STM JOURNALS

Research & Reviews: A Journal of
Immunology

ISSN: 2277-6206 (Online)
ISSN: 2349-1280 (Print)
Volume 14, Issue 1, 2024
January–April
DOI (Journal): 10.37591/RRJoI

http://stmjournals.com/index.php?journal=RRJoI&page=index

Review RRJoI

Food Allergy-practical Approach

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Abstract

There is a consistent increase in prevalence of food allergy (FA). The diagnosis of FA is based on thorough history supported by positive skin test, specific IgE (extract-and component-based), Basophil activation test (BAT) to reduce the need for Oral food challenge (OFC). OFC procedures may be conducted in cases of diagnostic uncertainty or to assess the presence or development of tolerance. Effective management of food allergy involves a comprehensive three-pronged strategy. Firstly, it includes implementing measures for avoidance and diet elimination to minimize exposure to allergens. Secondly, an emergency action plan, often involving the use of an Epipen autoinjector, is crucial for immediate response to accidental allergen exposure. Finally, the approach incorporates strategies to induce tolerance through a combination of oral immunotherapy (OIT) and the use of biological agents like Omalizumab etc.. This updated review provides a practical and comprehensive approach to the diagnosis and management of food allergies.

Keywords: Food allergy, Oral immunotherapy (OIT), Allergen immunotherapy (AIT), Subcutaneous immunotherapy (SCIT), Sublingual immunotherapy (SLIT), omalizumab, anti-IgE IgE-mediated food allergy, Non-IgE-mediated food allergy, Eosinophilic esophagitis (EoE) and Non EoE (EG-Eosinophilic gastritis, EGE- Eosinophilic gastroenteritis

INTRODUCTION

During the past two decades, there has been a rise in the prevalence of food allergy (FA), signifying a second wave of the allergic epidemic. FA imposes significant individual, social, and economic burdens. Changes in the environment, increased urbanization, global warming, decreased exposure to early life infections and changes in lifestyle and diet; all play their part in the development of food allergy. Although more than 170 foods have been recognized as potential allergens, a small subset comprising peanuts, tree nuts, fish, shellfish, milk, egg, wheat, soy, and sesame seeds, predominantly account for the majority of allergic reactions. The prevalence of food allergies, as determined through food challenges, is reported to be 0.6% for cow's milk, 0.2% for egg, 0.1% for wheat, 0.3% for soy, 0.2% for peanut, 0.5% for tree nuts, 0.1% for fish, and 0.1% for shellfish, varying across different geographical regions [1–3]. In some developed countries, 1 in 10 infants has challenge-proven immunoglobulin (IgE)-mediated Food allergy [4]. The prevalence of self-reported food allergy has increased by 1.2% per decade since 1988. By the year 2024, it is anticipated that food allergy rates in the United States will reach 8% among children and 11% among adults [5]. In several published studies, the estimate of FA prevalence is highest when based on self-report (approximate 12–13%) compared with those confirmed by oral food challenge test (approximate 3%) [6]. There is a high co-occurrence of FA with other atopic diseases including atopic dermatitis, allergic rhinitis, asthma, and eosinophilic esophagitis etc. Approximately 30% of children experience allergies to multiple foods. Lipid Transfer Protein (LTP) allergy has emerged as the leading cause of primary food allergy and food-induced anaphylaxis in older children and adults in Southern European regions, including the Mediterranean and

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Received Date: January 20, 2024
Accepted Date: January 21, 2024
Published Date: April, 24, 2024.

Citation: P.C. Kathuria, Manisha Rai. Food Allergy-practical Approach. Research & Reviews: A Journal of Immunology. 2024; 14(1): 32–53p.

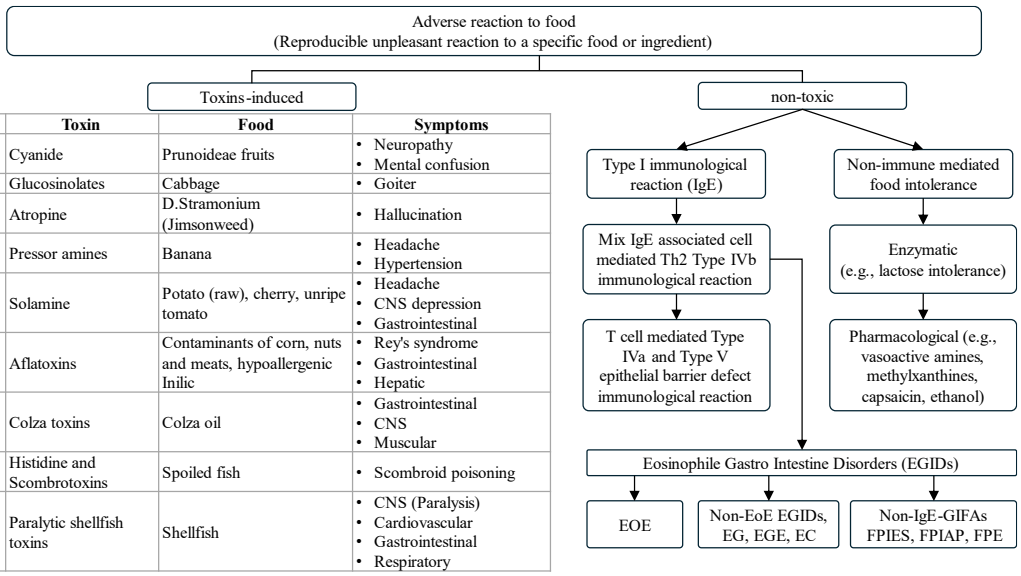
Atlantic areas. Indian cuisine is notably diverse. The general prevalence of allergic sensitization to 'any' food in India stood at 26.5% among adults and 19.1% among children, as determined through serum-specific IgE (extract-based testing). However, the prevalence was only 4.48% among children when assessed through skin prick tests [7–9]. It is necessary for a high-risk patient to be aware of the foods causing allergic severe immunological reaction. Great advances have been achieved in in-vitro allergy diagnostic tests (specific IgE-extract based, Component Resolved Diagnosis-CRD, Basophil Activation Test-BAT, and mast cell activation test-MAT) to reduce the need for oral food challenge (OFC). The primary approach to managing the condition remains avoiding the triggering food; however, this does not decrease the likelihood of unintentional allergic reactions. There is a growing body of evidence which supports that specific oral tolerance (OT) and sustained unresponsiveness (SU) can be achieved by combining oral immunotherapy (OIT) with biological (omalizumab). This review will focus on new diagnostic and therapeutic strategies in FA.

Adverse reaction to Food

Adverse reaction to foods includes immune-mediated and non-immune mediated reaction. The most common are IgE-mediated FA, Non-IgE-mediated-Gastrointestinal Food allergy-GIFA (FPIES-Food protein induced enterocolitis syndrome, FPIAP-Food protein induced allergic proctocolitis, FPE-Food protein induced enteropathy) and mixed-type FA that fall between IgE and non-IgE mediated FA e.g., eosinophilic gastrointestinal disorders (EGID) [Eosinophilic esophagitis (EoE) and Non EoE (EG-Eosinophilic gastritis, EGE- Eosinophilic gastroenteritis, EC-Eosinophilic colitis)]

Adverse reaction to food (Figure 1) can be broadly divided into:

1. Immune-mediated food reactions (Figure 2)
   i. IgE-mediated
   ii. Non-IgE mediated
   iii. Mixed (IgE and non-IgE)
2. Non-immune mediated (Table 1)
   i. Enzyme
   ii. Pharmacological
3. Toxin-induced reaction- food contaminated by bacteria or by alpha toxins or food-containing excess histamine such as spoilt fish (scombroid food poisoning) (Figure 1)



	Toxin	Food	Symptoms
1.	Cyanide	Prunoideae fruits	• Neuropathy • Mental confusion
2.	Glucosinolates	Cabbage	• Goiter
3.	Atropine	D.Stramonium (Jimsonweed)	• Hallucination
4.	Pressor amines	Banana	• Headache • Hypertension
5.	Solamine	Potato (raw), cherry, unripe tomato	• Headache • CNS depression • Gastrointestinal
6.	Aflatoxins	Contaminants of corn, nuts and meats, hypoallergenic Inilic	• Rey's syndrome • Gastrointestinal • Hepatic
7.	Colza toxins	Colza oil	• Gastrointestinal • CNS • Muscular
8.	Histidine and Scombrotoxins	Spoiled fish	• Scombroid poisoning
9.	Paralytic shellfish toxins	Shellfish	• CNS (Paralysis) • Cardiovascular • Gastrointestinal • Respiratory

Figure 1. Classification of adverse reaction to food.
(EoE-Eosinophilic esophagitis, EG-Eosinophilic gastritis, EGE- Eosinophilic gastroenteritis, EC-Eosinophilic colitis, FPIES-Food protein induced enterocolitis syndrome, FPIAP-Food protein induced allergic proctocolitis, FPE-Food protein induced enteropathy)

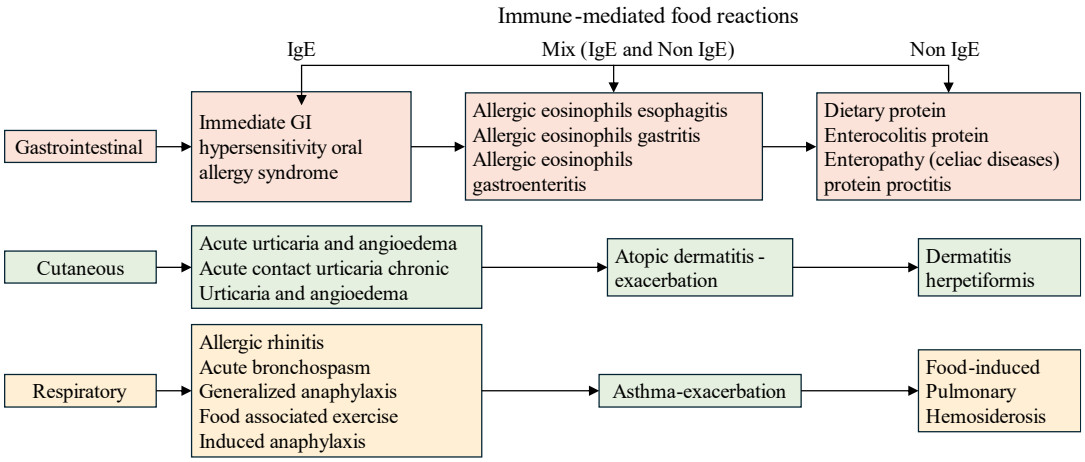


Figure 2. Classification of immune-mediated reactions [10].

Table 1. Non-immune mediated food reaction.

Natural salicylates	Tartrazine	Conditions	Deficiencies
Dried fruits	Fruit squash	Disaccharides deficiencies	Lactase
Berry fruits	Colored fizzy drinks	Galactosemia	sucrase
Oranges	Pickles	Phenylketonuria	Galactose-l phosphate uridyl transferase
Apricots	Bottled sauces	Alcohol intolerance	Phenylalanine hydroxylase
Pineapples	Salad cream	Favism	Aldehyde dehydrogenase
Cucumbers	Cakes (shop bought)		G6PD
Gherkins	Cake mix	**Chemicals**	**Foods**
Olives	Soups (packets and tines)	Caffeine	Coffee, soft drinks
Grapes	Custard	Theobromine	Chocolate, tea
Almonds	Instant pudding	Histamine	Fish, sauerkraut
Liquorice	Colored sweets	Tryptamine	Tomato, plum
Peppermints	Filled chocolates	Serotonin	Banana, tomato
Honey	Jelly	Tyramine	Cheese, pickled herring
Herbs	Ice cream and lollies	Glycoside alkaloid solanine	Potatoes, alcohol
Thyme	Jam		
Mint	Marmalade	**Sulphur dioxide**	**Flavoring agents and preservatives**
Paprika	Curry powder	Salads	Sodium metabisulfite
Rosemary	Mustard	Wines, chilled fruit juices	Monosodium glutamate
Curry	Yoghurt	Pickled onions, dried fruits	Nitrites / nitrates
Tomato sauce, Tea, wine		Commercial pre-cut chips	Dyes (Tartrazine)

IMMUNE-MEDIATED FOOD REACTION

IgE Mediated Food Allergy

It is characterized by the development of IgE inflammation against food allergen. It can be associated with cellular component and activation of mast cell, basophil, eosinophil, and T cell. Identification of individuals with IgE-mediated food allergy can be achieved through the detection of food-specific IgE in both serum and bodily fluids using components. Milk, egg, peanut, tree-nut, fish, shell fish, soya, wheat, and sesame are responsible for 85% of IgE mediated food allergy. The allergenic epitopes within these food proteins are typically small, ranging from 10 to 70 kilodaltons in size. These glycoproteins are soluble in water, resistant to denaturation by heat or acid, and can therefore remain intact even after undergoing processing, storage, cooking, and digestion. When distinguishing between a food allergy and food intolerance, symptoms affecting the respiratory, cutaneous, ocular, and cardiovascular systems are more indicative of an allergic reaction than intolerance. The initial defense against allergens involves

the innate immune system and local mechanisms, utilizing digestive enzymes, stomach acid, IgA secretion, epithelial tight junctions, and antimicrobial peptides such as defensins and cathelicidins. Dendritic cells play a role in capturing peptides on major histocompatibility complex class II and presenting them to naïve T cells, with the immune response being influenced by the expression of co-stimulatory molecules. However, intestinal antigen-presenting cells exhibit relatively low expression of co-stimulatory molecules such as CD80 and CD86, which interact with CD28 on T cells [11–13].

IgE-mediated

1. Reaction occur when allergens bind to Immunoglobulin E (IgE) antibodies, bound to mast cells resulting in the release of histamine and other inflammatory mediators.
2. Symptoms are usually of rapid onset (<30 minutes in children and usually < 2hr in adults)
3. Diagnostic Tests (e.g., Skin Prick Test and Specific IgE (Extract and Component based)) are usually positive.
4. Children with Peanut and Tree nut sesame, fish and shellfish allergy usually do not outgrow but 85% of children outgrown allergy to Cow's milk, Egg, Soy and Wheat by age 3–5 years
5. In adults, the most common food triggers are those of peanut, Tree nut, Sesame seeds and sea foods.
6. The common risk factors are genetics (Filaggrin mutation), environmental substances (e.g. toxins, detergent, nutrition), and low vitamin D serum level [11].

In the absence of additional co-stimulatory proteins, presenting antigens through major histocompatibility complex class II proteins can induce T cell anergy or deletion, resulting in reduced responsiveness of the gut immune system. Protective T cell subtypes play a role in suppressing the immunological response [14]. For example, Th3 cells release transforming growth factor B (TGF-B), which stimulates IgA production in B cells, while Tr1 cells release IL-10, inducing antigen-specific anergy in T cells. During allergic responses, dendritic cells (DCs) and epithelial cells begin to express co-stimulatory molecules, thereby priming the effector cells or IgE-producing plasma cells. The immune response and the Th1/Th2 balance are influenced by the type of co-stimulation, the DCs involved, and the cytokine response [15]. For instance, CD86/CD28 co-stimulation and lymphoid DCs tend to favor Th2-type responses, while CD80/CD28 co-stimulation and myeloid DCs favor Th1 responses. Various cytokines, including IL-13 and IL-4, contribute to the shift from IgA production to IgE synthesis [16, 17]. IgE antibodies specific to food attach to receptors on mast cells, causing the crosslinking of adjacent IgE antibodies bound to receptors. The cross-linking of the various inflammatory cells releases pharmacologically active substances like histamines, cytokines, and other inflammatory molecules that leads to allergic response [18]. The breakdown of oral tolerance, coupled with alterations in mucosal barriers and the gut microbiome, facilitates immunologic hypersensitivity and allergic reactions through IgE-mediated, non-IgE-mediated, or mixed mechanisms.

Plant food allergens are contained in only 20 families, constituting 0.25% of all families, these are water-soluble glycoproteins in food with molecular weights ranging from 10 to 70 kDa. Their stability to heat and resistance to digestive enzymes are often attributed to the majority of allergic reactions. These families resemble family 10 of the pathogenesis-related (PR-10) proteins and the *cupin family of proteins.* Allergenic members of the cupin family include the vicillins (major allergens for peanut soyabean, lentil, pea, walnut, cashew and sesame seed) and the legumins (peanut, soyabean, hazelnut, walnut, almond, Brazil nut, cashew, and coconut).

Plant food allergens are classified into four structural families [19].

1. Prolamin super family-composed of:
   i. Cereal storage proteins e.g., the omega-5 gliadin allergen of wheat).
   ii. Non-specific lipid transfer proteins such as Pru p 3 from peach and Zea m 14 from corn.
   iii. 2 S storage albumins e.g., Ber e I from Brazil nut.
   iv. Inhibitors of trypsin and alpha amylase.

2. The cupins, including 7S and 11S globulin storage proteins found in seeds, legumes, and nuts, house many allergens. Notably, allergens such as Ara h 1, Ara h 2, and Ara h 4 from peanuts are classified into two families: vicilins and legumins.
3. Bet V1 superfamily- Homologues of the major birch pollen allergen Bet v 1 (such as Mal d 1 in apple and Api g 1 in celery).
4. Minor families- include class-1 chitinases, Profilins, protease inhibitors, lectins, and thaumatin like proteins (TLPs).

The majority of animal food allergen can be classified into four protein groups:
1. Caseins
2. EF hand proteins / parvalbumins
3. Tropomyosin
4. Minor families- lipocalins, lysozomes, transferrins, serpins, oligosaccharides and ovomucoid.

Non-IgE Mediated Food Allergy

Non-IgE-mediated

1. Reactions occur, when the ingested food protein cause an immune response resulting in delayed inflammation in Skin or gastro-intestinal tract.
2. Symptoms usually occur 2–24 hours after ingestion of the food protein
3. Diagnostic tests are usually negative but OFCs are positive
4. Symptoms include – Delayed flare up of Eczema, Delayed vomiting and diarrhea, Frequent bowel movement (Blood or mucus in stools) etc.
5. Specific condition- Celiac disease/FPIES/Proctocolitis and Food protein induced enteropathy.

A. Type Antibody

Antibody Dependent Cytotoxicity (ADCC)- e.g., Milk induced thrombocytopenia. Here specific antibody will react with antigen or hapten on cell wall and will induce complement activation, which will induce inflammatory mediators and leads to tissue e but the role of ADCC in clinical food allergic reactions remains to be established [20].

B. Type Antigens-Antibody Complexes

In this case, there is an elevation of antibodies in the bloodstream or secretions, leading to the formation of immune complexes that deposit on the intestinal tissue and cause mucosal edema. However, it is uncertain whether this condition is a food-sensitive enteropathy or an inflammatory bowel disease such as Ulcerative Colitis. Multiple position papers discourage the use of food antigen IgG testing for diagnosing food allergies due to a lack of substantial experimental evidence supporting Type III reactions [21].

C. Type Hypersensitivity

Mainly driven by specific T cell responses to food antigens, Type IV hypersensitivity can cause damage to the gut mucosa and is linked to conditions such as celiac disease. Celiac disease involves a hypersensitivity reaction to the wheat gluten fraction (gliadins and glutenins), and Type IV hypersensitivity reactions also play a role in disorders like food protein-induced enterocolitis, proctitis, celiac disease, and the related skin condition dermatitis herpetiformis (Figure 3). Celiac disease is associated with a gluten-specific immunoglobulin A (IgA)-mediated sensitivity to gluten, a protein present in wheat, barley, rye, and certain other grains, leading to chronic inflammation and villi damage in the small intestine. Celiac Disease (CD) is a chronic immune-mediated enteropathy of the small intestine that develops in genetically susceptible individuals upon exposure to gluten proteins found in cereals such as wheat, rye, and barley. Deamination of gluten peptides by Type 2 transglutaminase (TG2) is a crucial pathogenic event that heightens gliadin immunogenicity in CD and worsens the severity of the disease. Diagnosis confirmation involves serological testing using anti-gliadin antibodies, TG2 or EM specific antibodies, along with HLA-typing (DQ2 and DQ8) and mucosal biopsy. Dermatitis herpetiformis is a persistent skin disorder that can occur concurrently with or

independently of celiac disease. Food protein-induced enterocolitis (FPIES) is a gastrointestinal food hypersensitivity not mediated by IgE, affecting the entire gastrointestinal tract. It is characterized by repeated, severe vomiting starting about 2 hours after consuming the triggering food and may later involve watery diarrhea. FPIES appears to involve a combination of innate and cellular immune processes, including antigen-specific T cells and cytokines, leading to inflammation in the colon and ileum. Non-IgE mediated food allergies exhibit subacute and chronic symptoms primarily localized to the gut but may also impact the skin or lungs [22–24].

Mixed IgE and Non-IgE-Mediated Allergy

Non-IgE and mixed gastrointestinal food allergies present various specific, well-characterized clinical picture like eosinophilic gastrointestinal disorders such as eosinophilic esophagitis, allergic eosinophilic gastroenteritis, and eosinophilic colitis. This includes eosinophilic gastrointestinal disorders (EGID) such as eosinophilic esophagitis (EoE) and other conditions such as exacerbation of atopic eczema and asthma (Table 2).

Table 2. Eosinophilic gastrointestinal disorders (EGIDs).

Disorders	Eosinophilic esophagitis	Eosinophilic gastritis	Eosinophilic gastroenteritis
Clinical features	Abdominal pain, dysphagia, nausea, emesis, esophageal food impaction, heartburn, diarrhea, chest pain, bloody stools, failure to thrive	Abdominal pain, vomiting, diarrhea, bloody stools, iron-deficiency anemia, malabsorption, protein losing enteropathy, and failure to thrive (mucosal form); GI obstructive symptoms (muscularis form)	Abdominal pain, vomiting, diarrhea, bloody stools, iron-deficiency anemia, malabsorption, protein losing enteropathy, and failure to thrive (mucosal form); GI obstructive symptoms (muscularis form)
Endoscopic findings	Furrows, white plaques, loss of vascular pattern, rings, stricture, shearing	Micronodules (and/ or polyposis) often with aggregates of lymphocytes and eosinophils	Flattening of small intestinal villi
Histologic findings	Eosinophils on biopsy	Eosinophils on biopsy	Eosinophils on biopsy
Associated inflammatory cytokine	IL-5, IL-13, IL-15 plasma basic fibroblast growth factor	IL-4, IL-5, IL-13	IL-3, GM-CSF, and IL-5

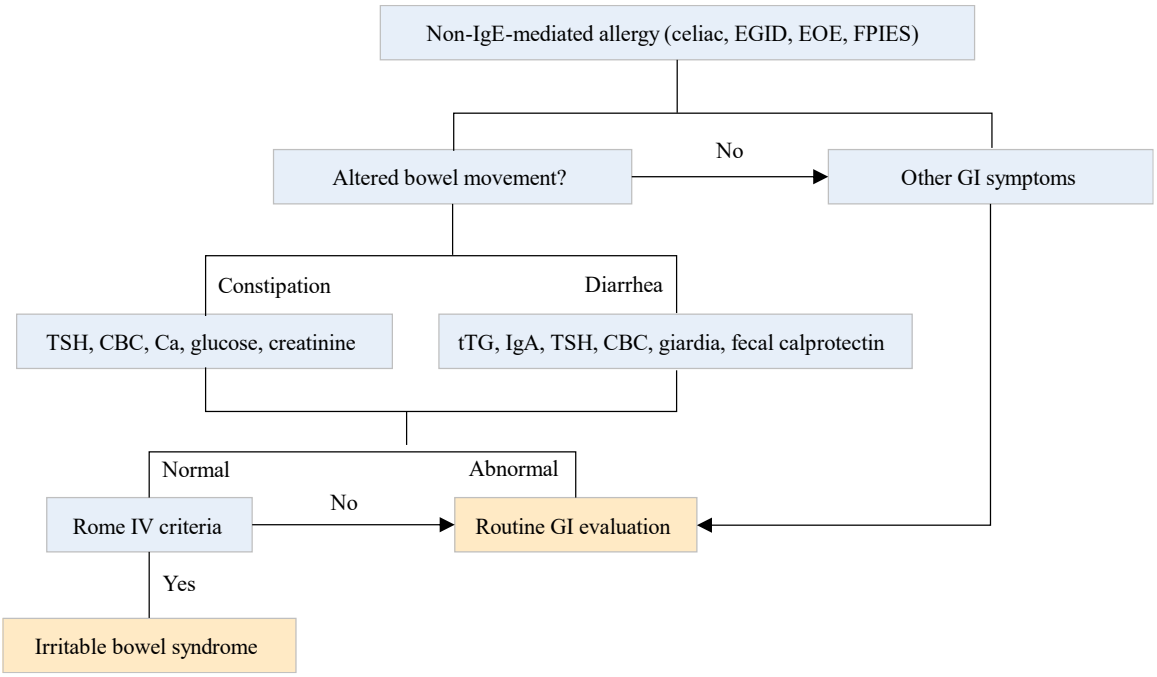


Figure 3. Diagnostic algorithm of non-IgE mediated food adverse reaction.

DIAGNOSIS

An accurate diagnosis is a fundamental step in management of food allergy.

1. History and physical examination
2. Skin prick test and Prick-prick test
3. In-vitro test
   i. Extract-based specific IgE
   ii. Component Resolved Diagnosis (CRD)
   iii. Basophil activation test (BAT)
4. Oral food challenge (OFC)

History and Physical Examination

The clinical history is critical in diagnosis of food allergy (FA). The details of history are used to generate an estimate of patient's pre-test probability of having allergic disease. Clinical history aims to identify food 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.

It is important to enquire about all suspect foods and to discuss the manner of food preparation (e.g., cooked, raw, added spices, or other ingredients). Time of onset of symptoms in relation to food exposure, symptom duration and severity as well as reproducibility of the symptoms in case of recurrent exposure should be determined (Figure 4). In physical examination, one should look for supporting evidence of atopy and other allergic diseases (e.g., atopic dermatitis, asthma, and allergic rhinitis). It is also useful to assess the nutritional status and growth in children.

Recommendation 1: In patients with suspected Ig E mediated food allergy, a detailed allergy-focused clinical history is recommended as the first step of the diagnostic work-up (low certainty of evidence, expert opinion)

Four ways of clinical presentation:

1. "Whenever I eat nuts, I get swollen lips hives Then itchy spots and I sometimes vomit."
2. "I can't eat nuts" (reason why vague or based on a single episode long ago).
3. "I wonder if this rash could be caused by something in my diet?"
4. "I have given up eating nuts because the lady in the health food shop says I must be allergic to them."

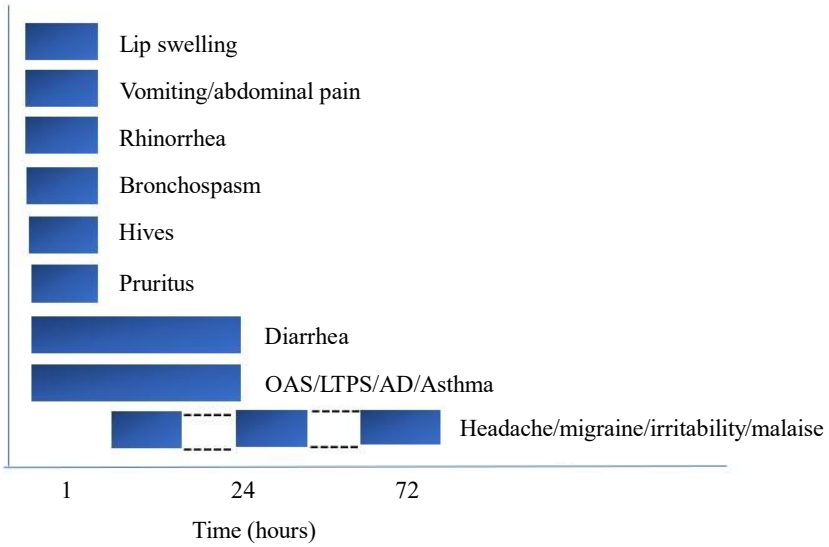


Figure 4. Time course of symptoms of food allergy (IgE and non-IgE).

Questions:

- What are the ill effects of food?
- Are there any local or generalized symptoms by food?
- What is the effect on the severity of itchiness etc. or worsening of symptoms?
- What are the offending foods?
  - Foods of Animal origin e.g., Milk, Egg, Fish, Meat, Poultry and Sea foods
  - Foods of vegetable origin e.g., a. Nuts and seeds, b. Fruits and Vegetables, c. Herbs and spices, d. Grain products, e. Drinks such as wine, bear, Tea, cola, etc.

Signs and Symptoms of Food-induced Allergic Reactions in Various Target Organs

- Skin
  - Urticaria/angioedema flushing
  - Erythematous pruritic rash atopic dermatitis
- Gastrointestinal tract
  - Pruritus and /or swelling of the lips tongue, or oral mucosa nausea
  - Abdominal cramping or colic or reflux diarrheal
- Respiratory tract
  - Nasal congestion
  - Rhinorrhea
  - Pruritus/sneezing
  - Laryngeal edema, staccato cough and/or dysphonia
  - Wheezing /repetitive cough
- Cardiovascular
  - Hypotension/ shock
  - Dizziness
- Other

Cramping back pain (uterine contraction), feeling of "impending doom"

Skin Prick Test and Specific IgE (Extract and Component-based) Interpretation in Food Allergy

Clinical history, targeted SPT and sIgE are the cornerstones to confirm the diagnosis of FA (Table 3). To improve this, applying 95% positive predictive cutoffs to sIgE and SPT for specific allergens can be useful. A negative SPT confirms the absence of IgE-mediated reaction with 90–95% of accuracy. It is highly sensitive (90%) but only moderately specific (50%).

Table 3. Diagnostic cutoffs for specific IgE (extract based) and skin prick testing with 95% positive predictive.

Foods	Specific IgE 95% PPV	Specific IgE 50% NPV	Skin prick test 95% PPV
Cow's milk	15 kU/L	2 kU/L	≥8 mm Infants ≤ 2y: 6 mm
Egg	7 kU/L Infants ≤2y: 2 kU/L	2 kU/L	≥7 mm Infants ≤2 y: 4–5 mm
Peanut	15–34 kU/L	2 kU/L if history of reaction 5 kU/L if no history of reaction	≥ 8 mm Infants ≤2y: 4 mm
Fish	20 kU/L	-	
Tree nuts	20 kU/L		≥8 mm for walnut ≥12 mm for cashew
Sesame	50 kU/L (86% PPV)		≥8 mm

PPV-positive predictive value, NPV-negative predictive value, kU/L- kilo units per liter

Extracts of milk, eggs, peanuts, tree-nuts, soy, fish, and shell-fish are usually reliable, while extracts of fruits and vegetable are not so reliable because of labile allergen which may have been altered during processing. Prick-prick testing with fresh fruits and vegetables, although less convenient has a higher correlation to clinical reactivity. The larger the wheal, the greater the likelihood of clinical allergy Importantly, the size of the skin test does not correlate with the severity of a clinical allergic reaction. According to a study of 467 children with a median age of three years, a peanut SPT >8 mm was '100 percent' diagnostic for a positive food challenge to peanut [25, 26].

Recommendation 2: For individuals with a suspected history of IgE-mediated food allergy, the initial diagnostic tests recommended are the skin prick test and/or measurement of specific IgE in the serum, supported by strong evidence certainty [24].

These numbers were derived from uncooked milk and direct egg and do not apply to baked milk or baked egg [26]. The interpretation of skin prick test (SPT) and specific IgE depends on: Technical performance, Allergen quality, Patient sample (quality), Cross-reactivity The SPT and specific IgE positivity should be interpreted with care. The presence of IgE antibodies to food does not mean that the patient is clinically allergic to it. Many atopic people have IgE antibodies but no symptoms, therefore positive results must be interpreted in conjunction with a careful history. Food should not be restricted based on a positive result, if no clinical symptoms. On the other hand, a negative skin test or specific IgE result is considered as good evidence that a reaction to food is not mediated by IgE but it does not exclude sensitivity mediated by non-IgE mechanism. It is to be noted that IgE-antibody to foods appear during infancy and disappear during childhood, whereas IgE-antibody to inhalants appear later and in increasing frequency from two years of age. Patients presenting with symptoms of food allergy and low IgE levels have a higher probability of obtaining resolution of their allergy after several years, while patients with high food-specific IgE levels (3 times or more) have a low probability of outgrowing their hypersensitivity to these foods even after five years**.** It is therefore useful to perform follow up food specific IgE assays to determine the optimal time for a repeat challenge test. Allergist should have the accurate knowledge of botanically related foods before interpretation of skin test and specific IgE e.g., if the SPT is positive to Nuts (peanuts), it may also be positive to Soyabean; but a Double-blind placebo control food challenge (DBPCFC) with these cross-reactive foods may be negative. It's crucial to emphasize that the degree of positivity does not indicate the severity of the condition. Additionally, a significant number of individuals exhibit results within the intermediate range, situated between the negative predictive value (NPV) and positive predictive value (PPV), making it challenging to provide a definitive diagnosis. In such cases, an oral food challenge (OFC) is frequently necessary [27]. In one study, 1247 individuals, SPT wheal size and specific IgE cut off with maximum cumulative dose of 500 mg for specific foods [almond (12mm, 12.2kU/L), cashew (4.5mm, 1.2 kU/L), egg (13mm, 9.6 kU/L), hazelnut (7mm, 14.6 kU/L). milk (8mm, 20.1 kU/L), peanut (9mm, 10.7 kU/L), pecan (7mm, 1.8 kU/L), sesame (11mm, 7.5 kU/L), walnut (4mm, 13.5 kU/L), and wheat (5.5mm, 43.1 kU/L) were found positive to OFCs [28].

Additional testing with specific IgE components may offer diagnostic advantages for certain allergens, particularly peanut and hazelnut. If the collective information from clinical history, skin prick test (SPT), and specific IgE component testing, including positive predictive value (PPV) cutoffs, indicates a high likelihood of a reaction, an oral food challenge (OFC) may not be recommended to confirm the diagnosis. However, in cases where the results of these tests are inconclusive, the basophil activation test (BAT) could be a valuable tool (Figure 5). A strongly positive BAT result can indicate a likelihood of a positive outcome in an oral food challenge (OFC). If BAT reveals non-responsive basophils or obtaining a suitable fresh sample within the required testing timeframe is impractical, the mast cell activation test (MAT) might serve as an alternative testing option. Combining CRD and BAT can provide additive diagnostic accuracy of FA. Moreover, up until now, none of the specific IgE cut-off have shown a specificity and sensitivity as accurate as OFC which is a gold standard in diagnosing FA. The currently suggested clinical strategy for diagnosing IgE-mediated food allergy includes CRD, BAT (Basophil Activation Test), MAT (Mast Cell Activation Test), and OFC (Oral Food Challenge) [26–29].

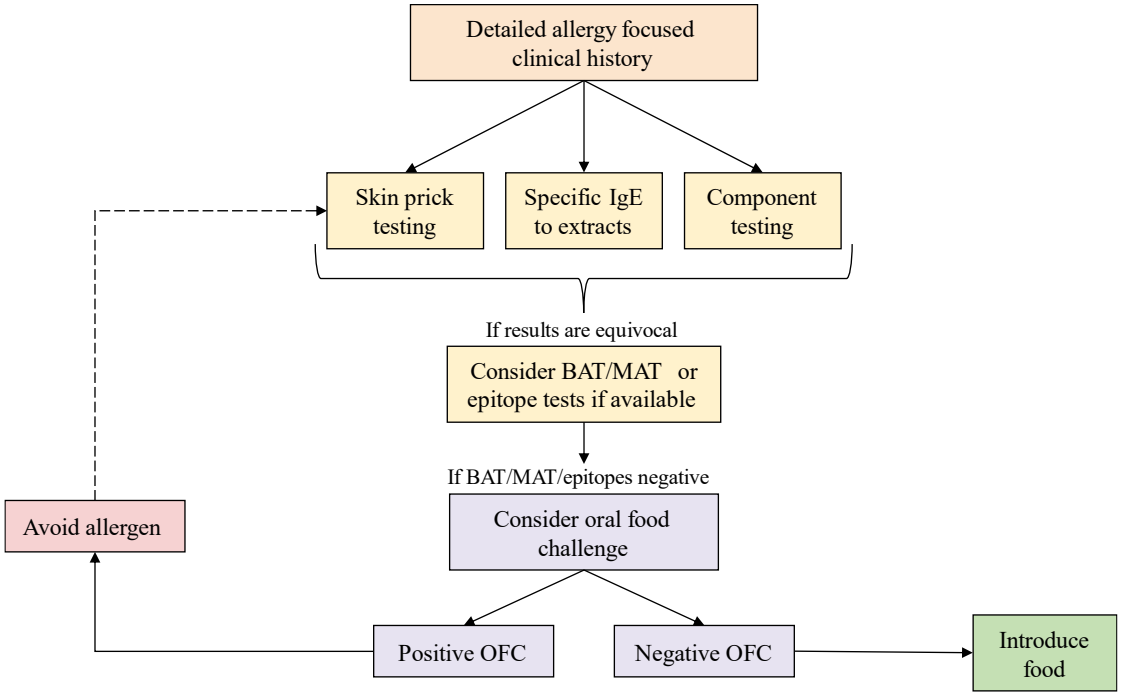


Figure 5. Diagnostic algorithm of IgE-mediated food allergy.
(BAT, Basophil activation test; MAT, mast cell activation test; OFC, oral food challenge)

Component Resolved Diagnosis (CRD) in Food Allergy

Component resolved diagnosis (CRD) is significant in food allergy diagnostics over the past decades. CRD has been shown to significantly improve the predictive value of in-vitro test for biological activity of food allergen specific IgE, thereby reducing the need for OFC. Molecular diagnostics can aid in more effectively distinguishing various disease phenotypes and endotypes. This approach has established a foundation for risk stratification and enhanced the implementation of allergen-specific immunotherapy. Determining the sensitizing component and its associated allergen family, one can aide the clinician in determining the level of risk. Combing CRD with clinical history identifies better than extract-based specific IgE in assessing the risk of severe reaction. This will ultimately improve the management of the allergic patients and high-risk patients can be trained to use adrenaline injector pens while in low-risk patients' reassurance can be given along with preventing unnecessary dietary restriction and anxiety.

Plant protein families have homologous protein between species such as storage proteins, nsLTP, PR-10, profilin proteins and CCDs (cross-reactive carbohydrate determinants). Dairy products such as milk and egg are associated more with pediatric allergy which children tend to outgrow at a young age. However, in a recent longitudinal egg allergy studying the UK, Clark *et al.* showed that many children do not outgrow their egg allergy until well past 5 years old, in fact the median age in this study was 10 years of age for egg allergy resolution. Egg and milk contain allergen components that are likely to be linked to more severe symptoms; these allergens are resistant to metabolic change (hen's egg Gal d 1 Ovomucoid; cow's milk, Bos d 8 Casein). Therefore, patient groups negative to these tests have been observed to tolerate cooked forms of the allergen. Conversely persistent allergy is associated with the same epitopes, which again can be used as risk markers. In particular 2S albumins from legumes (e.g., Ara h 2) and tree nuts (e.g., Cor a 14) have proven to be useful diagnostic tools (Figure 6).

There are five merits of component resolved diagnosis (CRD):

1. *Molecules of low abundance and/or weak stability*- (i.e., Gly m 4 vs soy extract, omega-5-gliadin vs wheat extract) cannot be detected by SPT or extract-based specific IgE
2. *Risk*- or severity-associated molecules i.e., storage proteins Ara h 1, 2, 3, 6 vs whole peanut extract can be confirmed by CRD.

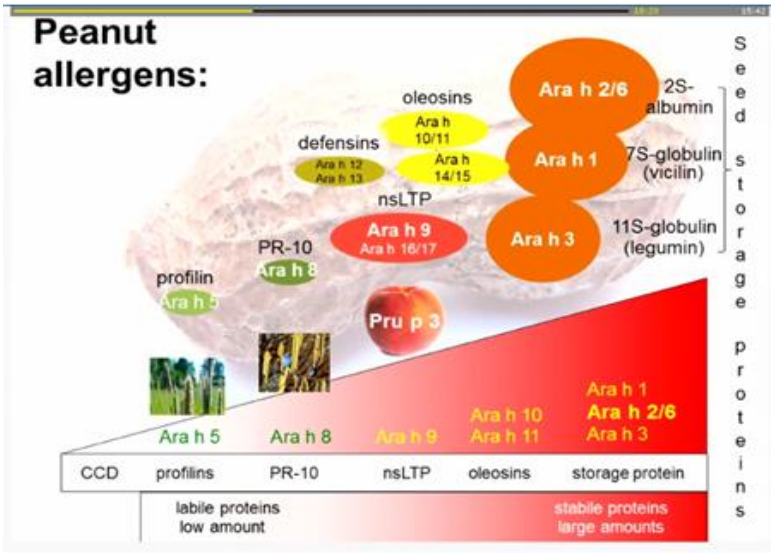


Figure 6. CRD in peanut allergy (IgE to Ara h 2 (storage protein) and to a much lesser extent Ara h 1, Ara h 3, Ara h 6, and Ara h 9 are the most important predictors of symptomatic peanut allergy. Ara h 8 is a Bet-v 1 homolog and can indicate pollen-food syndrome) [30, 31].

3. Indicator of cross reactivity e.g., profilin or polcalcin, members of plant panallergen families can be demonstrated.
4. Marker of genuine (species-specific) sensitization e.g., marker allergens Ves v 1 and Ves v 5 from yellow jacket venom and marker allergens Api m 1, Api m 3, Api m 10 from honey bee venom vs hymenoptera whole venom preparations from the corresponding species are also confirmed with CRD and allergenic specificity of foods.
5. *Predict the outcome of FA:* Spontaneous remission, persistent response to OIT [30].
   i. *Milk*- the major allergens in cow milk are Bos d 8 and Bos d 5. Higher levels of Bos d 8 have been suggested as predictor of baked milk reactivity as casein is resistant to extensive heating. Casein (Bos d 8) / Bos d 4 (62% sensitivity, 87% specificity) for baked milk allergy.
   ii. *Egg*- ovomucoid (Gal d 1) and ovalbumin (Gal d 2) are the major allergens in Hen's eggs. Higher Gal d 1 IgE is associated with persistent of egg allergy. Ovomucoid (Gal d 1) [Heated] (sensitivity- 4.2%, specificity 89.8%). Raw (sensitivity- 60.6%, specificity (97.1%)
   iii. *Wheat*- the major wheat allergens are gliadins and glutenin's. Omega-5-gialdin (Tri a 19) is associated with wheat dependent exercise induced anaphylaxis (WDEIA).
   iv. *Peanut*- Ara h 6 (sensitivity- 94%, specificity-95%) / Ara h 2 for peanut allergy
   v. Hazelnut Cor a 14 (sensitivity-100%, specificity-93.8%)
   vi. Shrimp Lit v 1 (sensitivity-82%, specificity-56%).

Recommendation 3: For individuals with a suspected history of IgE-mediated allergy to peanut, hazelnut, or cashew nut, it is advisable to include component-based specific IgE testing for Ara h 2, Cor a 14, and Ana o 3, respectively, if accessible. This recommendation is in addition to conducting skin prick tests and/or measuring IgE to extracts, aiming to enhance diagnostic precision (high certainty of evidence) [24].

It has the characteristic to improve the precision to identify the causative allergen and to differentiate from the cross-reactive allergen. In a patient with specific IgE to LTP and with a clear clinical tolerance as shown by regular consumption of vegetable foods containing LTP, there is no indication to eliminate such diets. But, if the patient has history of severe anaphylactic reaction to given food, if specific IgE to LTP positive, then he must be instructed to avoid that food in the future. ***Parvalbumins-*** Cyp c 1 (carp, oily fish) and Gad c 1 (cod, white fish) are both major fish allergen proteins and markers for fish

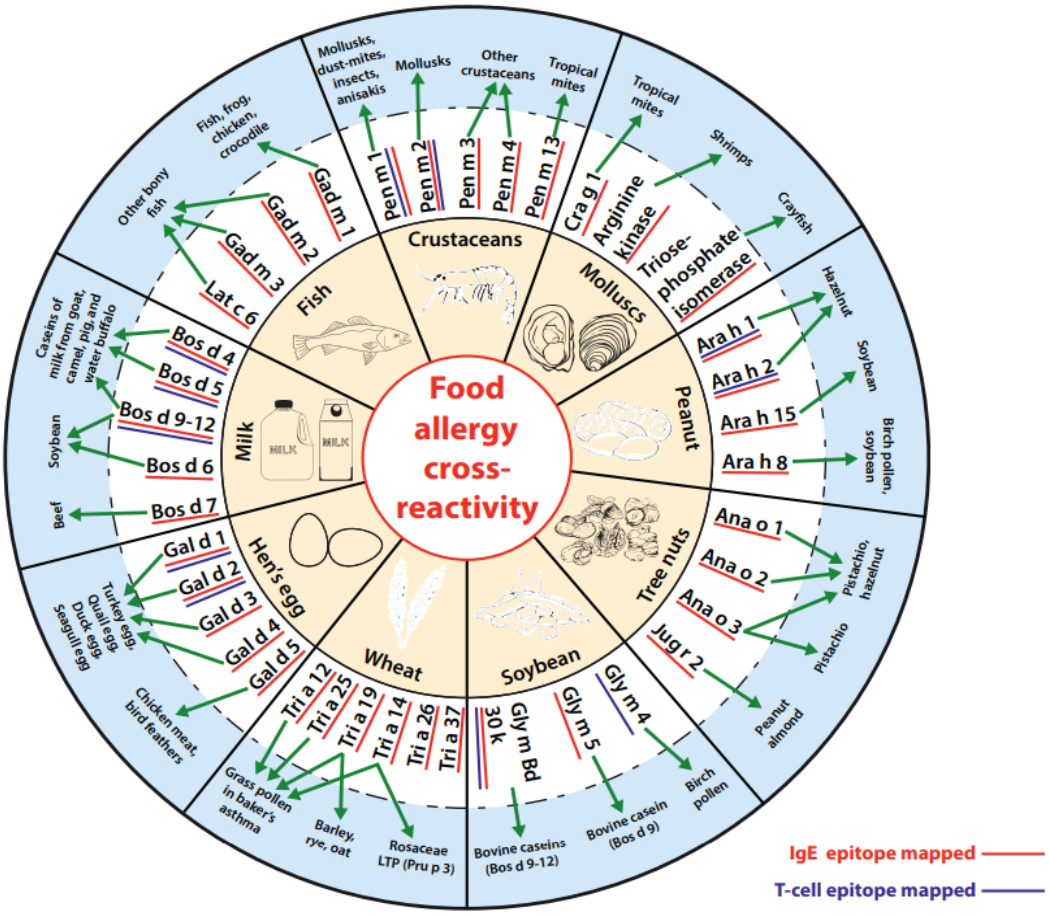


Figure 7. CRD in food allergy-species-specific and cross-reactive components [32].

IgE sensitization. Some fish species, such as tuna, swordfish, and certain mackerel, exhibit lower levels of parvalbumins expression. This could potentially clarify why individuals with fish allergies may occasionally tolerate these particular species. Using Immunocap Cyp c 1and Gad c 1 gives broad spectrum coverage of the parvalbumins family and IgE analysis of fish. A negative result to both tests in a patient investigated for food allergy would inform the clinician of potential low risk of oral challenge and/or lead to further investigations for other possible culprit allergens. ***Tropomyosin*** proteins are highly cross-reactive actin-binding proteins located in muscle fibers amongst many invertebrate species such as shrimps (Pen a 1), dust mite (Der p10), cockroach (Bla g 7) and other crustacean foods such as crab, lobster, and mollusc. Hence, tropomyosin is an allergen that can elicit allergic reactions through both inhalation and ingestion. Approximately 10% of individuals allergic to dust mites possess IgE antibodies specific to tropomyosin. Certain studies propose that exposure to dust mite tropomyosin might induce sensitization to shrimp tropomyosin. ***Latex-***IgE antibodies to Hev b 1 and Hev b 3 are considered specific markers for latex allergy specially in multi-operated children/patients. Antibodies of the IgE type directed against Hev b 5 and Hev b 6 are primarily linked to occupational latex exposure, such as in healthcare professionals and food handlers who use latex gloves. Hev b 8 the profilin and Hev b 6.02 can be used for examining cross-reactivity. If an exclusive sensitization to latex profilin (Hev b 8) occurs, then clinically relevant allergic symptoms are hardly to be expected (Figure 7).

Basophil Activation Test (BAT) in Food Allergy

BAT considers functional crosslinking between IgE molecules requiring flow cytometry and fresh blood. In cases where skin prick tests (SPT) and specific IgE results are inconclusive, the basophil activation test (BAT) may serve as a secondary or tertiary diagnostic tool, potentially eliminating the need for oral food challenges (OFC). The BAT is suggested to offer elevated specificity and positive

predictive value (PPV). Complement diagnostic tests such as SPT and specific IgE. BAT can use a variety of allergen molecules, even recombinant proteins. The basophil activation test (BAT) for diagnosing food allergies demonstrates sensitivity ranging from 62% to 90% and specificity between 80% to 100%, depending on the allergen. BAT specifically for cow milk exhibits 100% sensitivity and specificity. When compared to specific IgE tests for Ara h 2 and Cor a 9/Cor 14 components, BAT for peanut and hazelnut shows higher diagnostic accuracy. In peach allergy, BAT targeting Pru p 3 proves more effective than BAT using peach extract. Additionally, BAT can be employed to diagnose allergies to unconventional allergens such as beer or cannabis, among others. BAT had 97% accuracy in peanut and 91% accuracy in sesame.

Recommendation 4: For individuals with an uncertain diagnosis of IgE-mediated peanut or sesame allergies, it is recommended, when applicable, to utilize basophil activation tests (BAT) specific to peanut or sesame. This can enhance diagnostic precision, supported by a high level of certainty in the evidence [24].

Food Challenge

The double-blind placebo-controlled food challenge is recognized as the ultimate standard for determining the presence of food allergies. The selection of foods to be taken in DBPCFCs is generally based on history and / or skin Test (RAST) results but before undertaking DBPCFC, several factors should be taken into account during a food challenge conducted in a fasting state. The process begins with a small initial dose (ranging from 125 mg to 500 mg of lyophilized food), and subsequently, the dose is doubled at intervals of 15 to 60 minutes, depending on the suspected type of reaction. After the patient has tolerated 10 gm. Of lyophilized food blinded in capsules or liquid, clinical reactivity is generally ruled out. If the blinded challenge is negative, however, it must be confirmed by an open feeding under observation to rule out rare false negative challenges. An equal number of food-antigen and placebo-challenge are necessary, to control the potential confounding factors. The order of administration should be randomized by a non-interested third party (e.g. dietician) A standardized scoring system should be utilized for all challenges. The time of observation depends on the type of reaction suspected (e.g., generally up to 2 hrs. for IgE mediated reaction and up to 4–8 hrs. for mild induced enterocolitis). Results of blinded challenges for objective signs and symptoms are rarely equivocal but can be made more objective by monitoring a variety of laboratory parameters (such as plasma histamine, pulmonary function tests and nasal airway resistance).

Oral Food Challenge (OFC)

1. Eliminate suspected food for 14 days before the challenge.
2. Discontinue antihistamine: minimize other medications.
3. Administer challenge to patient on an empty stomach.
4. An equal number of food and placebo challenges need to be administered randomized by Dietician
5. Lyophilized foods are blinded in liquid or capsules.
6. Administer 10 gm. Over one hr., Ist dose should be < 500 mg.
7. Utilize a standardized scoring system.
8. The length of the observation period expands on type of reactions being studied.
9. Appropriate equipment should be available to treat systemic anaphylaxis.
10. All negative challenges must be confirmed by an open feeding under observation.

Recommendation 5: A medically supervised oral food challenge (OFC) is recommended to confirm or exclude food. allergy in patients with an unclear diagnosis despite IgE sensitization tests (high certainty of evidence) [24].

Recommendation 6: A double-blind placebo-controlled food challenge (DBPCFC) is suggested if an open OFC. outcome is indeterminate and in research studies (low certainty of evidence) [24].

FOOD ALLERGY-MANAGEMENT

Prevention of Food Allergy

Maternal Diet in Pregnancy and During Breast Feeding (BF)

1. Maternal antigen avoidance diet as maternal dietary proteins are transferable into breast milk and can sensitize breastfed infants, but mothers should be encouraged to continue breast feeding for minimum of six months.
2. Diet indices -dietary factors that suppress FA (Hydrocarbon receptor ligands found in cruciferous vegetables (cabbage, Brussel sprouts, broccoli) or oat, rice and nuts
3. Nutrients / vitamin D / pre- and pro-biotics, Calcium supplement antioxidants

Infant Diet

1. Breast-feeding and formula feeding-Breastfeeding is the first choice for all infants including those with food allergy (Table 4)
2. Microbiome- Microbial treatments are currently in the works for addressing food allergies, either as independent therapies or in conjunction with oral immunotherapy (OIT). The underlying concept involves the microbiota's role in normalizing or improving the function of gastrointestinal Tregs to inhibit Type 2 responses. Clostridia, which are bacteria capable of forming spores, are recognized for their capacity to generate the short-chain fatty acid (SCFA) butyrate through the fermentation of dietary fibers. Butyrate, serving as a significant energy source for colonocytes, plays a crucial role in maintaining and supporting the function of the intestinal epithelial barrier.
3. Micronutrient / vitamin D / omega-3 fatty acids- Vitamin D deficiency is associated with food sensitization as well as IgE mediated food allergy. Insufficient levels of vitamin D lead to a compromised epithelial barrier, changes in the microbiome, and varying impacts on antigen-presenting cells.
4. Solid food should not be introduced before four months. There is evidence supporting common allergic foods (including cooked and raw egg, peanut, nuts, wheat) should not be delayed.

Elimination Diet

It is the best means of controlling for the variability of chronic disorders (e.g., Chronic Urticaria, atopic dermatitis, occupational bronchial asthma etc.). The procedure should take place in a clinical or hospital environment, particularly if there is suspicion of an IgE-mediated reaction, and only when there are adequately trained personnel and equipment available to manage systemic anaphylaxis. If life threatening anaphylaxis is suspected and the causative antigen cannot be conclusively determined by history, a challenge should be conducted in the intensive care unit of a center frequently dealing with food-allergic reactions (Figure 8).

Elimination Diet (PCK) for Two Weeks-depending on the Type of Reaction and the Suspected Ingredients

- The least antigenic cereal is rice, oat, corn, buckwheat
- Vegetables without peel and seeds
- *Fruits:* without peel and seeds
- *Pulses:* each pulse to be repeated every 72 hours

Table 4. Breast-feeding and formula feeding.

Feeding option	Indications
Breast milk	All infants
Soy formula	Confirmed CMA (not anaphylaxis)> 6 m.o. (not soy allergic)
Extensively hydrolysed formula (eHF)	Confirmed CMA (not anaphylaxis) < 6 m.o.
Amino acid formula (AAF)	Confirmed CMA (not anaphylaxis)> 6 m.o. if soy formula not tolerated SMA where soy and eHF not tolerated

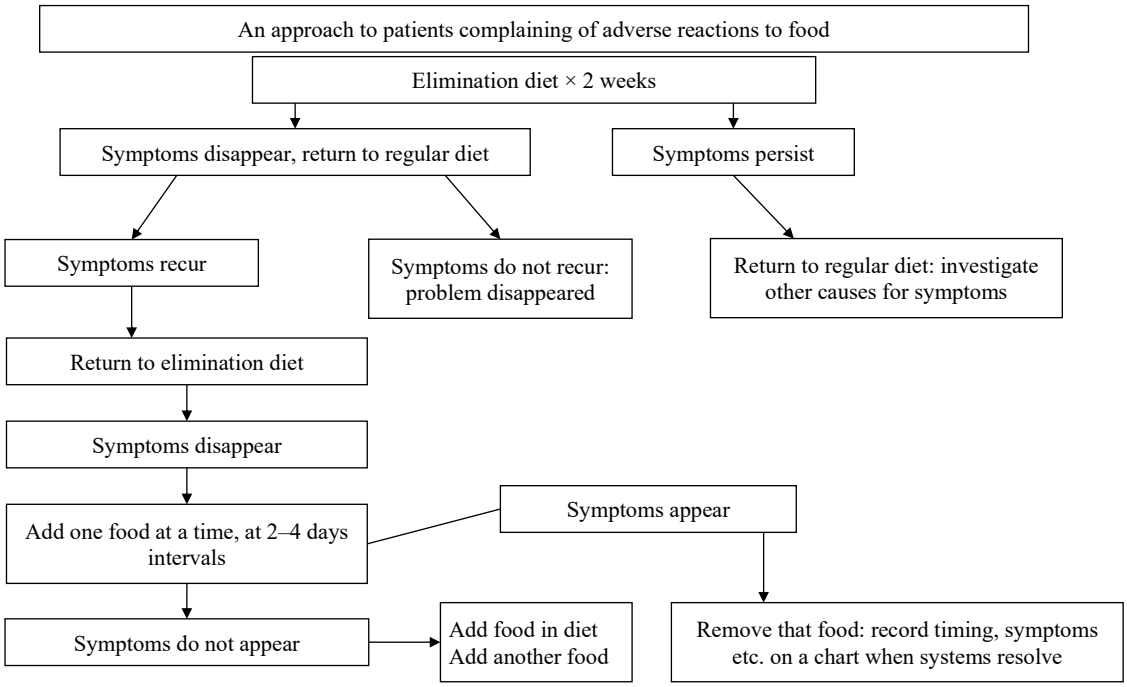


Figure 8. Proposed clinical approach to the diagnosis of IgE-mediated food allergy

- *Fat:* a refined vegetable seed oil, e.g., (cold pressed) sunflower or safflower or corn or soya
- The meat least likely to cause reactions is lamb
- *Drink:* Coconut water and sugar without sulfur, green tea, salt without iodine
- Avoid colored medicine

Acute Management of Food Allergy

Education is essential if patient is at-risk of anaphylaxis. In 2022, the EAACI Task-force on anaphylaxis recommended providing structural comprehensive training to improve knowledge and use of adrenaline auto-injector in people at-risk of anaphylaxis (Figure 10) [33, 34].

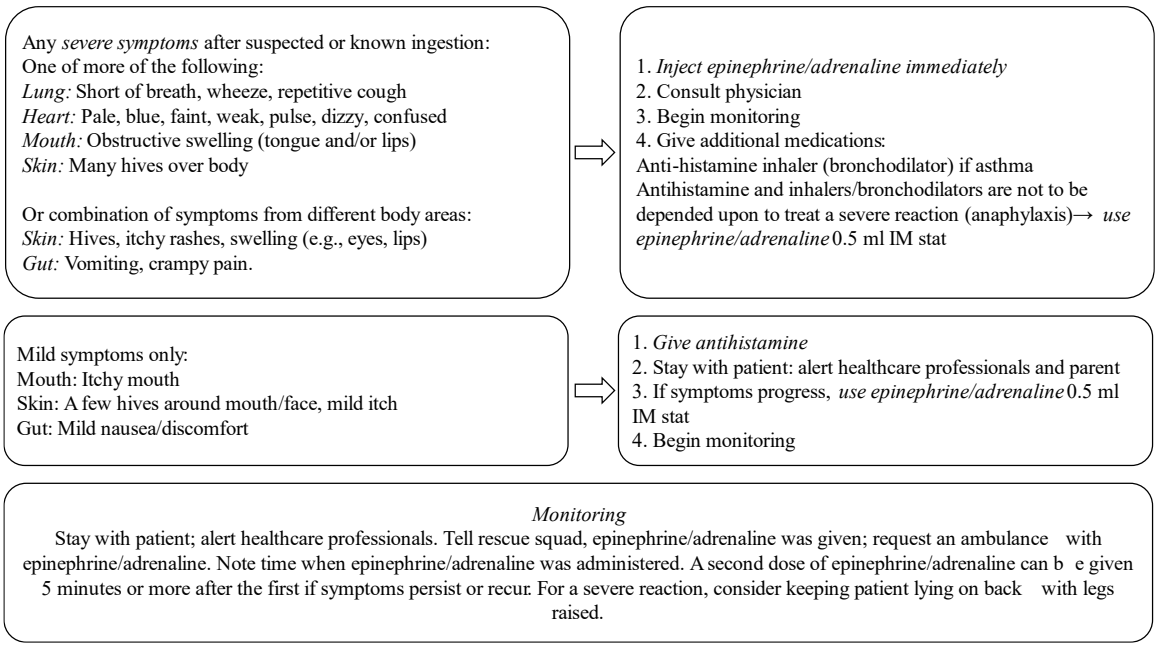


Figure 9. Food allergy emergency action plan (www.foodallergy.org).

Travelling with Food Allergy

Patients/paraents should be educated about how to be prepared when travelling with food allergy including:

- Checking travel insureacne.
- Checking airline policies in advance, particularly for international travel.
- Prepare and carry ASCIA action plan for Anaphylaxis and ASCIA Travel plan (these can be complted by general pracititionrs).
- Informing airlines and travel attendants.
- Other strategies:
  - Carry own food.
  - Wipe down tray tables.
  - Food exclusion zones- some airlines have food exclusion zones as part of their management policy.

Tolerance Induction Strategy-Allergen Immunotherapy

Currently, oral immunotherapy stands out as the most extensively researched method for addressing food allergies. Immunotherapy, a type of therapeutic intervention, involves the utilization of a substance to alter the immune response in the treatment of a disease [3, 8]. Research is currently underway to explore the potential use of four types of allergen immunotherapy in treating food allergies: subcutaneous immunotherapy (SCIT), oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epi-cutaneous immunotherapy (EPIT) [5]. Studies have shown efficacy of SCIT in pollen associated food allergy; SLIT in peanut, hazelnut and peach induced FA; OIT in milk, hen's egg, and peanut allergy [35–37]. To reduce allergenicity while maintaining immunogenicity, efficacy, safety; there are three selective approaches based on modified allergen:

1. Synthetic allergen-derived peptides that contain allergen-specific T-cell epitopes without IgE reactivity [38].
2. Recombinant hypoallergenic allergen derivatives are characterized by strongly reduced IgE reactivity, and contain allergen-specific T-cell epitopes. After internalization, they can induce allergen-specific IgG responses [39].
3. Carrier-bound peptides that contain B-cell epitopes are fusion proteins that consist of an allergen-unrelated carrier protein and nonallergenic peptides from the IgE binding sites of allergens. They lack IgE reactivity and most allergen-specific T-cell epitopes, but can induce allergen-specific IgG antibodies [40].

Since OIT is the long-term treatment to induce tolerance, there is a significant interest in the dose and dosing schedule which balance the risk and benefit. Slow up-dosing regimen every two weeks appear to reduce adverse events versus quicker regime (Figure 10). Indications and contraindications are mentioned in (Figure 11).

OIT may alter the T cell responses including exhaustion or deletion of pro-allergic T cell responses, the switch in T cell effector immune responses or the induction of concurrent immune-regulating T cells. OIT decreases airway epithelial apoptosis and repairs impaired epithelial tight junction of gastrointestinal tract (Figure 12).

Palforzia, an oral immunotherapy, has earned the distinction of being the inaugural FDA-approved treatment for peanut allergies. During Palforzia studies involving 944 children with a median age of 9 years and a treatment duration averaging 49 weeks, 87.8% (829 participants) encountered adverse effects related to the treatment [41].

OIT has mainly been studied for cow milk, egg, and peanut allergy [42]. An analysis combining data from 36 randomized controlled trials involving 2126 participants, predominantly children, who underwent oral immunotherapy (OIT) for allergies to cow milk (CM), eggs, and peanuts, revealed that

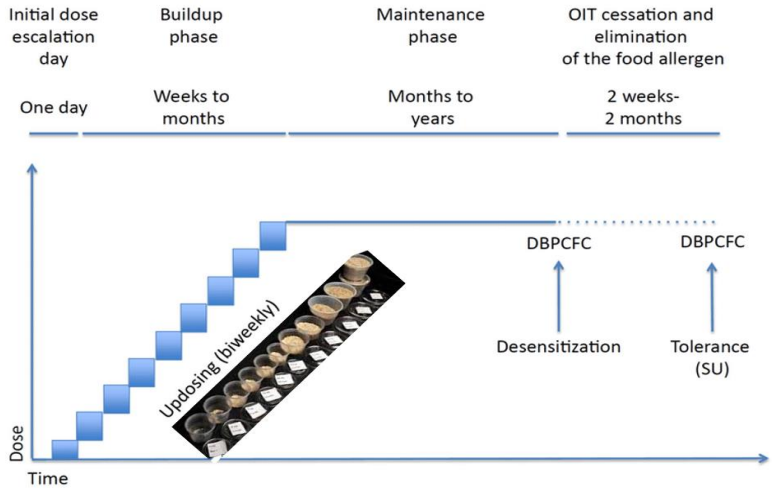


Figure 10. Classic protocol of oral immunotherapy, OFC, oral food challenge.

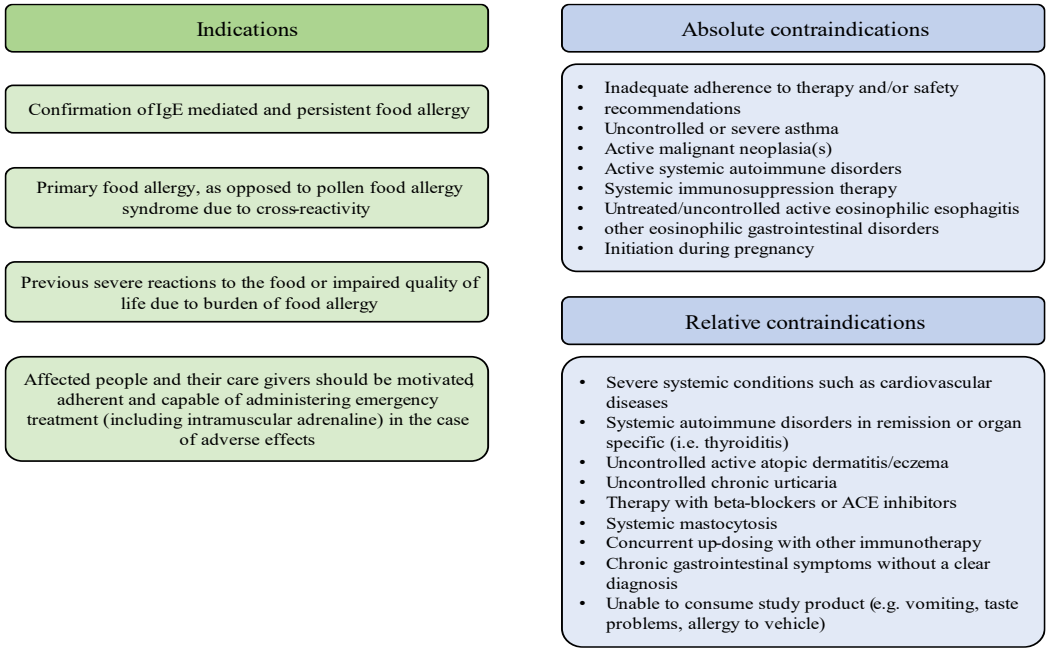


Figure 11. Fundamental considerations and contraindications that physicians should acknowledge before initiating OIT.
(OIT, oral immunotherapy; IgE, immunoglobulin E; FA, food allergy)

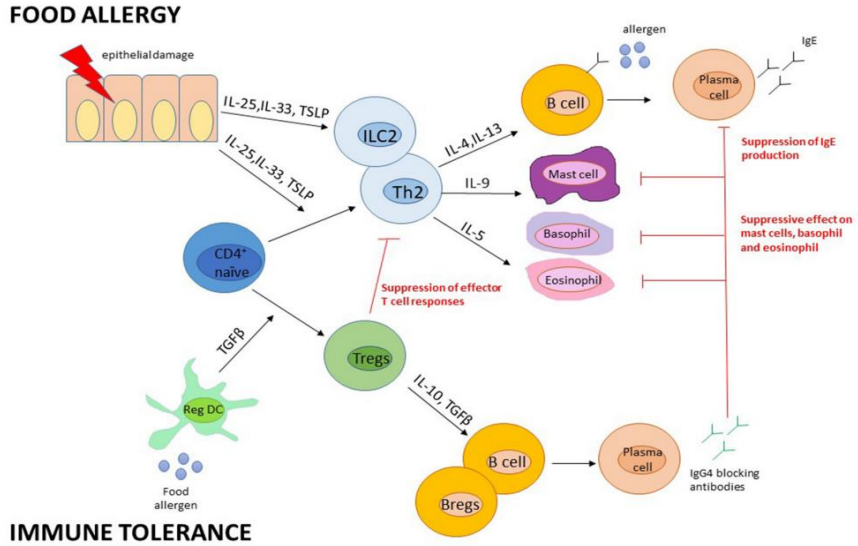


Figure 12. Mechanism of oral immunotherapy in food allergy.

OIT resulted in desensitization (DS) in 68% of individuals with CM and peanut allergies, and 84% of those with egg allergies [43]. A different meta-analysis, encompassing 18 randomized controlled trials (8 comparing with a placebo) and 5 non-randomized studies, encompassing nearly 1000 patients with allergies to cow milk, eggs, or peanuts, demonstrated that 76.9% of individuals undergoing oral immunotherapy (OIT) achieved desensitization, compared to only 8.1% of control subjects [44]. In a Cochrane meta-analysis that included 10 controlled trials (3 comparing with a placebo) assessing oral immunotherapy (OIT) based on eggs in 249 children, desensitization (DS) was achieved in 82% of children who underwent OIT (involving the consumption of 1–7.5 g of egg protein), while only 10% of the control group experienced desensitization [45]. According to a Cochrane meta-analysis, oral immunotherapy (OIT) for cow milk (CM) allergy resulted in desensitization (DS), defined as the consumption of 150–243 ml of milk, in 62% of the 106 children who underwent OIT. In comparison, only 8% of the 90 control subjects achieved desensitization [46]. In a meta-analysis of 9 randomized controlled trials assessing the effectiveness of peanut oral immunotherapy (OIT) over a median duration of 1 year involving 917 participants, the relative risk of experiencing no reaction during an oral food challenge (OFC) with peanut was found to be RR 12.42 (with a 95% confidence interval of 6.82–22.61), favoring the use of OIT [47]. The likelihood of experiencing anaphylaxis seems to be elevated in the context of oral immunotherapy (OIT) for cow milk (CM). A study examining 1100 instances of OIT involving various foods (milk, egg, peanut, sesame seeds, nuts) indicated that allergic reactions necessitating the use of adrenaline, both in healthcare settings and at home, were more common in OIT for CM allergy compared to OIT for other foods (26.8% versus 11.3% and 13.8% versus 5.8%, respectively) [48]. In monitoring the adverse effects associated with oral immunotherapy (OIT), it is crucial to also investigate the presence of eosinophilic esophagitis (EO). The incidence of EO in OIT is estimated to range from 0.5% to 5% [49–51]. Vickery and colleagues conducted a study on the effectiveness of peanut oral immunotherapy (OIT) in young children, aged 9–36 months, utilizing both low-dose (300 mg/day) and high-dose (3,000 mg/day) OIT. Their findings revealed that, on the whole, 78% of patients achieved sustained unresponsiveness. This was defined as the ability to ingest 5 g of peanut protein without experiencing symptoms that limit the dosage during a concluding double-blind, placebo-controlled food challenge (DBPCFC) conducted four weeks after discontinuing OIT, allowing the reintroduction of peanuts into the diet [52]. Literature has evidence to indicate that SCIT by primary inhalant allergen can also result in clinical improvement of pollen-associated FA, though controlled trials are not available [53]. In some patients, food desensitization may benefit from the addition of biologicals as adjunctive therapy. At present, various studies are employing omalizumab and dupilumab, either independently or in conjunction with oral immunotherapy (OIT). The author has published case series of combining omalizumab and subcutaneous immunotherapy with specific allergens (Cynodon dactylon, Artemesia vulgaris, Prosopis juliflora, Haloptelea intergrifolia) in patients

of urticaria, angioedema, anaphylaxis due to nuts and seeds co-morbid with allergic rhinitis with intermittent asthma. He hypothesized that combining omalizumab and AIT provides early tolerance and safe alternative for inhalant and food allergic patients. Although the questions for the development of long term tolerance remain unanswered but combining AIT (OIT / SLIT / SCIT) with biological is a hope for future treatment and needs further research [54–56].

CONCLUSION

The large proportion of allergy burden is due to genetic predisposition. Studies on the changes in gene function in relation to environmental influences (i.e., epigenetic modification) provide us the mechanism underlying the increase in the prevalence of food allergy. Sensitization and FA commonly occurs in infancy but there is poor evidence of dietary intervention in high risk pregnant and/or lactating women for prevention of FA. For high-risk infants who are not exclusively breast fed, the use of hydrolyzed formula might offer some protection against FA. The LEAP study findings have already influenced recommendations across many allergic societies for the introduction of peanut in at-risk population. The public awareness, the medical community, and food industry should be aware of potential serious allergic reaction from inadvertent ingestion of specific allergenic foods by high-risk individuals. FA diagnosis at molecular level (CRD) has significant implication to characterize more precise accurate diagnosis to differentiate severe reaction to food (parvalbumins, tropomyosin, LTPS) from mild reaction to food (profilin, CCD). Molecular diagnosis might also be a basis for specific food allergen immunotherapy. We still have a long way to go before BAT and MAT will be used routinely in clinical practice. Emergency action plan (epinephrine auto-injector) is recommended as a guide during serious life-threatening symptoms of urticaria, angioedema, or anaphylaxis. Active disease-modifying therapy by OIT, SLIT, or SCIT with biological has been studied in recent years to induce oral tolerance (OT) and sustained unresponsiveness (SU). In an era of omics and artificial intelligence it is expected that combinations of old and new biomarkers will further improve diagnostic accuracy and modulate the gut micro environment and balance immune response.

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