REVIEW ARTICLE

Asian Pacific Journal of
Allergy and Immunology

APJAI

Adult IgE-mediated food allergy is on the rise: A review of phenotypes, pathophysiologic mechanisms, diagnosis, and advances in management

Chanita Unhapipatpong,[1] Narachai Julanon,[2]* Thanachit Krikeerati,[3,4] Irin Vichara-anont,[3,4] Mongkhon Sompornrattanaphan[3,4]*

Abstract

The prevalence of adult food allergies is increasing worldwide. Many aspects of food allergy in adulthood are different from childhood. We review the current evidence on adult food allergy regarding the global prevalence, adult phenotypes, cofactors, diagnostic methods, and management. A high proportion of severe reactions and unique phenotypes in adults have been characterized. Individual comorbidities could be risk factors for severe reactions and complicate the physician's diagnosis as various conditions can mimic food allergies. Many cofactors affect the eliciting threshold of reaction, affecting whether a reaction occurs and its severity. Large and complex meals, various food allergens, and contaminants increase diagnostic difficulties. An action plan should be devised to add a framework for national policies, thereby lessening the biophysical and health-related quality of life impacts of food allergy. Research into novel treatments is ongoing.

Key words: Anaphylaxis, epidemiology, food allergy, immunoglobulin E, phenotype, prevalence

Citation:
Unhapipatpong, C., Julanon, N., Krikeerati, T., Vichara-anont, I., Sompornrattanaphan, M. (2022). Adult IgE-mediated food allergy is on the rise: A review of phenotypes, pathophysiologic mechanisms, diagnosis, and advances in management. *Asian Pac J Allergy Immunol*, 40(4), 308-320.
https://doi.org/10.12932/ap-101122-1499

Affiliations:
[1] Division of Clinical Nutrition, Department of Medicine, Khon Kaen Hospital, Khon Kaen, Thailand
[2] Division of Dermatology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[3] Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[4] Faculty of Medicine Siriraj Hospital, Center of Research Excellence in Allergy and Immunology, Mahidol University, Bangkok, Thailand

*These co-first authors contributed equally to this work

Corresponding author:
Mongkhon Sompornrattanaphan
Division of Allergy and Clinical Immunology, Department of Medicine
Faculty of Medicine, Siriraj Hospital, Mahidol University
2 Prannok Rd., Bangkok Noi, Bangkok 10700, Thailand
E-mail: mongkhon.som@mahidol.ac.th, bankallergymed@gmail.com

Abbreviations:

AAAAI	American Academy of Allergy, Asthma & Immunology
AUC	Area under the curve
BAT	Basophil activation test
BBEA	Bead-based epitope assay
CRD	Component-resolved diagnosis
DBPFC	Double-blinded, placebo-controlled food challenge
EPIT	Epicutaneous immunotherapy
FDEIA	Food-dependent exercise-induced anaphylaxis
HWP	Hydrolyzed wheat protein
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
MAT	Mast cell activation test
NPV	Negative predictive value
NY	New York
OFC	Oral food challenge
OIT	Oral immunotherapy
PTP	Prick-to-prick
sIgE	Specific Immunoglobulin E
SLIT	Sublingual immunotherapy
SPT	Skin prick test
Th1	T helper 1
Th2	T helper 2

Introduction

Food allergy in adulthood is one of the greatest clinical challenges across diagnosis and management. To date, most studies have focused on pediatric-onset food allergies. However, the prevalence of food allergy has been increasing in adult populations.[1] Due to their stage in the lifecycle, adults often play an important role in self-care, which is different from children who require supervision from caregivers.[2] Adult food allergy might impact health-related quality of life, and an individual's confidence while socializing. The clinical course of adult-onset food allergy might have onset during early childhood or adulthood. Several mechanisms underlying adult-onset food allergy are responsible for their occurrence and have been investigated. One of the mechanisms of adult-onset food allergy is the breakdown of oral tolerance found in adult patients previously tolerating certain foods.[3] The standard guidelines and current treatments beyond food avoidance and symptomatic treatments are still in an early stage of development for adult patients compared with those for children.[4] In this report, we aim to narratively review all aspects of adult food allergy. We searched Pubmed Medline on 15 October 2022 using keywords for food allergy, adult, anaphylaxis, and specific food allergens (i.e., shellfish, wheat, tree nut, peanut, fruits, etc.). All kinds of articles were considered for eligibility according to relevance.

Epidemiology of food allergy in adulthood

In the last 2 to 3 decades, prevalence rates of food allergy have been increasing worldwide in both pediatric and adult populations. Contributions to the increasing prevalence include early recognition, more exposure to food allergens, and changing environmental factors leading to the breaking of immune tolerance.[5] Industrialized/Westernized societies are more affected than agricultural/non-Westernized ones, and children are more affected than adults. Few studies have estimated the population-based prevalence of food allergy in adults while many have reported estimates for children.[6,7] The prevalence varied according to the region and eating habits.[5] Studies investigating the population-based prevalence of self-reported food allergy in adults are summarized in **Table 1 and Figure 1**. The true prevalence of food allergy is hard to establish due to their various type of clinical manifestations, definitions, and diagnostic methodologies.[8] From the recent self-reported survey, the prevalence of self-reported food allergy among adults in the United States (US) was 19%, but the prevalence of adults with probable IgE-mediated food allergy by consistent symptoms and specific allergens was only 10.8%.[9] The prevalence of adult-onset food allergy defined as the first diagnosis of food allergy occurring after the age of 18 years was 5.2%.[9]

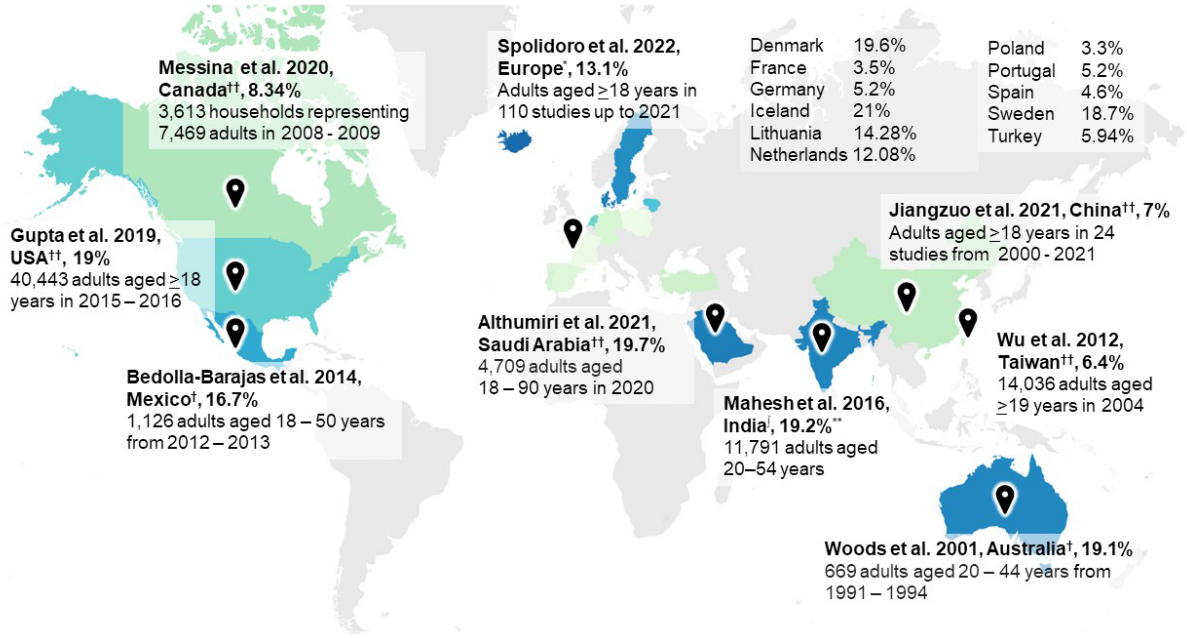

Figure 1. Map of the reported global point prevalence of self-reported food allergy in adults.

†cross-sectional study; ††national cross-sectional study; ∫two-stage study (screening followed by case-control study); *meta-analysis; **using weighted population prevalence

Asian Pac J Allergy Immunol 2022;40:308-320 DOI 10.12932/AP-101122-1499

Table 1. Population-based prevalence of self-reported food allergy worldwide.

Region or country	Year of publication	Point prevalence (%)										Comments
		Any food	Cow's milk	Peanuts	Tree nuts	Fish	Shellfish	Soy	Egg	Wheat	Fruit/ vegetables	
North America												
Mexico[55]	2014	16.7	1.5	0.6	0.18	1.42	4.97	NA	0.4	0.7	6.12	Patient self-report
USA[9,11,12]	2019	19.0	1.9-2.0	0.5-1.8	0.5-1.2	0.7-0.9	1.5-2.9	0.05-0.6	0.6-0.8	0.5-0.9	1.6-2.8	Patient self-report
Canada[56,57]	2020	8.34	1.89	0.78	1.07	0.6	1.91	0.16	0.67	0.86	1.29-1.61	Patient self-report
Europe[58-60]	2022	13.1	2.14	6.73	2.5	0.95	1.34	0.6	1.09	3.15	≤ 2.02 [61]	Meta-analysis
East Asia												
Taiwan[62]	2012	6.4	0.48	0.48	NA	1.17	7.05	0.15	0.31	NA	1.3	Patient self-report and expert-screened diagnosis
China[63]	2022	7.0	NA	NA	NA	NA	NA	NA	NA	NA	NA	Meta-analysis
South Asia												
India[64]	2016	19.2	2.39	2.22	NA	3.5	0.68	0.01	1.14	0.64	NA	Weighted population prevalence
Middle East												
Saudi Arabia[65]	2021	19.7	2.6	3.0	1.7	2.5	3.1	0.9	3.7	0.8	NA	Patient self-report
Oceania												
Australia[66]	2001	19	NA	NA	NA	NA	NA	NA	NA	NA	NA	Patient self-report

Abbreviation: NA, not applicable

A report from one large adult allergy center showed that adult-onset food allergy contributed to up to 15% of adult cases.[10] The onset of the first reaction was in the early fourth decade of life (mean age 31 years [range 18-86]) and the highest prevalence of adult food allergy was at the age of 50-59 years old.[9-11] Older age at diagnosis was associated with a higher risk of severe reactions.[10] Generally., the proportion of physician-diagnosed food allergies was half that of self-reported food allergies, reflecting the overdiagnosis by self-reported prevalence in adults, resulting in unnecessary food avoidance.[11,12] Up to 70% of patients with food allergies have a history of atopic disease, mostly allergic rhinitis.[10] Approximately half of the food-allergic adults had experienced severe reactions, and around 20% had multiple food allergies.[9] This reflects the urgent need for food allergy awareness, early diagnosis, and proper management in adults.

The ranked prevalence from most to least common of various adult-onset food allergens differ by region. In one US allergy center, they were shellfish, tree nuts, and finned fish.[10] In a US population-based study, they were wheat, shellfish, and soy in US population-based study.[9] In a study of Japanese adults, they were wheat, finned fish, crustaceans, and fruits.[7] Prevalence rankings from our center (unpublished data), Siriraj Hospital, the largest tertiary hospital in Thailand, was shellfish as the most common, followed by wheat, and fruits/vegetables.

The natural course of adult food allergy is poorly understood. Several food allergies, such as milk, egg, wheat, and soy are usually resolved in childhood and adolescence, but some food allergies, such as peanut, tree nut, seeds, fish, and shellfish tend to persist into adulthood.[8] The most common new-onset food allergies in adults were shellfish, tree nuts, fish, soy, and peanut.[10] Investigations of the natural course and the new onset of food allergy in adults play an important role in managing food allergies in the era of increasing adult-onset food allergy prevalence.

Phenotypes of IgE-mediated food allergy

Food allergy symptoms vary in severity from mild symptoms to severe life-threatening conditions such as anaphylaxis.[5] Some presentations of non-immune-mediated food hypersensitivity reactions may mimic the presentation of immune-mediated food allergy, making clinical diagnosis difficult. Immune-mediated food allergy could be classified based on pathophysiologic mechanisms into IgE-mediated, non-IgE-mediated, and mixed types. This review focuses mainly on IgE-mediated food allergy. Phenotypes of IgE-mediated food allergy are summarized in **Table 2**.

Table 2. Adult IgE-mediated food allergy phenotypes.

Subtypes	Onset	Remarks	Relevant investigation
Typical IgE-mediated - Urticaria/angioedema - Anaphylaxis	Within 2-3 hours	Anaphylaxis definition, according to WAO anaphylaxis guidance 2020[67] criteria include: • Acute onset of skin and/or mucosal lesion with at least one of the following: respiratory compromise, hypotension, and severe gastrointestinal symptoms • Acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known allergen or highly probable allergen	• Skin tests food extracts/components • Specific IgE to food extracts, components, or peptides • Oral food challenge (gold standard) • Novel *in vitro* diagnosis - Basophil activation test - Mast cell activation test
Food-dependent exercise-induced anaphylaxis	Within 4-6 hours	• Causes: Most are caused by wheat and other grains, vegetables, seafood, legumes, fruits, etc. • No symptoms during ingestion alone but if there are some cofactors (e.g., NSAIDs, alcohol, or exercise) anaphylactic symptoms may occur	• Skin tests food extracts/components • Specific IgE to food extracts, components • Oral food challenge (using cofactors)
Oral allergy syndrome	Within a few minutes	• Sensitization to a cross-reacting inhalant allergen, such as birch pollen with fresh fruits and vegetables (known as pollen-food allergy syndromes, PFAS) • Causes: Plants or non-plant foods • Symptoms: pruritus and/or swelling of lips, tongue, and mouth, as well as rarely anaphylaxis	• Skin tests to foods extracts/components and also related pollen allergens (in PFAS) • Specific IgE to food extracts, components • Oral food challenge
Delayed anaphylaxis (alpha-gal syndrome)	> 3 to 6 hours	• IgE antibody response against carbohydrate Galα1-3Galβ1-4GlcNAc-R (α-Gal) • Primary sensitization by tick bites • Causes: Allergy to non-primate mammalian meat (red meat) and derived products or a hypersensitivity reaction to cetuximab (upon the first dose) • Diagnosis: anti-α-Gal IgE titers (cutoff ≥ 0.35 IU/mL)	• Skin tests with mammalian meats extracts, including prick-prick tests to cooked meats • Anti-α-Gal IgE (> 0.1 IU/mL, specificity of 92.3%, sensitivity of 100%)
Occupation-related food allergy	Varied	• Transdermal or respiratory exposure to food-related allergens resulting in sensitization • Examples: fish and seafood allergies in cooks, a latex-fruit syndrome in health care workers, baker's asthma in bakers	• Establishing occupational relationship • Skin tests, specific IgE to food extracts/components

Abbreviation: NSAID, non-steroidal anti-inflammatory drug; WAO, The World Allergy Organization

Pathogenesis of IgE-mediated Food Allergy

Normally, macrophages and dendritic cells along the gastrointestinal tract prevent food allergy via immune tolerance by IL-10 secretion, inducing type 1 regulatory T-cells. The mechanism of adult-onset food allergy remains unclear, but the breakdown of oral tolerance in previously tolerant patients might be an initiating event of allergic sensitization, leading to food allergy.[13]

Allergic sensitization to food allergens could occur either directly from food allergens, leading to primary sensitization and the classic form of food allergy, or indirectly via cross-reactivity with nonfood allergens, e.g., aeroallergens due to antigen similarity or sequence homology.[1,14] The proposed mechanism responsible for many allergic diseases is the epithelial barrier hypothesis, in which the individual is exposed to barrier-damaging agents from environmental triggers such as trauma, drugs (e.g., anti-ulcer drugs), toxins, detergents, particles, allergens, or smoking, which cause inflammation of gut epithelium, microbial dysbiosis, and activation of systematic immune response via Th2 cell-mediated inflammatory response in the gut as initial sensitization.[5,15] Apart from the damage to gut epithelial cells, damaged skin or airways also allow antigen entry, causing sensitization that produces food allergen-specific IgE, which will be captured by FcεRI on mast cells and basophils, thereby leading to an immediate type of food allergy (**Figure 2**).[5] A population-based study also supports the epithelial barrier hypothesis[6] in that there was an association between food allergy and the presence of other atopic diseases, i.e., atopic dermatitis, hay fever, and asthma. Percutaneous sensitization from epidermal barrier disruption is one of the pathophysiologic mechanisms of atopic disease and food allergy.[16] The breakdown of the stratum corneum and tight junction of the skin barrier leads to allergen uptake and thereby activation of the Langerhan's cell network. As a result of Langerhan's cell activation and migration, T cells and B cells are activated, leading to atopic disease and food allergy.[16] An example of this mechanism is the high incidence of hydrolyzed wheat protein (HWP) allergy due to a facial soap containing HWP.[17] The pattern of this allergy was different from conventional wheat allergies, which mostly react with high molecular weight glutenin and gliadin in wheat protein. Instead, HWP allergy involves repeated skin exposure to Glupearl 19S, inducing Glupearl 19S-specific IgE (sIgE) antibodies, leading to

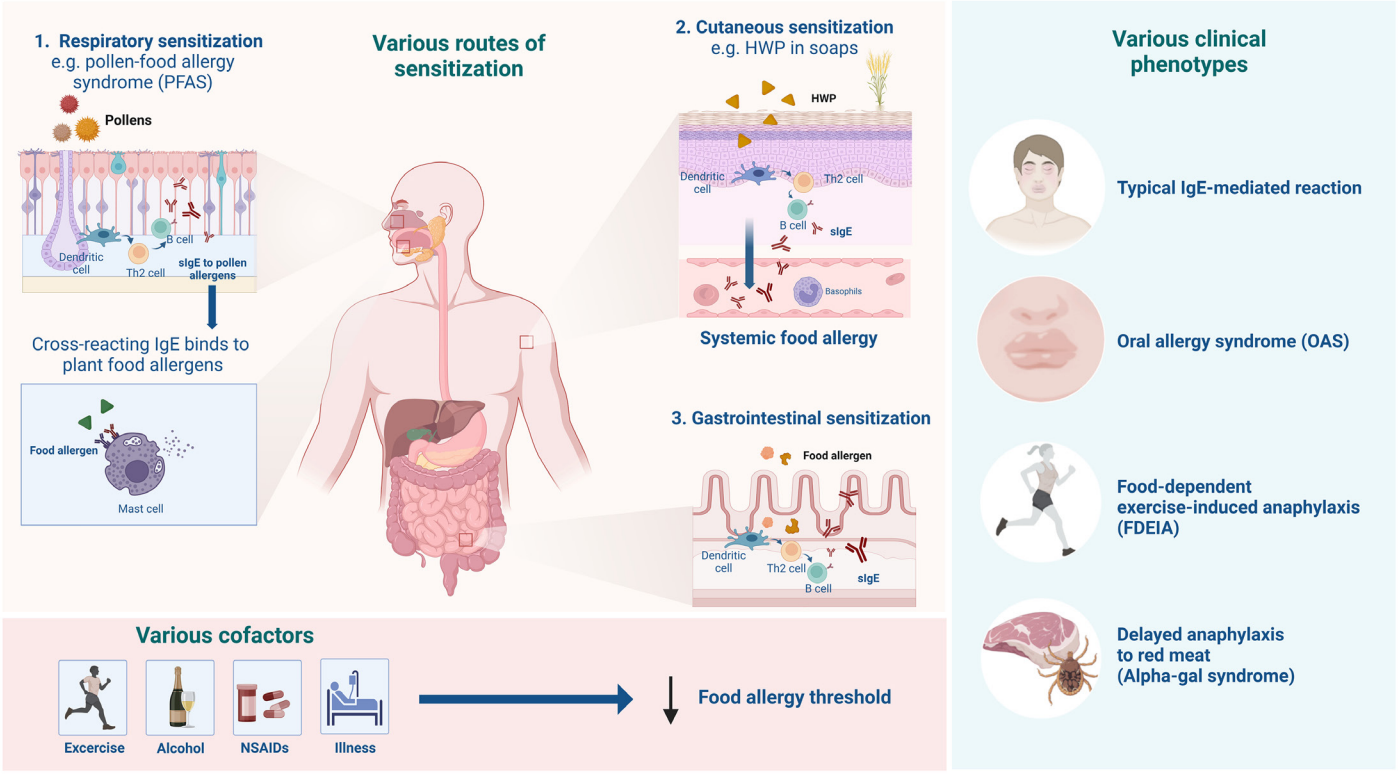

Figure 2. Unique characteristics of food allergies in adults.

Notes: Food allergies in adults had unique characteristics, including various routes of sensitization, various cofactors, and various clinical phenotypes. At least 3 routes of allergen sensitization in food allergy were demonstrated. Gastrointestinal sensitization (defined as type I food allergy) represents the classic route of food allergy by which allergens penetrate via gut epithelium. Respiratory sensitization (e.g., pollen food allergy syndrome, PFAs) represents sensitization by pollen allergen in nasal mucosa produces sIgE to pollens that cross-react to the protein structure of plant food. Cutaneous sensitization (e.g., hydrolyzed wheat protein allergy in soap) represents wheat protein in soap penetration of the skin barrier, after which the protein is processed by the immune system, producing IgE in circulation, subsequently causing wheat allergy due to intake. The main cofactors that result in a decreased threshold of food allergy have been described including exercise, alcohol intake, non-steroidal anti-inflammatory drugs (NSAIDs) use, and acute illnesses.

The figure was created by Biorender.

Abbreviation: HWP, hydrolyzed wheat protein; NSAID, non-steroidal anti-inflammatory drugs; OAS, oral allergy syndrome; PFAS, pollen food allergy syndrome; WDEIA, wheat-dependent exercise-induced anaphylaxis.

primary sensitization and then possible cross-reaction with deamidated peptide from gluten in food, triggering an allergic reaction.[17] Alpha gal syndrome also represents this pathophysiologic mechanism of food allergy. Alpha gal is an oligosaccharide present in tissues of non-primate mammals. Bitten by the lone star tick (*Amblyomma americanum*), the bitten person subsequently produces Alpha-gal molecule-sIgE, causing delayed anaphylaxis after red meat consumption.[18] Apart from sensitization via the gut and skin, the airway is also an important route of sensitization. Inhalation of aeroallergens can not only cause the development of asthma and allergic rhinitis, but they can also cause sensitization and cross-reactivity with food, leading to food allergy.[19] Cross-reactive aeroallergens can originate from plant, such as grass, birch, and latex, from fungus, and from animals, such as house dust mite and mammalian epithelium.[19] sIgE molecules from sensitization to pollen-derived epitopes were cross-reactive with vegetable- or fruit-protein epitopes.[5] The prototype of pollen-related food allergies is the birch-fruit-vegetable syndrome. Cross-reactivity of allergen Bet v 1 from birch pollen (*Betula verrucosa*) and homologues in Rosacea family fruit (e.g, cherry, apple, peach, and pear) cause immediate-type food allergic reactions, i.e., oral allergy syndrome, in which localized oral symptoms occur where the culprit food contacts the mucosa, causing a syndrome possibly including itching and swelling of lips, tongue, and throat, as well as abdominal pain. Systemic reactions were infrequent due to the breakdown of food allergens by digestive enzymes, and systemic reactions involved urticaria, respiratory wheezing, or anaphylaxis.[1,20]

Cofactor-dependent food allergy and anaphylaxis are responsible for approximately 30% of all anaphylaxes in adults with several cofactors playing important roles in modulating the onset and severity of reactions,[21] of which food-dependent exercise-induced anaphylaxis (FDEIA) is a classic model. Common cofactors in the adult are drugs (e.g., non-steroidal inflammatory drugs and proton pump inhibitors), alcohol, physical exercise, stress, infection, and others, including sleep deprivation, dehydration, and menstruation.[22] The main mechanisms of cofactor-dependent food allergy are that the cofactors can increase allergen uptake. Moreover, cofactors can decrease the reaction threshold at the cellular level, leading to mast cell and basophil activation, and could cause hyperosmolar conditions, resulting in increased basophil histamine releasability. These mechanisms allow lower thresholds of eliciting doses of food allergens and sometimes more severe reactions.[21,22] The unique characteristics of adult food allergy include various possible routes of sensitization, cofactors, and clinical phenotypes, as demonstrated in **Figure 2**.

Diagnosis

The first-line approach to food allergy diagnosis is a thorough and focused clinical history and physical examination. History taking is crucial to distinguish food allergy from food intolerance, to determine the possible underlying pathophysiologic mechanisms, and to identify specific causes and cofactors. Allergy-focused information is summarized in **Table 3**. The most frequent symptoms of IgE-mediated food allergy were urticaria and angioedema.[23] Reproducible IgE-mediated food allergy symptoms after exposure to the same food, especially only one pure food allergen ingredient, markedly increase the pre-test probability of IgE-mediated food allergy triggered by that culprit food.[24-26] A combination of a thorough history and evidence of IgE sensitization (i.e., skin prick test (SPT) with commercial extract, prick-prick with food, or food-sIgE) may suffice in the diagnosis of probable IgE-mediated food allergy to advise food elimination, especially in patients with a severe patient self-reported reaction. However, oral food challenge (OFC) remains the gold standard for confirmed diagnosis. In the case of equivocal skin test or food-sIgE results, an OFC test should be performed to confirm the culprit food and plan for management.

Table 3. An essential history for food allergy diagnosis.

Event-related information • Details of events (i.e., symptoms, time of the meal, and severity) • Cofactors (e.g., exercise, alcohol, NSAIDs, and acute illness) • Onset of reaction after ingestion
Food-related information • Name of suspected food/dish, ingredients • Names of accompanying sauces, dressings, side dishes, fruits, and beverages • Amount of food intake
Previous treatment • Medications are given during treatment episodes (e.g., H1-antihistamine, corticosteroid, and epinephrine) • Number of hospital visits
Other allergic diseases and co-morbidities

Abbreviation: NSAID, non-steroidal anti-inflammatory drug;

Many factors modulate the manifestations of food-related symptoms, leading to difficulty in diagnosing food allergies. **Table 4** shows factors associated with the unstable nature of food-related symptoms between exposure events. Oral mite anaphylaxis, or pancake syndrome, is a syndrome with severe allergic reactions from ingestion of mite-contaminated wheat flour, especially stored flour. The risk of reaction is increased if ingesting more than 500 mites per gram of flour, or 1 mg of mite allergen.[27]

The syndrome can be discriminated from wheat allergy by a positive test of IgE-mediated sensitization to mite allergens, a positive skin test of the culprit flour, a negative skin test of wheat and uncontaminated flour, and positive microscopic identification of mites.[28] The definite diagnosis work-up benefits those without true food allergies because of avoiding unnecessary avoidance of related foods.

Table 4. Factors associated with the unstable nature of food-related symptoms between exposure events in adult food-allergic patients

Differential diagnosis of food allergy
Food allergy mimics: • A flare-up of concomitant urticaria, eczema, or respiratory allergies
Contamination of non-food allergens: • Oral mite anaphylaxis (pancake syndrome) • Histamine intolerance (including scombroidosis) • Drugs (NSAIDs, antibiotics) • Parasites (*Anisakis simplex*) • Shellfish toxic syndromes
Mast cell disorder: • Mastocytosis, mast cell activation syndrome (primary/secondary)
True IgE-mediated food allergy
Food-related factors: • Amount of food ingested to reach eliciting threshold • Differences of allergen among genus/species/cultivars • Method of preparation: raw, cooked, processed food, peeled/unpeeled fruit
Cofactor effects[21]: • Exercise • NSAIDs • Alcohol • Proton-pump inhibitors • Others-illness, sleep deprivation, menstruation, etc.
Varied amounts of hidden ingredients in complex recipes: • Broth cube: shellfish allergens • Curry paste: shellfish allergens • Soup, sukiyaki, shabu: shellfish flavor • Batter-fried food: wheat allergens • Dessert, beverages, fruits allergens
Food additives hypersensitivity • Food colorings: carmine, annatto • Flavors: ethyl vanillin, cinnamic aldehyde • Preservatives: anti-browning (potassium metabisulfite), antimicrobial agents (benzoic acid) • Cannabis

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs;

The National Institute of Allergy and Infectious Diseases-sponsored expert panel report recommends performing standardized tests for diagnosis of IgE-mediated food allergy i.e., SPT, food-specific serum IgE and double-blind placebo-controlled food challenge (DBPCFC), but it does not recommend other non-standardized tests for routine investigation, such as the basophil activation test (BAT), lymphocyte stimulation, or provocation neutralization.[4] The tests are summarized in the following sections.

1. Skin prick test

The skin prick test (SPT), or the skin puncture test, is a convenient and highly sensitive method for detecting IgE-mediated food allergy.[29] A positive test provides the sensitization profile to the allergen extract, which is a simple liquid extract from a crude allergen source. Sensitivity, specificity, and predictive values have varied depending on the type of food. SPT of in-house preparations of food allergens (e.g., raw *P. monodon* and *M. rosenbergii* extracts) demonstrated a negative predictive value (NPV) of around 50 to 66.7%, but commercial allergens from *Paeneus aztecus* (Center Laboratory, Port Washington, NY) only demonstrated an NPV of 30% in Thai shrimp-allergic children.[30] A positive SPT without clinical correlation should not be considered a food allergy. On the other hand, a highly-suggestive clinical history, but negative SPT cannot exclude food allergy. A false negative test is not uncommon in food allergens, especially fruits and vegetables. Major fruit and vegetable allergens are heat- and acid-labile. They are easily degraded or denatured during the processing of commercial extracts. This resulted in poor diagnostic performance.[31] Therefore, prick-to-prick (PTP) testing is used to help diagnose fruit and vegetable allergies.[32] A previous study showed that the NPV of PTP may reach 100%.[30]

Skin tests using allergen components that are either recombinant or purified naturally-derived allergen components are available in some countries.[33] Both preparations have been evaluated and compared. Recombinant allergens are highly specific and aim to decrease false positive results by eliminating cross-reactive allergens.[34] However, the precise role of recombinant allergens as an *in vivo* diagnostic tool remains to be fully elucidated.[33]

2. Specific IgE to food allergens

sIgE can be measured for allergen extracts, allergen components, or allergen peptides.[35] The test provides a direct demonstration of IgE sensitization of allergens. The standard methods used for the detection of sIgE are immunoblotting as well as fluorescence enzyme assay, and both tests have a high agreement of 87% to 92.9% for food allergen components.[36] Two types of testing were demonstrated: sIgE to food extracts and sIgE to component-resolved diagnosis (CRD), a highly-pure single allergenic molecule. A molecular diagnosis (i.e., sIgE to CRD) may enhance the sensitivity of antibody testing in the case of low abundance or weak stability of the allergenic molecules, and some additionally offer improved selectivity and clinical assumptions (e.g., clinical severity). Similar to SPT, sIgE must have a clinical correlation for the diagnosis of food allergy. False-negative results depend on the level of sIgE (e.g., < 20 kU/L), an insufficient amount of allergen or non-presentation of the epitope of the allergen reagent, or the analytical performance of the assay.[37] Sensitivity, specificity, and predictive values varied by food type, and predictive values also vary by setting-specific prevalence.

3. Oral food challenge

The gold standard for food allergy diagnosis is OFC.[38] After risk-benefit considerations and discussion with patients and/or their families, OFC is useful and is suggested in the following situations: inconsistency between sIgE and/or SPT results and patient history, minimizing diet restriction, assessing food tolerability to cross-reactive foods/processed food, and determining the causal relationship between food allergens in chronic conditions such as atopic dermatitis or eosinophilic esophagitis and immediate reaction.[39] Safety should be considered first. Generally, OFC should be performed in a clinic well-equipped with emergency medications and well-trained, available medical staff, and the patient must be healthy on the day of OFC. Certain medications that might interfere with interpretation and/or treatment or worsen reaction severity should be discontinued for the suggested time, which is based on 5 half-lives.[39] For the aforementioned reasons, OFC is not ubiquitously available and is a resource-, and time-consuming. Proposed alternative diagnostic techniques will be discussed later.[39]

In clinical practice, either single-blinded (i.e., patient-blinded) or an open-food challenge is a proper diagnostic study. Generally, an open-food challenge is more convenient and practical than a single-blinded challenge. However, for some patients with co-existing medical conditions (e.g., psychological disorders) that might interfere interpretation of food challenges, a single-blinded protocol may be useful. DBPFC has the lowest risk of misclassification because neither doctor nor the patient knows whether food or placebo is administered. Thus, DBPFC is considered the gold standard test to diagnose food allergy, especially in research practice. As another variant of IgE-mediated food allergy, FDEIA may need a modified OFC protocol. An example protocol was proposed by Thongngarm et al.[40] Suggested stopping criteria that are considered positive results for food allergy are discussed elsewhere.

According to the current American Academy of Allergy, Asthma & Immunology OFC guideline,[39] open OFC with a cumulative dose equivalent to an age-appropriate serving of the food is suggested in general practice. A 4- or 6-dose protocol can be used depending on the history of a severe reaction. If there were a high probability of reaction or history of anaphylaxis, dividing food into at least 6 steps starting with less than 1% of the total dose is recommended (e.g., 1%, 4%, 10%, 20%, 30%, and 35% of the total). In the case of low-risk OFC, a 4-step protocol (i.e., 1/12th, 1/6th, 1/4th, and 1/2th of the total serving) can be performed typically at 15 to 30 minutes intervals apart for each dose. **Table 5** summarizes the comparative features of different OFC methods.

4. Other diagnostic techniques

Alternative diagnostic techniques for food allergy are currently a focus of attention. Bead-based epitope assay (BBEA), BAT, and mast cell activation test (MAT) are under investigation. Despite high sensitivity and specificity, BBEA is currently only available for peanuts. Thus, its use is limited to only specific groups of patients.[41] Several studies of BAT have demonstrated promising results, but variable specificity and sensitivity.[42,43] Despite its potentially good diagnostic

Table 5. Comparison of features of OFC method.

Feature	Method		
	Open OFC	Single-blinded OFC	Double-blinded OFC
Clinical setting	General clinical practice	Clinical practice complicated by patient's psychological concern	Research study
Blinding (to challenging food)	No	Only patients were blinded	Both patient and healthcare providers were blinded
Dosing protocol	Flexible	Flexible Food and placebo on separate days	Recommended protocol: Food and placebo on separate days
Food masking	No	Yes	Yes
Accuracy	Controversy: may be influenced by patient or observer bias (i.e., the physician's observer bias)	Controversy: may be influenced by observer bias (i.e., the physician's observer bias)	Gold standard
Advantages	Simple, convenient, and less expensive	Simpler than DBPFC. Decreases patient bias or influence by patient's comorbidities (e.g., psychiatric disorder) on adjudicating the outcome.	Lessens the possible risk of the psychological influence of patient or provider bias
Disadvantages	High risk of psychological influence	Possible risk of psychological influence	Complicated, resource-intensive, time-consuming, costly, and needs experienced personnel
Consider if…	Negative outcome is expected, or the purpose is to confirm an age-appropriate amount of food that can be eaten safely.		Positive or inconclusive outcome expected, previous consumption led to subjective/unconvincing objective symptoms, or comorbidities present that may influence the outcome, e.g., eczema or psychological disorders

Abbreviation: OFC, oral food challenge; DBPFC, double-blinded, placebo-controlled oral food challenge.

performance, BAT requires a trained immunologist to perform it, and it has no consensus on cut points. Another limitation of BAT is that fresh blood is required, resulting in inconvenience for use in daily clinical practice. The MAT test overcomes this limitation by using only serum or plasma instead of whole blood. However, the data on MAT testing in the literature are limited.

Management

The management checklist for food allergy is summarized in **Figure 3**.

1. **Avoidance.** The mainstay treatment is specific allergen avoidance. The avoidance plan must consist of reading food labels and asking questions about food preparations. When dining out, individuals with food allergies should tell the staff and present written chef cards to the chef/cook.[8] Currently, no prophylactic medications are recommended for IgE-mediated food allergy.

2. **Adrenaline (Epinephrine)**. A non-selective alpha- and beta-adrenergic receptor agonist is a cornerstone of treatment in severe allergic reactions.[44] Self-injectable epinephrine is available in form of either an epinephrine-prefilled syringe or an autoinjector with fixed doses of 0.3 mg and 0.5 mg. An epinephrine dose of 0.5 mg revealed a higher peak and larger area-under-the-curve plasma epinephrine level.[45] Epinephrine-prefilled syringes are cheaper and more available than autoinjectors. The epinephrine-prefilled syringe is physically and chemically stable and is sterile for at least 3 months in an opaque box. Previous studies proved this by high-performance liquid chromatography and by negative cultures for bacteria and fungus after 3 months.[46] Moreover, a recent prospective trial reported that caregivers were more successfully able to administer epinephrine-prefilled syringes than autoinjectors.[47] Patients with severe food allergy, especially anaphylaxis, or who are at risk of food allergy should be prescribed and self-carry 2 doses of self-injectable epinephrine.[48] Unlike drug allergy, avoidance of food allergen is not always easy because many recipes, especially Asian recipes, contain many ingredients mixed together. Thus, epinephrine should always be self-carried.

3. **Action plan**. Patients with potentially severe food allergies and their families or close friends/colleagues should be advised and given a clear written emergency action plan. The emergency action plan should clearly instruct when and how to inject epinephrine, explain avoidance measures and monitoring measures, and provide emergency contact and contact person details. This written action plan should always be self-carried by the patients.

4. **Advanced treatments.** There are many options for advanced treatments. Food allergen immunotherapy can be administered via oral, sublingual, or epicutaneous routes. Immunotherapy helps induce allergen-specific immune tolerance. The administration is by titrating the dose of food allergens, which leads to desensitization and thereby food tolerance. The immune system was shifted from allergen-specific Th2 to Th1 response and allergen-specific IgE to IgG4. For sustained unresponsiveness or anergy, regulatory T cells are

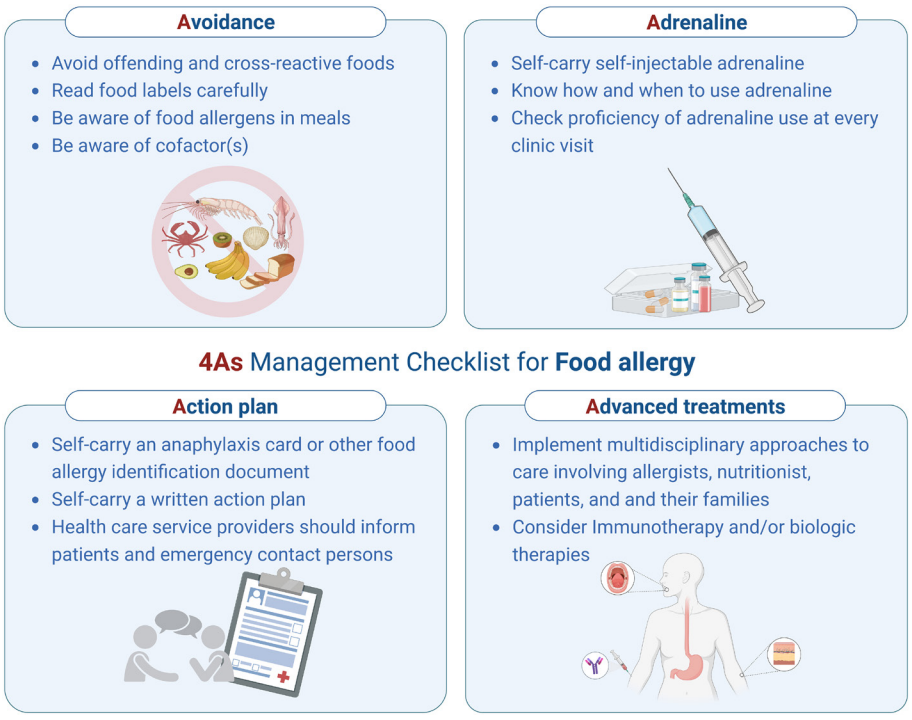

Figure 3. Management checklist of food allergy (4As).

Notes:- The figure was created by Biorender.

Table 6. Current evidence and ongoing studies of food immunotherapy efficacy in adults.

Author [year] (reference)	Type of food	Patients	Type/duration of active treatment	Number of participants	Route of IT	Outcomes
	Published studies					
Mempel [2003][68]	Kiwi fruit	Severe anaphylaxis	Case report/ 11 weeks	1	SLIT (kiwi fruit extract)	- ↓ SPT - ↑ sIgE and sIgG4 to kiwi
Enrique [2005][69]	Hazelnut	Immediate reaction to peach (OAS, 54.5%; SR, 45.5%)	DBRPCT/8-12 weeks	12	SLIT (hazelnut extract)	- ↑ amount of hazelnut to induce reactions - ↑ sIL-10 and sIgG4 to Hazelnut
Fernandez-Rivas [2009][70]	Peach	Immediate reaction to peach (OAS, 62.2%; SR, 37.8%)	DBRPCT/6 months	37	SLIT (Pru p3 extract)	- ↑ dose of Pru p3 extract to induce reactions - ↓ SPT - ↑ sIgE and sIgG4 to Pru p3 - Similar frequency of SR but higher LR in active group
Syed [2014][18]	Peanut	Immediate reaction	Open-label/24 months	23	OIT	- ↑ Treg function and hypomethylation of FOXP3
Mäntylä [2018][71]	Peanut Milk Egg	All systemic reaction	Open-label/515 days	Milk (10) Peanut (9) Egg (4)	Single OIT	- ↑ dose of milk (60-fold), peanut(8-fold), egg (35-fold) - Tended to ↓ sIgE, sIgG4 (NS)
Study name [year of trial pre-registration]; ClinicalTrials.gov identifier	**Ongoing trials**					
Oral Mucosal Escalation Goal Assessment (OMEGA) study [2020]; NCT04603300	Peanut	Immediate reaction	DBRPCT phase 1 / 48 weeks	NA	OMIT (toothpaste)	Safety of INT301, pharmacologic requirements, maximally tolerated dose, immunological profiles, and response to OFC
Salvage Peanut Oral Immunotherapy (SOIT) Study [2017]; NCT03251508, [2019] NCT04163562, [2020] NCT04222491, and [2021] NCT04974970	Peanut	Immediate reaction	Open-label [NCT03251508 (6 months), NCT04974970 (3 months), NCT04222491 (NR)], DBPRCT [NCT04163562 (6 months)]	NA	OIT	Safety profile, compliance, immunological profiles (sIgE, sIgG4, SPT, BAT) dose and result of OFC, desensitization
Food Allergen OIT for Shrimp and Cashew (MOTIF) [2018]; NCT03504774	Shrimp, or cashew	Immediate reaction	Open-label/ 52 weeks	NA	Single OIT	Immunological profiles (Expression of CD28 on CD4+ allergen specific (CD154+) T cells, cytokine levels)
Immunological Response After Shrimp Oral Immunotherapy Treatment Study [2020]; NCT04552522	Shrimp	Immediate reaction	Open-label/ 12 months	NA	OIT	Immunological profiles from desensitized patients

Abbreviations: OAS, oral allergy syndrome; SR, systemic reaction; LR, localized reaction; sIgE, specific IgE; sIgG4, specific IgG4; NA, not applicable; DBRPCT, double-blinded, randomized, placebo-controlled trial; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; Treg, regulatory T cells; NS, not significant; IT, immunotherapy; BAT, basophil activation test

developed and effector T cells are depleted.[49] Oral immunotherapy, sublingual immunotherapy, and epicutaneous immunotherapy are currently under investigation. Data on the efficacy of immunotherapy and protocols in adults are limited. Most studies enrolled mainly children and adolescents and were small sample sizes. A summary of the efficacy of immunotherapy for food allergy is shown in **Table 6**. In addition, biological therapies (e.g., anti-IgE, omalizumab, and anti-IL33, etokimab) as adjunctive therapy to immunotherapy (e.g., ClinicalTrials.gov identifiers: NCT03679676, NCT03682770, NCT03881696, and NCT04045301) or monotherapy (e.g., ClinicalTrials.gov identifiers: NCT04984876 for ligelizumab and NCT03793608 for dupilumab) have been investigated for food allergy.[50,51] Omalizumab, an anti-IgE humanized monoclonal antibody, is one of the most investigated biological treatments for food allergy. Sampson et al. conducted a 4-week randomized double-blinded, placebo-controlled study in peanut-allergic adolescents and adults using omalizumab monotherapy and found that active treatment groups had an 80-fold improvement in the tolerated dose of peanut proteins at 24 weeks compared with baseline while placebo groups experienced only a 4-fold improvement.[52] Fiocchi et al. conducted a retrospective observational study in pediatric patients who used omalizumab for 4 months and also found a similar trend in the efficacy of omalizumab for egg-, milk-, baked milk-, and wheat-allergic patients. In addition to improvement in tolerated dose, health-related quality of life was also significantly improved.[53] The results of biological therapies were promising. However, the body of evidence is currently insufficient to support the use of biological therapies in routine clinical practice.

Knowledge gaps and future directions

In light of current knowledge, adult food allergies tend to persist. However, high-quality, high-resolution data regarding the natural history of the disease are very limited, especially for adult-onset food allergies. Apart from OFC, the gold standard diagnostic method with a risk of a severe reaction, there are currently no alternative confirmatory diagnostic tests for food allergy. The use of biological therapies is also drawing attention in clinical practice, but large, standardized clinical trials are also very limited. The ultimate goal of treatment for food allergy is to induce permanent tolerance to the culprit food. Currently, although specific immunotherapy provides a period of desensitization or increases the threshold for food allergy, it has not yet achieved the most desirable status of long-term, sustained unresponsiveness.[54] Further research should extensively focus on filling the gaps in understanding the natural history, developing improved, high-yield, and harmless diagnostic tests, as well as efficacious treatments with a view to sustained unresponsiveness to culprit foods to enhance the health-related quality of life of food allergic patients.

Conclusion

IgE-mediated food allergies in adults frequently have severe reactions and unique phenotypes. Many factors complicated the diagnosis and management. We encouraged more research on novel treatments, the natural history, and measures to prevent new-onset food sensitization and allergies in adulthood.

Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

Not applicable

Acknowledgments

We would like to thank Dr. Anthony Tan for editing the English language.

Conflicts of Interest

All authors declare no personal or professional conflicts of interest relating to this review article.

References

1. Kivity S. Adult-onset food allergy. Isr Med Assoc J. 2012;14(1):70-2.
2. Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food Allergy from Infancy Through Adulthood. J Allergy Clin Immunol Pract. 2020; 8(6):1854-64.
3. Sampath V, Abrams EM, Adlou B, Akdis C, Akdis M, Brough HA, et al. Food allergy across the globe. J Allergy Clin Immunol. 2021;148(6): 1347-64.
4. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. J Allergy Clin Immunol. 2010;126(6):1105-18.
5. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol. 2016;16(12):751-65.
6. Schäfer T, Böhler E, Ruhdorfer S, Weigl L, Wessner D, Heinrich J, et al. Epidemiology of food allergy/food intolerance in adults: associations with other manifestations of atopy. Allergy. 2001;56(12):1172-9.
7. Ebisawa M, Ito K, Fujisawa T, Ebisawa M, Ito K, Fujisawa T, et al. Japanese guidelines for food allergy 2020. Allergol Int. 2020;69(3):370-86.

8. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41-58.
9. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and Severity of Food Allergies Among US Adults. JAMA Netw Open. 2019;2(1):e185630.
10. Kamdar TA, Peterson S, Lau CH, Saltoun CA, Gupta RS, Bryce PJ. Prevalence and characteristics of adult-onset food allergy. J Allergy Clin Immunol Pract. 2015;3(1):114-5.e1.
11. Vierk KA, Koehler KM, Fein SB, Street DA. Prevalence of self-reported food allergy in American adults and use of food labels. J Allergy Clin Immunol. 2007;119(6):1504-10.
12. Verrill L, Bruns R, Luccioli S. Prevalence of self-reported food allergy in U.S. adults: 2001, 2006, and 2010. Allergy Asthma Proc. 2015;36(6): 458-67.
13. Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ, Nadeau KC. Molecular and cellular mechanisms of food allergy and food tolerance. J Allergy Clin Immunol. 2016;137(4):984-97.
14. Ramesh M, Lieberman JA. Adult-onset food allergies. Ann Allergy Asthma Immunol. 2017;119(2):111-9.
15. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nat Rev Immunol. 2021;21(11):739-51.
16. Kubo A, Nagao K, Amagai M. Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. J Clin Invest. 2012;122(2): 440-7.
17. Yagami A, Aihara M, Ikezawa Z, Hide M, Kishikawa R, Morita E, et al. Outbreak of immediate-type hydrolyzed wheat protein allergy due to a facial soap in Japan. J Allergy Clin Immunol. 2017;140(3):879-81.e7.
18. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). The Journal of allergy and clinical immunology. 2014;133(2):500-10.
19. Faber MA, Van Gasse AL, Decuyper, II, Sabato V, Hagendorens MM, Mertens C, et al. Cross-Reactive Aeroallergens: Which Need to Cross Our Mind in Food Allergy Diagnosis? J Allergy Clin Immunol Pract. 2018;6(6):1813-23.
20. Price A, Ramachandran S, Smith GP, Stevenson ML, Pomeranz MK, Cohen DE. Oral allergy syndrome (pollen-food allergy syndrome). Dermatitis. 2015;26(2):78-88.
21. Shin M. Food allergies and food-induced anaphylaxis: role of cofactors. Clin Exp Pediatr. 2021;64(8):393-9.
22. Kulthanan K, Ungprasert P, Jirapongsananuruk O, Rujitharanawong C, Munprom K, Trakanwittayarak S, et al. Food-Dependent Exercise-Induced Wheals, Angioedema, and Anaphylaxis: A Systematic Review. J Allergy Clin Immunol Pract. 2022;10(9):2280-96.
23. Alexiou A, Höfer V, Dölle-Bierke S, Grünhagen J, Zuberbier T, Worm M. Elicitors and phenotypes of adult patients with proven IgE-mediated food allergy and non-immune-mediated food hypersensitivity to food additives. Clin Exp Allergy. 2022;52(11):1302-1310.
24. Panel NI-SE, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-58.
25. Begin P, Nadeau KC. Diagnosis of food allergy. Pediatr Ann. 2013;42(6): 102-9.
26. Umemneku Chikere CM, Wilson K, Graziadio S, Vale L, Allen AJ. Diagnostic test evaluation methodology: A systematic review of methods employed to evaluate diagnostic tests in the absence of gold standard - An update. PLoS One. 2019;14(10):e0223832.
27. Sanchez-Borges M, Capriles-Hulett A, Fernandez-Caldas E, Suarez-Chacon R, Caballero F, Castillo S, et al. Mite-contaminated foods as a cause of anaphylaxis. J Allergy Clin Immunol. 1997;99(6 Pt 1): 738-43.
28. Sánchez-Borges M, Suárez-Chacon R, Capriles-Hulett A, Caballero-Fonseca F, Iraola V, Fernández-Caldas E. Pancake syndrome (oral mite anaphylaxis). World Allergy Organ J. 2009;2(5):91-6.
29. Waserman S, Watson W. Food allergy. Allergy Asthma Clin Immunol. 2011;7 Suppl 1(Suppl 1):S7.
30. Jirapongsananuruk O, Sripramong C, Pacharn P, Udompunturak S, Chinratanapisit S, Piboonpocanun S, et al. Specific allergy to Penaeus monodon (seawater shrimp) or Macrobrachium rosenbergii (freshwater shrimp) in shrimp-allergic children. Clin Exp Allergy. 2008;38(6): 1038-47.
31. IV CFS, Gupta M, Sanders GM. Immunoglobulin E-mediated food allergy diagnosis and differential diagnosis. J Food Allergy. 2020;2(1): 26–30.
32. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014; 134(5):1016-25.e43.
33. Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, et al. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. World Allergy Organ J. 2020;13(2):100080.
34. Curin M, Garib V, Valenta R. Single recombinant and purified major allergens and peptides: How they are made and how they change allergy diagnosis and treatment. Ann Allergy Asthma Immunol. 2017; 119(3):201-9.
35. Foong RX, Dantzer JA, Wood RA, Santos AF. Improving Diagnostic Accuracy in Food Allergy. J Allergy Clin Immunol Pract. 2021;9(1): 71-80.
36. Wongpiyabovorn J, Suratannon N, Boonmee S, Chatchatee P. Comparison of specific IgE detection by immunoblotting and fluorescence enzyme assay with in vivo skin prick test. Asian Pac J Allergy Immunol. 2018;36(3):159-65.
37. Molecular Allergology User's Guide 2.0 [Internet]. EAACI Knowledge Hub. [cited 2022 Nov 11]. Available from: https://hub.eaaci.org/resources_guidelines/molecular-allergology-users-guide-2-0/
38. Calvani M, Bianchi A, Reginelli C, Peresso M, Testa A. Oral Food Challenge. Medicina (Kaunas). 2019;55(10):651.
39. Bird JA, Leonard S, Groetch M, Assa'ad A, Cianferoni A, Clark A, et al. Conducting an Oral Food Challenge: An Update to the 2009 Adverse Reactions to Foods Committee Work Group Report. J Allergy Clin Immunol Pract. 2020;8(1):75-90 e17.
40. Thongngarm T, Wongsa C, Pacharn P, Piboonpocanun S, Sompornrattanaphan M. Clinical Characteristics and Proposed Wheat-Cofactor Challenge Protocol with a High Diagnostic Yield in Adult-Onset IgE-Mediated Wheat Allergy. J Asthma Allergy. 2020; 13:355-68.
41. Sindher SB, Long A, Chin AR, Hy A, Sampath V, Nadeau KC, et al. Food allergy, mechanisms, diagnosis and treatment: Innovation through a multi-targeted approach. Allergy. 2022;77(10):2937-48.
42. Santos AF, Alpan O, Hoffmann HJ. Basophil activation test: Mechanisms and considerations for use in clinical trials and clinical practice. Allergy. 2021;76(8):2420-32.
43. Sato S, Yanagida N, Ebisawa M. How to diagnose food allergy. Curr Opin Allergy Clin Immunol. 2018;18(3):214-21.
44. Sicherer SH, Simons FE. Self-injectable epinephrine for first-aid management of anaphylaxis. Pediatrics. 2007;119(3):638-46.
45. Patel N, Isaacs E, Duca B, Mohammed H, Nagaratnam N, Donovan J, et al. What Dose of Epinephrine? Safety and Pharmacokinetics of 0.5 mg versus 0.3 mg Epinephrine by Autoinjector in Food-allergic Teenagers: a Randomized Cross-over Trial. J Allergy Clin Immunol. 2020 Feb;145(2):AB6.
46. Kerddonfak S, Manuyakorn W, Kamchaisatian W, Sasisakulporn C, Teawsomboonkit W, Benjaponpitak S. The stability and sterility of epinephrine prefilled syringe. Asian Pac J Allergy Immunol. 2010;28(1): 53-7.
47. Suwan P, Praphaiphin P, Chatchatee P. Randomized comparison of caregivers' ability to use epinephrine autoinjectors and prefilled syringes for anaphylaxis. Asian Pac J Allergy Immunol. 2018;36(4):248-56.
48. Song TT, Lieberman P. Who needs to carry an epinephrine autoinjector? Cleve Clin J Med. 2019;86(1):66-72.
49. Costa C, Coimbra A, Vítor A, Aguiar R, Ferreira AL, Todo-Bom A. Food allergy—From food avoidance to active treatment. Scand J Immunol. 2020;91(1):e12824.
50. Passanisi S, Caminiti L, Zirilli G, Lombardo F, Crisafulli G, Aversa T, et al. Biologics in food allergy: up-to-date. Expert Opin Biol Ther. 2021; 21(9):1227-35.
51. de Silva D, Singh C, Arasi S, Muraro A, Zuberbier T, Ebisawa M, et al. Systematic review of monotherapy with biologicals for children and adults with IgE-mediated food allergy. Clin Transl Allergy. 2022;12(9):e12123.
52. Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol. 2011;127(5):1309-10 e1.

53. Fiocchi A, Artesani MC, Riccardi C, Mennini M, Pecora V, Fierro V, et al. Impact of Omalizumab on Food Allergy in Patients Treated for Asthma: A Real-Life Study. J Allergy Clin Immunol Pract. 2019; 7(6):1901-9 e5.
54. Barbarot S, Wollenberg A, Silverberg JI, Deleuran M, Pellacani G, Armario-Hita JC, et al. Dupilumab provides rapid and sustained improvement in SCORAD outcomes in adults with moderate-to-severe atopic dermatitis: combined results of four randomized phase 3 trials. J Dermatolog Treat. 2022;33(1):266-77.
55. Bedolla-Barajas M, Bedolla-Pulido TR, Camacho-Peña AS, González-García E, Morales-Romero J. Food hypersensitivity in mexican adults at 18 to 50 years of age: a questionnaire survey. Allergy Asthma Immunol Res. 2014;6(6):511-6.
56. Messina M, Venter C. Recent Surveys on Food Allergy Prevalence. Nutr Today. 2020;55(1):22–9.
57. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St. Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol. 2012;130(4):986-8.
58. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69(8):992-1007.
59. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69(1):62-75.
60. Spolidoro GCI, Amera YT, Ali MM, Nyassi S, Lisik D, Ioannidou A, et al. Frequency of food allergy in Europe: An updated systematic review and meta-analysis. Allergy. 2022.
61. Lyons SA, Burney PGJ, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L, Clausen M, et al. Food Allergy in Adults: Substantial Variation in Prevalence and Causative Foods Across Europe. J Allergy Clin Immunol Pract. 2019;7(6):1920-1928.e11.
62. Wu TC, Tsai TC, Huang CF, Chang FY, Lin CC, Huang IF, et al. Prevalence of food allergy in Taiwan: a questionnaire-based survey. Intern Med J. 2012;42(12):1310–5.
63. Jiangzuo L, Qiuyu Z, Yanjun G, Junjuan W, Guirong L, Tao H, et al. Meta-Analysis: Prevalence of Food Allergy and Food Allergens — China, 2000–2021. China CDC Wkly. 2022;4(34):766-70.
64. Mahesh PA, Wong GW, Ogorodova L, Potts J, Leung TF, Fedorova O, et al. Prevalence of food sensitization and probable food allergy among adults in India: the EuroPrevall INCO study. Allergy. 2016;71(7):1010-9.
65. Althumiri NA, Basyouni MH, AlMousa N, AlJuwaysim MF, BinDhim NF, Alqahtani SA. Prevalence of Self-Reported Food Allergies and Their Association with Other Health Conditions among Adults in Saudi Arabia. Int J Environ Res Public Health. 2021;18(1):347.
66. Woods RK, Abramson M, Bailey M, Walters EH. International prevalences of reported food allergies and intolerances. Comparisons arising from the European Community Respiratory Health Survey (ECRHS) 1991-1994. Eur J Clin Nutr. 2001;55(4):298-304.
67. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100472.
68. Mempel M, Rakoski J, Ring J, Ollert M. Severe anaphylaxis to kiwi fruit: Immunologic changes related to successful sublingual allergen immunotherapy. J Allergy Clin Immunol. 2003;111(6):1406-9.
69. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol. 2005;116(5):1073-9.
70. Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, Diaz de Durana MD, Garcia BE, Gonzalez-Mancebo E, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009;64(6):876-83.
71. Mantyla J, Thomander T, Hakulinen A, Kukkonen K, Palosuo K, Voutilainen H, et al. The effect of oral immunotherapy treatment in severe IgE mediated milk, peanut, and egg allergy in adults. Immun Inflamm Dis. 2018;6(2):307-11.