunoCap ISAC®), testing a range of over 100 purified allergens simultaneously. A significant number of allergenic molecules contained in food have been characterized up to date, and their number is increasing. However, only some

of them can be used to perform *in vitro* tests. More recently, other tests have been developed, capable of detecting over 200 extracts and molecules at the same time. A recent EAACI Molecular Allergology User's guide proposed that Molecular Diagnostics (MD) can improve total allergen IgE testing where: (1) there are low abundant and/or labile food proteins in conventional allergy tests, (2) provides information on risk or severity associated molecules, and (3) provides indicators of food-related cross-reactivity or (4) markers of genuine (species-specific) sensitization. Other indications for the use of CRD include idiopathic anaphylaxis, delayed red meat anaphylaxis, wheat-dependent exercise-induced anaphylaxis, to differentiate between high versus low-risk molecules from foods giving rise to food-induced anaphylaxis (peanuts, nuts, shrimps, etc.), baked egg or milk allergy (ovomucoid, casein), etc. On the contrary, it is of little use when there is a convincing history of IgE-mediated allergy and a positive SPT or sIgE to the relevant whole food allergen; this information is already enough to make a diagnosis. However, CRD has some limitations in daily practice:

a) Only some allergenic molecules are commercially available. For example, it is impossible to dose Pru P7, which is contained in peach. Therefore, if CRD alone was to be used to look for specific peach IgE, there could be some false negative results. Furthermore, there are not assay able IgE to allergenic molecules for some food, like apricot, pine nut, etc.

b) The family of allergenic molecules suggests the severity of a potential reaction; however, it does not predict it with certainty. For example, positivity for PR-10 is commonly associated with mild reactions, however, sensitization to soy's Gly m4, belonging to the same protein family, can trigger severe reactions.

c) Testing positive for allergenic molecules does not imply a certain clinical reaction. As for SPT, higher IgE values for certain food are associated to a higher probability of an allergic reaction when performing an OFC.

d) Diagnostic methods can yield different results. The singleplex method provides quantitative results and it tends to be more precise with respect to the multiplex ones. The latter provides semi-quantitative results, that could be conflicting, depending on the methodology used.

**Table 3.** Food-induced allergic disorders, classified based on the age and underlying immunopathology.

Typical Age group	Disorder	Immunopathology	Clinical features	More common food*
Infant	Food protein induced proctocolitis	Non IgE Mediated	Mucoid and bloody stools in an otherwise healthy infant	Cow's Milk protein passed from mother milk, or rarely hen's egg
Infant	Acute Food protein induced enterocolitis	Non IgE Mediated	Vomiting (onset usually 1-4 h), decreased activity level, pallor, lethargy, diarrhea, hypotension, etc	Cow's Milk, soy, grains, legumen, poultry, fish
Infant	Chronic Food protein induced enterocolitis	Non IgE Mediated	Intermittent emesis, chronic diarrhea, poor weight gain, growth	Cow's Milk, soy, grains, legumen, poultry, fish
Infant	Food protein induced enteropathy syndrome	Non IgE Mediated	Failure to thrive, diarrhea, mucus and bloating, abdominal pain, faltering growth, hypoalbumaemia	Cow's milk, soya, hen's egg, wheat
Infant	Food protein induced GORD	Non IgE mediated	Intermittent Faltering growth, feeding difficulties, borborygmi with pain, painful vomiting/regurgitation,	Cow's milk and soya
Infant	Food protein induced constipation	Non IgE Mediated	Straining with soft stools, Faecal impaction, bloating, abdominal pain	Cow's milk and soya
Infant>child>adolescent	Atopic dermatitis	Mixed IgE and cell mediated	Associated with food in 30–40% of children with moderate/severe eczema	hen's egg, Cow's milk, Peanut, Soy
Infant/child/adolescent	Eosinophilic gastrointestinal disorders	Mixed IgE and cell mediated	Symptoms vary depending on the site of the intestinal tract involved and degree of eosinophilic inflammation	Cow's milk, soya, hen's egg, wheat
Infant/child/adolescent	Rhinoconjunctivitis/asthma	IgE mediated	Accompanies food-induced allergic reaction but rarely isolated symptoms	Cow's milk, hen's egg, Peanut and tree nut, fruits, fish
Infant/child/adolescent	Gastrointestinal symptoms	IgE mediated	nausea, emesis, abdominal pain, and diarrhea	Cow's milk, hen's egg, Peanut and tree nut, fruits, fish
Infant/child/adolescent	Anaphylaxis	IgE mediated	Rapid progressive, multisystem reaction	Cow's milk, hen's egg, Peanut and tree nut, fruits, fish
Child>adolescent	Food dependent exercise induced anaphylaxis	IgE mediated	Food triggers anaphylaxis only if ingestion is followed temporally by exercise	cereals, vegetables, nuts, fish, cow's milk, beef, pork, chicken/turkey, snails,
Child/adolescent	Pollen food allergy syndrome	IgE mediated	Pruritus, mild edema confined to oral cavity	uncooked fruits and raw vegetables
Child/adolescent	Urticaria, angioedema	IgE mediated	Wheals (hives), pruritus, erythematous or skin coloured swelling of the lower dermis and subcutis or mucous membranes,	Cow's milk, hen's egg, Peanut and tree nut, fruits, fish

\* More frequent foods may vary, however, depending on literature studies

**Table 4.** Cutoffs proposed for milk and egg allergy by the methodologically best studies. From: Calvani M et al., [48] and Cuomo B et al., modified [49].

	<b>Fresh Cow's Milk (SPT)</b>	<b>Author (reference)</b>	<b>&gt;2 years</b>	<b>Author (reference)</b>		<b>Raw Egg (SPT)</b>	<b>Author (reference)</b>	<b>&gt;2 years</b>	<b>Author (reference)</b>
	<b>&lt; 2 years</b>					<b>&lt; 2 years</b>			
Cow's milk (commercial extract)	6 mm (100% Sp) (LR 13.2)	Sporik [50]	8 mm (100% Sp) (LR infinite)	Sporik [50]	Raw egg (commercial extract)	4 mm (95% PPV) (LR 6.7)	Peters [54]	10 mm (95% Sp) (LR 5.2)	Vazquez-Ortiz [55]
Fresh cow's milk (PbP)	8 mm (98% Sp) (LR 9.5)	Saarinén [51]	9 mm (95% PPV)	Onesimo [52]	Raw egg (PbP)	-	-	4 mm (95% PPV)	Mehl [56]
$\alpha$ -Lactalbumin (commercial extract)	-	-	4.9 mm (95% PPV)	Onesimo [52]	Ovalbumin (commercial extract)	-	-	10 mm (95% Sp) (LR 5.2)	Vazquez-Ortiz [55]
$\beta$ Lactoglobulin (commercial extract)	-	-	5.6 mm (95% PPV)	Onesimo [52]	Ovomucoid (commercial extract)	-	-	8.5% mm (95% Sp) (LR 7.1)	Vazquez-Ortiz [55]
Casein (commercial extract)	-	-	4.3 mm (95% PPV)	Onesimo [52]					
	<b>Baked Cow's Milk (SPT)</b>					<b>Heated Egg (SPT)</b>			
Cow's milk (commercial extract)	-	-	15 mm (67% Sp) (LR 3.5)	Nowak-Węgrzyn [60]	Raw egg (commercial extract)	5 mm (100% Sp) (LR 7.3)	Sporik [50]	11 mm (95% Sp) (LR 2.3)	Vazquez-Ortiz [55]

*(continued on next page)*



**Table 4.** Cutoffs proposed for milk and egg allergy by the methodologically best studies. From: Calvani M et al., [48] and Cuomo B et al., modified [49].

	Fresh Cow's Milk (SPT)							Raw Egg (SPT)			
Cow's milk (baked liquid cow's milk)		7 mm (100% sp) (100% PPV)	Miceli Sopo [61]	Ovoalbumin (commercial extract)	-	10.5 mm (95% Sp) (LR 7.7)	Vazquez-Ortiz [55]				
				Ovomucoid (commercial extract)	-	13mm (95% Sp) (LR 2)	Vazquez-Ortiz [55]				
	Fresh Cow's Milk (sIgE)							Raw Egg (sIgE)			
Cow's milk	5 kU <sub>A</sub> /l (95% PPV) (LR 30)	-	-	Raw egg	Peters [54]	3.6 kU <sub>A</sub> /l (95% PPV) (LR 11)	-	1.7 kU <sub>A</sub> /l (95% PPV) (LR 21.2)			
	3.5 kU <sub>A</sub> /l (98% Sp) (LR 12.5)	-	-			6 kU <sub>A</sub> /l (95% PPV) (LR 6.4)	Sampson [57]				
	4.18 kU <sub>A</sub> /l (100% PPV) (LR 6.7)	-	-			7.3 kU <sub>A</sub> /l (95% PPV) (LR 11.4)	Ando [58]				

PPV, positive predictive value; Sp, specificity; LR, likelihood ratio; PbP, prick-by-prick.

Basophil activation tests (BATs) have been applied in the diagnosis of cow's milk, egg, and peanut allergies, showing higher specificity and more negative predictive value than SPTs and sIgEs, without losing sensitivity or positive predictive value. However, BATs are available only in a few laboratories, although still limited for FA research purposes.

## Prevention

In addition to genetic factors, pointed out by the family history of allergic diseases, several environmental factors have been shown to interfere with the development of allergic diseases. These can act above all during pregnancy (tobacco smoke, environmental pollution, unbalanced diet, etc) in the perinatal period (birth via caesarean section, pro and prebiotics, etc), and in the postnatal period (gut microbiota, infections, formula feeding, age of introduction of solid foods, etc). Among them, the age of introduction of solid food has always been crucial. In past years it was thought that delaying the introduction of food could prevent the development of food allergies. Later studies have shown that this approach was not effective and indeed that it could be the cause of an increased incidence of FA. Studies showed that the rate of peanut allergy is higher in countries where peanuts were avoided in pregnancy and infancy (62). Several studies have shown an association between atopic eczema in childhood and the development of food allergies, especially to egg, peanuts and cow's milk (63). Starting from these observations, Lack proposed the dual-allergen-exposure hypothesis for the pathogenesis of FA, as reported above. For this reason, seven prospective intervention studies have been carried out up to now to test whether the early introduction of solid foods into the diet was able to reduce the development of food allergies (Table 5). The first study, the Learning Early About Peanut allergy (LEAP) study, showed that in high risk children (severe atopic dermatitis and/or egg allergy and peanut SPT  $\leq 4$  mm), introduction of cooked egg between 4-6 months of life is associated with a lower risk of allergy (ORs 1.0 [95% CI]) compared to a later introduction at 10-12 months and after 12 months (adjusted odds ratios [ORs], 1.6 [95% CI

1.0-2.6) and 3,4 [95% CI, 1,8-6,5], respectively) (64). A subsequent study, the Enquiring About Tolerance (EAT study), carried out on the general population, assessed the effect of an early introduction (3 months of life) of peanut and other five foods (milk, egg, sesame, wheat and fish) (65). The study showed absence of FA reduction in the intention to treat group. The per-protocol (PP) analysis demonstrated a protective benefit of early feeding against the development of only peanut and egg allergies. However, the very low compliance to intervention (<40%) showed the difficulty in weaning at 3 months of age. As a result of this, a specific addendum for the prevention of peanut allergy in the United States has been published (66). In this document guidance on the timing of the introduction of peanuts, stratifying the child's population by the risk of developing allergy, has been provided. Overall six studies investigated the effectiveness of early egg introduction. Studies differ both in having involved the general population or those at risk of developing allergic disease and in using either cooked or raw egg. Risk of developing allergic disease and cooking are important data to consider in the efficacy and side effects analysis because it reduces the allergenicity risk of egg allergy. This may explain the differences in the studies' results. Two trials (Prevention of egg allergy in infants with atopic dermatitis (PETIT) study (67) and Enquiring About Tolerance (EAT) study) used heated egg protein. PETIT study showed significant benefit of early egg introduction without significant safety concerns in high risk population. EAT study, as mentioned above, showed FA reduction only in the per-protocol (PP) analysis. Four studies (Solids Timing for Allergy Research (STAR) (68), Starting Time for Egg Protein (STEP) (69), Beating Egg Allergy (BEAT) (70) and Hen's Egg Allergy Prevention (HEAP) (71) used raw egg. Two of these (STAR and BEAT) showed reduction of egg sensitization, but no reduction of egg allergy. HEAP study showed no significant reduction of sensitization nor egg allergy. STEP study showed no significant reduction of sensitization nor egg allergy. On the other hand, these studies showed that a percentage ranging from a 3.9% to 30% of children developed a reaction when egg was introduced for the first time. The frequency of reactions increases with the increase in the risk of developing allergic disease: 3.9%

**Table 5.** Prospective intervention studies carried out to test whether the early introduction of solid foods into the diet was able to reduce the development of food allergies

<b>Trial</b>	<b>Allergen</b>	<b>Population</b>	<b>Results</b>	<b>Notes</b>
Learning Early About Peanut allergy (LEAP) Du Toit et al	Peanut (peanut butter or snack) (6 gr of proteins/week)	High risk (severe atopic dermatitis and/or egg allergy and peanut SPT $\leq 4$ mm)	<u>Reduced risk for peanut allergy</u>	9.1% of subjects were excluded for peanut SPT > 4 mm at enrollment
Solids Timing for Allergy Research (STAR) Palmer et al.	Hen's egg (whole raw lyophilized) (0.9 gr of proteins, that is 1/6 of an egg/day)	High risk (moderate/severe eczema at 4 months of age)	Reduced sensitization to egg, no reduction of egg allergy	30% of subjects had a reaction when egg was introduced for the first time
Starting Time for Egg Protein (STEP) Palmer et al	Hen's egg (whole raw lyophilized) (0.4 gr of proteins/day that is 1/2 egg/week)	Moderate risk (no eczema, atopic mother)	No reduction of egg allergy in the <i>intention to treat</i> group. Reduction of egg allergy in the per-protocol analysis	6% had a reaction when egg was introduced for the first time, none had anaphylaxis
Hen's Egg Allergy Prevention (HEAP) Ballach J et al	Hen's egg (raw lyophilized egg white, 7.5 gr of proteins, that is 1 egg/week)	General population (infants not sensitized to egg)	No significant reduction of sensitization nor egg allergy	At 4-6 months of age 5.7% was already sensitized to egg, 3.9% had an allergic reaction, with anaphylaxis in 2/3 of cases
Enquiring About Tolerance (EAT) Perkin et al	Cow's milk, hard boiled hen's egg, sesame, wheat, peanut, <u>fish</u>	General population	Absence of food allergy reduction in the <i>intention to treat</i> group. In the per-protocol (PP) analysis demonstrated a protective benefit of early feeding against the development of any food allergy and specifically peanut and egg allergies	Very low compliance to intervention (<40%), showing the difficulty in weaning at 3 months of age
Prevention of egg allergy in infants with atopic dermatitis (PETIT) Natsume et al.	Hen's egg (whole cooked powdered - 25 mg of proteins/day from 6 to 9 months of age, then 125 mg/day)	High risk (subjects with atopic dermatitis)	<u>Reduced risk for egg allergy</u>	No reactions to first egg introduction
Beating Egg Allergy (BEAT) Tan et al.	Hen's egg (whole raw lyophilized)	Moderate risk (relatives with allergy and SPT $\leq 2$ mm)	Reduction of egg sensitization, no reduction of egg allergy	3.9% excluded for SPT > 4 mm at enrollment, 8.4% of enrolled subjects had a reaction when egg was introduced for the first time

in study enrolling general population (HEAP), 6–8.4% in study enrolling people at moderate risk (BEAT and STEP, respectively), 30% in high risk population, such as children with moderate/severe eczema at 4 months of age (STAR study). Finally, a meta-analysis by Ierodiakonou *et al.* based on 5 of these RCTs, including 1,915 children found “moderate certainty” of evidence that introducing egg from the between 4<sup>th</sup> till the and 6<sup>th</sup> month of age reduced the risk of egg allergy (RR, 0.56; 95%CI, 0.36–0.87) (72).

Considering these results, several discrepant recommendations have been suggested by diverse scientific societies. North American societies did not endorse the early introduction of egg products. According to the European Society of Paediatric Gastroenterology Hepatology (ESPGHAN) potentially allergenic foods may be introduced when complementary feeding is commenced any time after 4 months (17 weeks beginning at the 5<sup>th</sup> month of life), both in breast-fed and formula-fed infants and independently from the risk of atopy (73). The British Society of Allergy and Clinical Immunology (BSACI) suggests the early introduction (from the 4<sup>th</sup> month of life) of cooked egg only in children at high risk of allergy, warning potential allergic reactions (74). The Italian Society of Paediatric Allergy and Immunology (SIAIP) “food allergy study group” (75, 76) suggests the adoption of a peanut-like behaviour (66, 73, 74). In high risk infants, an evaluation of whole egg specific IgE serum antibody levels or performing skin prick tests for egg before the first administration should be recommended. If skin prick test or sIgE are negative, cooked egg can be introduced at a low quantity when complementary feeding is commenced. If skin prick test or sIgE are positive, egg must be introduced in a specialized setting with emergency support immediately available and under the supervision of an allergist with expertise in this field. Concerning the early introduction of other foods, current literature does not seem to suggest any benefits.

Finally, since atopic dermatitis is recognized as a FA risk factor and impaired barrier function and cutaneous inflammation permitting sensitization was proposed, several studies have sought to assess whether aggressive dermatitis therapy can reduce the development of atopic dermatitis, food sensitizations and food allergies. Some preliminary studies seemed to suggest

effectiveness of the application of emollient application in the prevention of both atopic dermatitis (77, 78) and allergic sensitivities. Thus, two large pragmatic prevention trials, The Preventing atopic dermatitis and ALLergies in children (PreventADALL) and The Barrier Enhancement for Eczema Prevention (BEEP) study, have been designed and started. Unexpectedly, the results of these studies does not support the use of these interventions to prevent atopic dermatitis. The PreventADALL study showed that neither regular skin emollients, applied from 2 weeks of age, nor early complementary feeding introduced between 12 and 16 weeks of age, can reduce the development of atopic dermatitis by the age of 12 months in 2397 infant from the general population. In the BEEP study, 1394 term newborns with a family history of atopic disease were randomly assigned the application of emollient daily for the first year plus standard skin-care advice (emollient group) or standard skin-care advice only (control group). The intervention did not prevent the development of eczema at age of 24 months, which occurred in 23% of the treated group and 25% of the control group. Moreover, the secondary outcome of food allergy seemed more frequent in the treated (7%) than in the control (5%) (adjusted relative risk 1.47, 95% CI 0.93–2.33). In the discussion, the author suggests that a more sophisticated emollient formulation might potentially have a protective effect. Thus, a large randomised controlled trial in high-risk infants, Prevention of Eczema by a Barrier Lipid Equilibrium Strategy (PEBBLES), is underway to confirm this hypothesis (79).

## Management

Primary treatment of FA includes strict avoidance of responsible food and prompt identification and treatment of anaphylaxis (80). Food avoidance represents the mainstay for preventing food-induced reactions in the long-term management of IgE- and non-IgE mediated FA. Patients and their families need to be instructed regarding food avoidance, underlining the importance of a strict adherence to the dietary indications provided, together with extreme care in cross-contact, safe storage, cleaning procedure as well as be

careful to ingredients and food. Precautionary allergen labelling indicating low amounts of potential allergens is not regulated in most countries including the EU. The use of labels, including “may contain traces,” “may contain” “processed in a facility with,” “manufactured on shared equipment with,” are voluntary, therefore, families must be aware of cross-contamination possibility. However, diffuse and conflicting use of these expressions, resulted in an underestimation of this warning, becoming ignored in up to 40% of patients (81). Food avoidance could have detrimental effects on nutrient intake, resulting in nutritional deficiencies (82, 83) therefore nutritional counseling and growth monitoring are recommended for children and patients with single or multiple FA. FA has an impact on the quality of life of affected children and adolescents as well as their families and caregivers (84). Moreover, following food avoidance often involves a household economic effort (85).

### Pharmacotherapy

Food allergy therapy depends on the severity of reactions and symptoms. Antihistamines such as diphenhydramine (1-2 mg/kg/dose max 50 mg iv) and cetirizine are commonly given for mild food-induced reactions, like angioedema or urticaria only. Similarly to antihistamines, glucocorticoids ( Prednisone 1 mg/kg (maximum 60 to 80 mg os), methylprednisolone 1 mg/kg (maximum 60 to 80 mg iv) should be used as

an adjunctive therapy for skin, mucous or respiratory symptoms, especially in asthmatic patients. Both drugs may be useful in reducing symptoms but they do not halt the progression of an allergic reaction nor are life-saving nor they have a supportive role in treating anaphylaxis. They have a delayed effect onset and despite the scarce evidences supporting their role in anaphylaxis, they are commonly used in this setting (86). Identification of anaphylaxis is the first essential treatment step. Sudden occurrence and heterogeneous clinical presentation are typical of anaphylaxis. Epinephrine (adrenaline) at 0.01 mg/kg (maximum dose 0.5 mg) intramuscular injection in the mid-outer thigh (vastus lateralis muscle) is the treatment of choice in anaphylaxis (41). Through its vasoconstrictor effect epinephrine prevent or decreases upper airways mucosa edema, hypotension and shock. It also has an important bronchodilator effects, together with cardiac inotropic and chronotropic effects (87, 88). Prompt treatment with epinephrine may slow or halt progression of severe anaphylaxis. Other treatment, according to symptoms and severity, including bronchodilators, oxygen, antihistamines, corticosteroids, intravenous fluids, vasopressors, glucagon, or atropine, etc (42). Anaphylaxis mostly occurs in nonmedical settings, therefore, use of an epinephrine auto-injector is vital for prompt management and should be prescribed to all patients who have experienced anaphylaxis or those who are at risk for anaphylaxis. Dosing of available autoinjector device is detailed in Table 6. Personalized emergency action plans listing medications and their doses, and detailing

**Table 6.** Available Epinephrine autoinjectors in Italy

Brand	Dose	Needle length	Expiry in (months)	Cost (€)
Fastjekt®	150 mcg (for children 15-30 kg)	16 mm	19-20	77.90
	300 mcg (for children >30 kg)	16 mm		
Jext®	150 mcg (for children 15-30 kg)	13 mm	18	74.01
	300 mcg (for children >30 kg)	15 mm		
Chenpen®	150 mcg (for children 15-30 kg)	10±1.5 mm	21-24	62.13
	300 mcg (for children >30 kg)	10±1.5 mm		
Epinephrine doses may need to be repeated every 5–15 minutes				
Epinephrine autoinjectors should be kept at 20°C to 25°C.				

emergency follow-up procedures including activation of emergency medical services, should be provided to all patients at risk of anaphylaxis.

### Food desensitization

Food allergen-specific therapies include oral (OIT), sublingual (SLIT), and epicutaneous (EPIT) immunotherapy (89, 90). Several studies have shown that SLIT and EPIT are less burdened by side effects (allergic reactions and eosinophilic esophagitis) but also much less effective than OIT. Several studies were carried out to demonstrate the effectiveness and safety of OIT. A variety of food allergens have been tested, but most randomized controlled trials focused on peanut, milk, and egg. Regarding effectiveness, a systematic review and meta-analysis by Nurmatov stated that, in the case of IgE-mediated FA, OIT may be effective in inducing desensitization, which consists of raising the threshold of reactivity to foods, while receiving food (91). A recent Cochrane review on OIT and SLIT, involving a total of 439 children with egg allergy, showed that most children (82%) could ingest a partial serving of egg (1-7.5 g) compared with 10% of the control group (RR: 7.48, 95% CI: 4.91-11.38) (92). EAACI guidelines on allergen immunotherapy recommended OIT as a therapeutic option to increase the reaction threshold during treatment in children with persistent cow's milk, egg, and peanut allergy from the age of about 4-5 years of life (93). OIT is not yet recommended as a treatment option to achieve post-discontinuation effectiveness, that is, a lack of clinical reaction against a food allergen after active therapy discontinuation for some time. Finally, oral tolerance, which is the complete lack of clinical response after exposure to food, even without its assumption, has not yet been demonstrated for any of the three most frequently tested foods mentioned above (94).

As regards safety, a meta-analysis done by Nurmatov showed that both systemic and local reactions were higher in children receiving OIT than in those receiving control. Thus, later EAACI guidelines on allergen immunotherapy suggest several recommendations on safety, including carefully monitoring patients for allergic reactions, especially during the up-dosing

phase of OIT, and monitoring for symptoms of new-onset eosinophilic esophagitis. Moreover, a careful explanation of both the risk of reactions is recommended before starting OIT and a careful evaluation of risk factors for adverse events. A recent systematic review and meta-analysis (PACE) of 12 studies, involving >1000 patients, treated with OIT for peanut, showed that, compared with allergen avoidance or placebo, OIT increased allergic reactions, anaphylaxis, and use of epinephrine (95). Thus, OIT is an effective practice in IgE mediated FA. Approaches that increase safety need to be implemented.

### Conclusions

The FA diagnosis and management remains a challenge despite improvements and greater availability of newly developed diagnostic and therapeutic equipment. In the future further investigations are required on developing a prevention strategy as well as safe and effective therapies provide more useful guidelines based on a precision medicine approach enabling us to fully confront FA.

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