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FOOD ALLERGIES, PATHOPHYSIOLOGY, DIAGNOSIS AND MANAGEMENT

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ABSTRACT

Food allergy is a condition with significant social and economic impact and a topic of intense concern for scientists and clinicians alike. Worldwide, over 220 million people suffer from some form of food allergy, but the number reported is just the tip of the iceberg. Recent years have brought new perspectives in diagnosing food allergy. Elucidating incriminated immunological mechanisms, along with drawing the clinical phenotype of food hypersensitivity reactions ensures an accurate diagnosis of food allergy. Moreover, molecular based allergy diagnosis, which is increasingly used in routine care, is a stepping-stone to improved management of food allergy patients. The aim of this review is to summarize the topic of IgE-mediated food allergy from the perspective of current diagnostic methods.

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INTRODUCTION

Food allergy is defined as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food"¹ or as "an adverse reaction to food in which immunologic mechanisms have been demonstrated"². These reaction can be considered toxic or nontoxic (Figure 1).³ Food allergy is increasing in prevalence⁴ for reasons that are not yet clear. One in 10 Australian children had a food allergy at one year of age⁵. The most common forms of immune-mediated adverse reactions to foods (type I reactions)

always are characterized by the development of IgE against food allergens.

Patients with IgE-associated food allergy can be identified based on the detection of food allergen-specific IgE in serum and body fluids, and by measuring IgE-mediated cellular and in vivo responses.⁶ 10.8% (>26million) of US adults are food allergic, whereas nearly 19% of adults believe that they have a food allergy.⁷

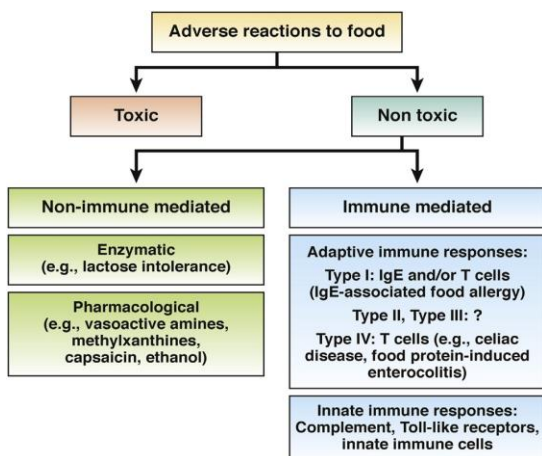


Figure 1. Classification of food intolerance. Adverse reactions to food can be classified as toxic or nontoxic reactions.³

The umbrella term of food hypersensitivity reactions encompasses “any adverse reaction to food”. Food allergy refers to the subgroup of reactions triggered by food allergens in which immunologic mechanisms are involved, IgE mediated, non IgE-mediated or mixed IgE and non IgE-Mediated. Non-allergic food hypersensitivity reactions, known in the past as “food intolerance”, have different etiologies, clinical

presentation and approach from immune mediated reactions to trophallergens.^{8,9}

Mechanism of Anaphylaxis

IgE-mediated food allergy is triggered by allergen cross-linking of IgE bound to the surface of mast cells or basophils. The most severe manifestation is anaphylaxis^{2,10,11}. Histamine correlates with anaphylaxis severity¹² and histamine receptor blockers are the first line treatment to relieve mild to moderate allergy symptoms.

Factors that contribute to the type and severity of re- actions include the amount of ingested allergen, the stability of the allergen against digestion, and the permeability of the epithelial barrier (Figure 2C). The immediate allergic reaction leads to intense inflammation that can become life- threatening. The release of vasoactive mediators into the circulation can lead to vascular collapse and anaphylactic shock.¹¹

Allergic Sensitization and Secondary Immune Responses

Two routes of allergic sensitization are well established (Figure 2A). Class 1 food allergens (eg, milk, egg, or peanut) are oral allergens that cause sensitization via the gastrointestinal tract.¹² Class 2 food allergens are aero- allergens (eg, major birch pollen allergen Bet v 1) that cause sensitization via the respiratory tract. Analyses of the time courses of allergic sensitization to respiratory and food allergen sources in large birth cohort studies have shown that food allergies and their associated symptoms develop before respiratory allergies.¹³

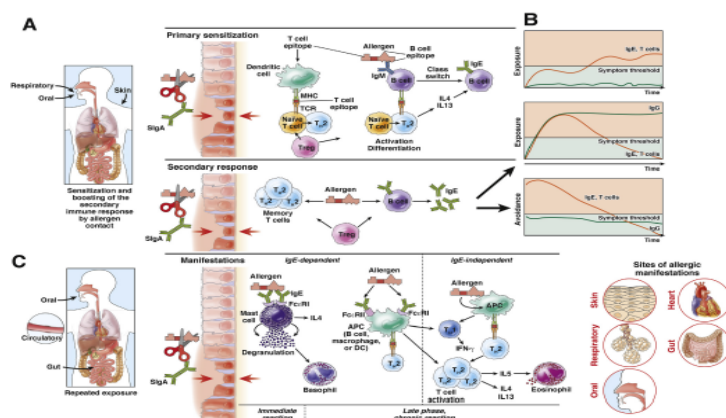


Figure 2. Time course, pathogenesis, and manifestations of food allergies. IgE-associated food allergies appear to develop early in childhood. This process is termed allergic sensitization. (A) Allergen contact via the gastrointestinal tract, via the respiratory tract, and eventually via the skin induces IgE production (primary sensitization) in genetically predisposed individuals. Repeated allergen contact activates allergen-specific T cells and induces IgE responses during the secondary immune response. Factors that affect the epithelial barrier (red arrows) and the extent to which allergens are digested or degraded are important for primary sensitization and boosting of secondary immune responses. SigA and T-regulatory cells may be important for exclusion of allergens from the intestinal lumen and induction of tolerance, respectively. (B) The balance between allergen-specific IgE and blocking IgG helps determine whether or not a patient will develop symptoms. Allergen avoidance could reduce levels of allergen-specific IgE to below the threshold for symptom induction (lower panel), whereas exposure could increase production of IgE, leading to symptoms (upper panel). If allergen exposure induces allergen-specific IgG, which blocks the interaction between the allergen and IgE, then symptoms might be reduced (middle panel). (C) Allergy symptoms are caused by repeated contact with the oral allergen, via the immediate allergic reaction (allergen-induced cross-linking of mast cell-bound IgE by allergen and then activation of allergen-specific T cells), and then by other inflammatory cells, such as eosinophils and basophils, during late-phase and chronic inflammation. Factors that affect the epithelial barrier and the extent of allergen degradation affect the amount of allergen intrusion and the magnitude and type of inflammation. After allergen ingestion, inflammation develops not only in the intestine, but in other organs, such as the skin, respiratory tract, and circulatory system (right). These allergens and allergen fragments are internalized and distributed throughout the body (left). MHC, major histocompatibility complex; T-reg, T-regulatory cell; TCR, T-cell receptor.

Figure 2. Time course, pathogenesis, and manifestations of food allergies¹³

Immune profile of food allergy

Food allergy is commonly referred to as a failure of oral tolerance, a systemic state of antigen-specific immune suppression that is mediated by regulatory T cells. However, there is little information on the role of Tregs in food allergy. Despite the fact that IgE plays a central role in the pathogenesis of food allergy, measurement of food-specific IgE is not diagnostic in isolation. Quantification of food-specific IgE antibody levels in serum can identify patients in the pediatric population who are highly likely (N95%) to experience clinical reactions to egg, milk, peanut or fish, as recently reviewed.¹³ However lower levels poorly discriminate between those who are sensitized versus allergic. Detection of IgE reactivity against components of food (for example the protein allergen Ara h 2 in peanut or Cor a 14 for hazelnut) improves specificity¹⁶⁻¹⁸.

Upon interaction with food antigens, IgE becomes cross-linked and binds to mast cells and basophils via the high-affinity receptor FcεRI (Figure 2C).¹⁹ This process activates these cells, leading to the release of granules that contain preformed inflammatory mediators (eg, histamine), as well as de novo synthesis and/or release of inflammatory mediators (eg, leukotrienes), proteases (eg, tryptase), inflammatory cytokines (eg, IL4), and chemotactic molecules. Mast cells and basophils are activated within a few minutes of IgE cross-linking, therefore this process is called an immediate allergic reaction; symptoms occur shortly after allergen contact.

Emerging evidence for the role of the skin in food allergy

Majority of patients with peanut or tree nut allergy experienced their first reaction the first time that the food was knowingly ingested, so previous sensitization to the allergen has been proposed to occur in utero, through breast-milk, or by another route of exposure, such as topical exposure. Eczema is a risk factor that strongly associated with food allergies.²⁰ Alteration of the skin barrier facilitates contact with the allergen.

High levels of environmental exposure to peanut due to household consumption during infancy have been related with sensitization.^{21,24} These peanut dust proteins are biologically active and able to activate immune system cells.²² Although environmental peanut exposure has been postulated as a risk factor for food allergies, exposure to allergens via the skin does not by default lead to sensitization. Other factors that promote sensitization through the skin include damage, such as that caused by tape stripping that models damage

induced by scratching in eczema. Some allergens can induce sensitization in the absence of any exogenous adjuvant or damage. Peanut or tree nuts can induce sensitization when applied topically.²⁵

Innate immune responses in the skin are critical for promoting sensitization to foods. In models driven by adjuvants or skin damage, TSLP, IL-6, and IL-1β contribute to the generation of Th2 and Tfh cells.^{25,26} Thus, multiple immunemechanisms by a variety of environmental triggers can lead to Th2 skewing and IgE production when allergen exposure occurs via the skin.

The dual exposure hypothesis of food allergy proposes that exposure through the skin promotes sensitization, while early exposure through the gastrointestinal tract is tolerogenic. This is supported by clinical findings that early consumption of food, such as peanuts, fish or wheat is associated with a lower incidence of food allergy.²⁷⁻²⁹ Study results showed a sustained protection from peanut allergy in those who had ingested peanut early in life.²³ The tolerogenic response to foods encountered through the gastrointestinal route in early life is consistent with the concept of oral tolerance, which is a state of antigen-specific systemic unresponsiveness that is mediated by Tregs educated by a tolerogenic population of gastrointestinal DCs.³⁰ See Fig. 3 for a schematic illustrating the site-dependent hypothesis of food allergy and tolerance.

It has been demonstrated that commensal bacteria regulate the production of IgE. There is evidence that a difference in microbial composition can increase susceptibility to food allergy. In this study, the authors showed that food allergy-prone mice with a gain-of-function mutation in the IL-4 receptor α-chain (Il4raF709) are susceptible to oral sensitization with OVA.³¹ The protective effect of commensal organisms has been shown to be regulated by metabolic products, such as short chain fatty acids³⁰, suggesting that factors such as high fiber diet that also promote short chain fatty acids may have a similar protective effect.

Role of dietary factors

The relationship between diet during infancy (other than the a

llergenic food itself) and development of allergic diseases remains poorly understood. Infants can be breast-fed, formula-fed, or experience the combination of both. According to the current food allergy and anaphylaxis guidelines of the European Academy of Allergy and Clinical Immunology,³¹ there are no restrictions regarding diet for mothers during pregnancy and lactation. The bacterial composition of the

breastmilk varies depending on maternal dietary habits, the genetic background, and demographic factors. Cessation of breastfeeding is a more significant factor in the composition of the intestinal microbiota than the

introduction of solid foods.³² There is a lack of unifying immune evidence on the impact of breastfeeding on development of food allergy.³³

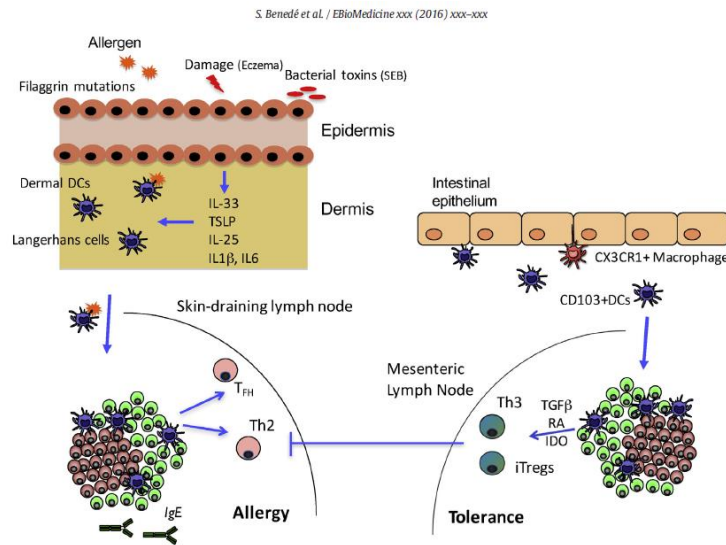


Figure 3. Allergen exposure through the skin in the presence of skin damage, filaggrin mutation or bacterial toxins (SEB) promotes sensitization. Depending on the nature of the allergen and adjuvant, epithelial cells produce cytokines that instruct dendritic cells on the skin. They transport the antigen to the skin-draining lymph nodes, where Th2 and T follicular helper (Tfh) cells are generated and promote IgE class-switching. Antigen exposure by oral route leads to tolerance. CX₃CR1+ macrophages sample antigen from the lumen and transfer it to CD103 + DCs that transport the antigen to the mesenteric lymph nodes and promote the induction of Tregs. Oral tolerance can prevent the development of sensitization through the skin.³³

Vitamin D deficiency is associated with food sensitization³⁶, as well as IgE-mediated food allergy.³⁷ Low vitamin D results in compromised barrier function, altered microbial composition of the gut, and together with effects on antigen presenting cells and T cells predisposes an individual to allergic responses to food

allergens.³⁷ Other dietary factors that suppress food allergy include aryl hydrocarbon receptor ligands, found in cruciferous vegetables such as cabbage, Brussels sprouts, and broccoli.³⁹ See Fig. 4 for a schematic illustrating the role of microbiota and the diet in allergy and tolerance to foods.

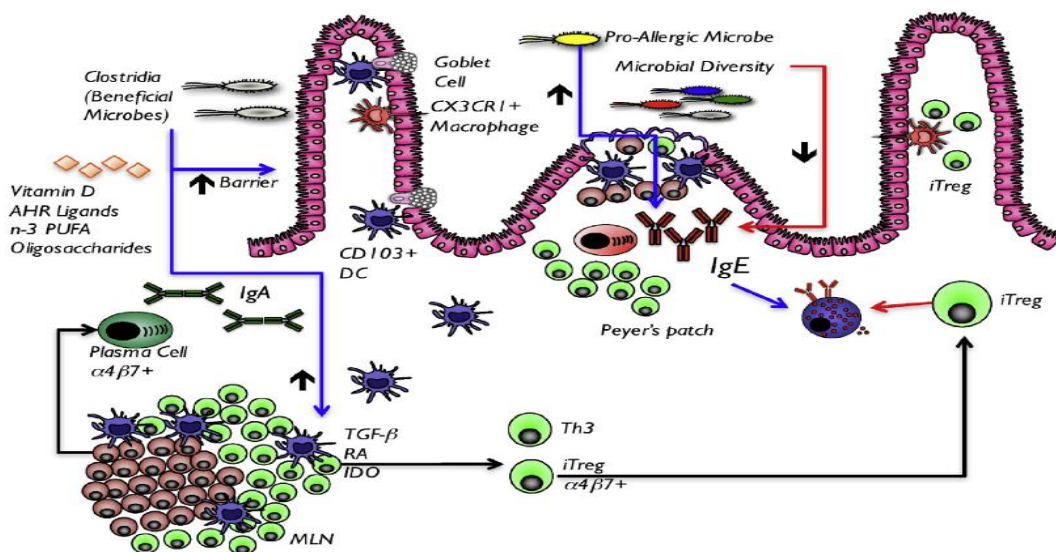


Figure 4. Microbiota and diet influence the development of allergy and tolerance. Microbial diversity suppresses IgE class-switching, which occurs within the Peyer's patch. Strains of bacteria including Clostridia have been shown to suppress allergy, and to enhance the generation of Tregs and improve epithelial barrier function. There is also evidence that microbial composition can promote food allergy, suggesting the role of pro-allergic bacteria. Nutrients including vitamin D, aryl hydrocarbon receptor (AHR) ligands, polyunsaturated fatty acids (PUFA) and oligosaccharides can also suppress food allergy through enhancement of regulatory responses.³⁵

Diagnosis and Management

Once a patient is diagnosed with a food allergy, it becomes important to identify the allergen(s) that cause the disorder and determine if it is mediated by IgE. If so, treatments for IgE-associated allergies can be selected (Figure 5). Oral provocation tests are the most accurate in the diagnosis of clinically relevant IgE-associated food allergies once allergen-specific IgE has been detected. Clinical history and examination are the first-line approach in diagnosing food allergy. The evaluation of a patient with suspected food allergy begins with obtaining a thorough clinical history that considers the symptoms indicative of allergic reactions to food. The clinical presentation of food allergy reactions varies within wide ranges and provides information about the incriminated mechanism (Table I).^{8,38,39,40}

Table 1. Food allergy – clinical presentation and mechanisms.

Pathology	Clinical presentation
1. IgE mediated	<ul style="list-style-type: none"> • Generalized – anaphylaxis, food associated, exercise-induced anaphylaxis; • Cutaneomucous – urticarial ± angioedema, contact urticaria, atopic dermatitis/eczema; • Digestive - oral allergy syndrome (pollen-associated food allergy syndrome), immediate gastrointestinal hypersensitivity; • Respiratory – allergic rhinitis, asthma. • Other¹
2. Non-IgE or cell-mediated	<ul style="list-style-type: none"> • Cutaneous – allergic contact dermatitis, atopic dermatitis/eczema; • Digestive – food protein induced-enterocolitis syndrome, food protein-induced allergic proctocolitis, Coeliac disease; • Respiratory - Heiner syndrome.
3. Combined IgE and cell-mediated	<ul style="list-style-type: none"> • Cutaneous – atopic dermatitis; • Digestive – allergic eosinophilic esophagitis, eosinophilic gastroenteritis.

¹An unusual form of delayed allergy to mammalian meat (which sets on about 4-6 hours after ingestion) has been recently described and linked to the production of IgE to alpha-gal protein, a carbohydrate found in beef, lamb and pork. This type of reaction was documented in individuals with a history of tick bite, so it was possible to elucidate the mechanism involved: exposure to certain proteins in tick saliva can induce a specific humoral immune response against alpha-gal. This results in delayed anaphylaxis after consumption of red meat

(38)

Currently the standard of care for food allergy is strict food avoidance and use of epinephrine injection pens for accidental exposures. The elimination diet is the most important and relevant long-term management

strategy for food allergies.³⁸ Once the offending food allergens have been identified the allergenic food must be avoided.

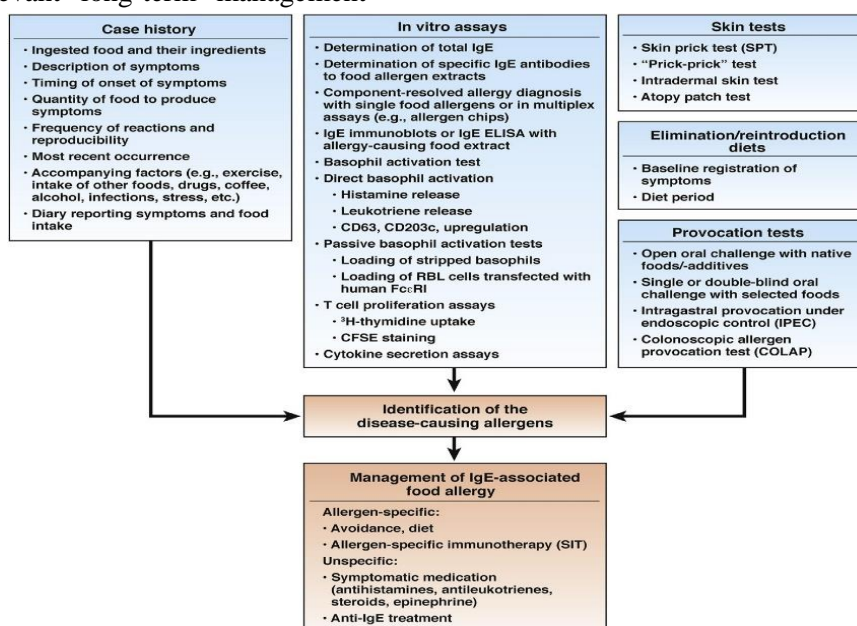


Figure 5. Diagnosis and management of IgE- associated food allergies.³⁸

Researchers have produced recombinant allergens comprising repertoires of the most common antigens. Instead of ill-defined allergen extracts, which are prepared from the allergen sources (eg, wheat, apple, milk, or peanuts) and consist of mixtures of various allergens and nonallergenic materials, pure allergen molecules are available for diagnosis and allergen-specific therapy. Purified recombinant allergens can be used to determine a patient's IgE reactivity profile. Many allergen sources contain antigens that have little or no clinical relevance because they are poor inducers of allergic reactions.

These include IgE-reactive carbohydrate epitopes without allergenic activity, or molecules that induce only mild or local symptoms. Other molecules

can induce severe systemic allergic reactions. Marker allergens have been identified from the most common food allergen sources (eg, apple, peanut, milk, and wheat). Marker allergens are those found only in specific sources, and can be used to confirm sensitizations to these sources. Other allergens are present in different food sources. Patients who are sensitized to these can develop symptoms after ingestion of seemingly unrelated foods. The diagnosis of food and other allergies has transitioned from the identification of allergen sources without knowledge of the molecules that cause the symptoms, to the precise identification of allergy-inducing molecules. These processes are called "component-resolved allergy diagnosis" and "molecular allergy diagnosis."

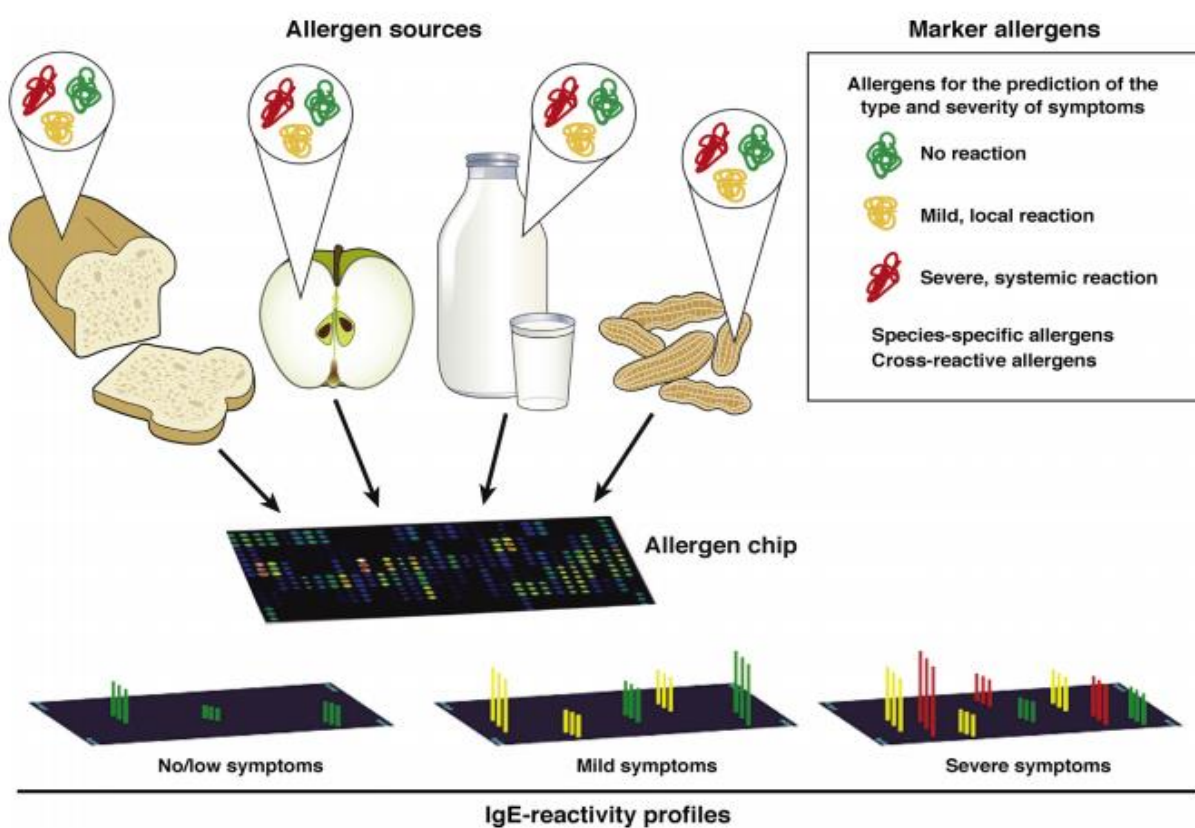


Figure 6. Component-resolved diagnosis of a food allergy. Different sources of food allergens contain several allergenic molecules (components); these can be produced as recombinant proteins or purified from natural sources. These allergens can be classified into IgE-reactive components (green), which are poor activators of inflammatory cells and therefore induce little or no clinical reactions; components that induce mild or mainly local symptoms (yellow); and components that often are associated with severe and systemic allergic reactions (red). Microarray technology can be used to determine reactivity profiles of patients. This process can be used to identify individual allergens that cause disease and foods to which patients are most likely to respond. The severity of reactions also can be predicted.³⁹

In vivo testing.

Skin prick tests (SPTs) are a fast and effective method of assessing sensitization to food allergens. Commercially prepared food extracts or fresh food can be used. In evaluating sensitisation to fruit and vegetables, or to food for which extracts are not available, the prick-to-prick method may be used with

fresh food or slurry made from food and sterile saline solution. SPTs are highly reproducible and less expensive than in vitro testing. Skin testing can be safely performed in patients of any age; it causes minimal patient discomfort, and yields results within 15 minutes. PTs for food allergens are highly sensitive (greater than 90%), but moderately specific (approximately 50%).

However, there are a few exceptions to this rule, as it was shown that a positive skin test indicates a greater than 95% likelihood of clinical reactivity in patients with a relevant clinical history to certain food and in whom sensitization to the respective food is documented (see Table II). In addition, the accuracy of negative predictive values provided by skin testing is uniformly high; a negative skin test to food excludes an IgE-mediated reaction by 90 to 95%. Thus, skin testing is highly useful to confirm the absence of an IgE-mediated food allergy. Apart from low specificity, SPTs were reported to lead to variable wheal sizes depending on the population and the food being studied.

Therefore, skin reactivity should not be interpreted as clinical reactivity. When considering the diagnosis of food allergy, the clinician should perform SPTs only for the suspected food allergens, and interpretation of results should be considered in the light of the clinical history. Determining the clinical relevance of sensitization is crucial to reducing over-diagnosis and unnecessary dietary eliminations. Intradermal testing to food is not recommended in the diagnosis algorithm of food allergy, because of the high rate of false-positive results, and the high risk of systemic life-threatening reaction. Atopy patch tests (APT) involve the topical application of a food-containing solution to the skin for 48 hours. Currently, there are no standardized reagents, application methods, or guidelines for interpretation of APTs. Although APT is not routinely recommended for investigating patients with suspected food allergy, it can be useful in assessing the relevance of food triggers in pediatric patients suffering from eosinophilic esophagitis.

In Vitro Testing

In vitro evaluation, or the determination of food-specific serum IgE (sIgE), prevails when in vivo testing is contraindicated or ineffective (extended dermatitis, dermographism, severe atopic dermatitis, medication that inhibits cutaneous reactivity). Radioallergosorbent tests (RASTs) and fluorescence enzyme immunoassay (FEIA) tests are in vitro assays used to identify food-specific IgE antibodies in the serum.

Serum IgE testing is an important adjunct tool in accurate identification of causal food allergens. Testing to large panels of food allergens disregarding the clinical history is not recommended, as false positive results can lead to unnecessary dietary elimination of safe food, and subsequently to unjustified nutritional deficiencies. Thus, selecting in vitro testing for sensitization to food should be based on medical history. The negative and positive predictive accuracy of in vitro testing varies

within wide ranges, with a few exceptions. Clinical studies have provided predictive thresholds for certain food (egg, milk, peanuts, nuts, and fish). These cut-offs correlate with clinical reactivity with a positive predictive value greater than 95% (Table II), which proves their utility in determining whether an open food challenge is warranted, and also to accurately advise patients. Overall, higher sIgE levels are more likely to indicate clinical reactivity. However, the predictive value of sIgE levels varies within wide ranges and with different factors (population, age, time since last ingestion of suspected food, other associated disorders). A negative result does not exclude the diagnosis. Arguing in favor of reintroduction of food based solely on negative sIgE results is not recommended because of the risk of systemic life-threatening allergic reactions. Both in vivo and in vitro testing only detect sensitization, not clinical allergy; they cannot predict prognosis or severity of subsequent reactions. It is of utmost importance that results be interpreted within the framework of the patient's clinical history.

Factors that dictate the impact of sensitization on the severity of the food allergy reaction (such as ingested amount, concomitance of other atopic diseases, asthma, general health) are currently the subject of study and interpretation. A recent study published in the *Journal of Allergy and Clinical Immunology* revealed that 1.6-10.1 mg of hazelnut, peanut or celery protein, and 27.3 mg of fish and 2.5 g of shrimp protein are needed to trigger allergic reaction in highly sensitized patients. This discovery is a new step in understanding food allergies and could also contribute to improving food labeling. In certain situations, as is the case of allergy to cow's milk, in dynamic results of in vivo and in vitro tests to sensitization along with the clinical context are factors with prognostic role in the natural history of the disease and provide important information on when to reintroduce the food into the diet. Other tests detecting sensitization include the basophil activation test (BAT), which evaluates the in vitro basophilic activation by specific allergens.

According to a recently published study, BAT effectively discriminates between allergy and tolerance in peanut-sensitized children, showing 97% accuracy, 95% positive predictive value, and 98% negative predictive value. Therefore, BAT promises to bring real improvement in diagnosing food allergy.

Component-resolved Diagnosis

The last decade brought about a "refining" of food allergy diagnosis by identifying clinically relevant allergenic fractions. Molecular-based allergy diagnostics

also referred to as component-resolved diagnostics (CRD), uses purified native or recombinant allergens to detect IgE sensitivity to individual allergen molecules. This method of investigation is not routinely recommended in diagnosing food allergy. However, it proved to increase the accuracy of food allergy diagnosis and establish sensitization patterns with particular prognostic outcomes in a relatively small number of foods. Recent studies propose Ara h2 (storage proteins found in peanuts), as well as Cor a 9 and Cor a 14 (hazelnuts) as the most common allergens to be associated with clinical reactivity, whereas Ara h8 (Bet v1 related) is more likely to cause mild, local reactions or to be tolerated. These findings suggest that component-resolved diagnosis has the potential to enhance diagnostic accuracy by discriminating between clinically significant and irrelevant sIgE results, as well as to enhance therapeutic approach by excluding the need for unnecessary open food challenges. Although the search for other clinically relevant molecules is needed and on going, studies are limited and inconsistencies exist. Thus, in certain geographic areas, such as the Mediterranean area, Ara h9 proved to be the major allergen, while a number of studies brought inconsistent CRD results across different parts of the world. Further studies are needed to define the clinical utility of component resolved diagnosis.

Elimination Diets

Elimination diets are used in the management of patients suffering from food allergies, as well as a part of evaluation for food allergy, and refer to the avoidance of incriminated food. Therefore, elimination diets target different aspects in clinical practice: removing one or several suspect food from a patient's diet is sometimes useful in determining if they are causing or exacerbating a condition; prescribing an "oligo-antigenic" diet in which food that is commonly-involved in allergic disorders is removed temporarily from the diet may be useful in the evaluation of patients with chronic conditions, such as atopic dermatitis or chronic urticaria, in which food allergy is suspected, but no specific food can be incriminated; elemental diets, such as extensively-hydrolyzed or amino acid-based formulas, are used by some allergy specialists in the evaluation of disorders associated with multiple food sensitivities, such as eosinophilic esophagitis. Such diets should only be prescribed with great caution, particularly in infants and children, to avoid nutritional deficiencies; complete removal of the suspected trophallergen is recommended prior to food challenges, to ensure that the specific food is not interfering with the ability to appreciate a reaction.

Although elimination diets can be used as an adjunctive mean of diagnosing food allergy, they cannot confirm the diagnosis on their own.

Supervised food challenges are structured protocols in which the patient ingests the suspected food under a clinician's supervision. They are sometimes required for the definitive diagnosis of food allergy, with double-blind placebo-controlled food challenge (DBPCFC) being the most accurate form of challenge. Food is selected for testing based upon the history and the results of skin and/or in vitro testing. DBPCFC is currently the "golden standard" in the diagnosis of food allergy. It helps identify the causative agent, the amount of food needed for a reaction / tolerated dose, and establish the significance of existence of co-factors (e.g. exercise in patients with food dependent anaphylaxis, induced by exercise). Challenge tests are often the only way to confirm the clinical relevance of sensitization. At the same time, they are time-consuming, resource-intensive and produce the risk of inducing systemic, severe allergic reaction.^{7,8} Food allergy has a characteristic and reproducible clinical presentation. Testing for food allergy is highly sensitive, but it has a low positive predictive value and often identifies clinically insignificant sensitization. The only life-saving treatment for food-induced anaphylaxis is epinephrine. Egg allergy is not a contraindication to influenza or measles-mumps-rubella vaccination. Allergies to milk, egg, soy and wheat will resolve in most instances; allergies to peanuts, tree nuts and seafood tend to persist. IgE-mediated food reactions occur when a food allergen binds allergen-specific IgE present on mast cells and basophils, which leads to the release of multiple mediators such as histamine. The reactions occur rapidly (within two hours) and may include one or more of cutaneous, respiratory, gastrointestinal or cardiovascular symptoms (Table 2). Symptoms resolve within hours and occur reproducibly with repeat exposure to the culprit food. An unusual exception to the otherwise rapid onset of symptoms is one form of allergy to red meat attributed to IgE anti-bodies against the sugar moiety galactose- α -1,3-galactose, where symptom onset is delayed two to six hours. Cutaneous symptoms are by far the most common. Although respiratory symptoms are often observed during a food allergy reaction, isolated chronic respiratory symptoms (e.g., asthma and rhinitis) are not typically attributable to food allergy. Headaches, chronic abdominal pain and chronic behavioural symptoms are unlikely to represent food allergy. Food allergy only accounts for about 20% of all acute urticaria and is not a likely cause of chronic urticaria (defined as frequent daily hives for more than

six weeks). Pollen–food allergy syndrome, also known as oral allergy syndrome, typically presents with isolated oropharyngeal symptoms (e.g., pruritus and mild angioedema) after ingestion of raw fruit or vegetables. The syndrome is due to protein cross-reactivity between

heat-labile proteins in food and in pollens. Most patients can tolerate the cooked form of the food because the causal protein is degraded by heat. Common associations include birch tree pollen with pitted fruit (e.g., apple, peach and pear) and ragweed pollen with melons.⁴¹

Table 2. Classification Of Food Allergy³⁷

Type of food allergy	Examples
IgE-mediated	Anaphylaxis, pollen–food allergy syndrome, contact urticaria
Non-IgE-mediated	Food protein-induced enterocolitis syndrome, food protein-induced proctocolitis
Mixed IgE- and non-IgE-mediated	Eosinophilic esophagitis

Table 3. Symptoms Of Food Allergy³⁷

Organ system	Examples
Cutaneous	Urticaria, angioedema, flushing, pruritus
Upper respiratory	Sneezing, rhinorrhea, congestion, conjunctivitis
Lower respiratory	Shortness of breath, wheeze, cough
Gastrointestinal	Nausea, vomiting, diarrhea, pain
Cardiovascular	Hypotension, syncope
Central nervous system	Sense of impending doom

Clinical food allergy management guidelines recommend intramuscular epinephrine as first line treatment for food-induced anaphylaxis. All patients diagnosed with a food allergy should be prescribed epinephrine because of the inability to accurately and reliably estimate the severity of future allergic reactions. Our data suggest that approximately one-quarter of adults with food allergy possess a current epinephrine prescription, with higher rates among adults reporting history of severe reactions and life time food allergy–related ED visits.^{7,37}

In light of the considerable economic and quality of life consequences associated with allergen avoidance and other food allergy management behaviors, individuals with a suspected food allergy should receive appropriate confirmatory testing and counseling to counter unnecessary avoidance of allergenic food. Greater patient education efforts regarding key differences between food intolerances and allergies also maybe warranted. Adults need to be encourage to see their physician to receive proper diagnosis, epinephrine prescription, and counseling for their food allergy. Given the increasing evidence for the

preventive benefit so fearly allergen exposure during infancy and potential treatment options, adults should be made aware of these new practices to potentially prevent food allergies in their children or consider treatments in the near future.^{7,37}

Allergen Immunotherapy

Allergen-specific immunotherapy (SIT) is currently the only allergen-specific and disease-modifying treatment that has long-term effects.³⁷ Allergen immunotherapy is an approach to desensitization in which increasing amounts of allergen are administered to reduce reactivity of allergic effector cells. A major limitation of SIT is the difficulty in preparation of effective and safe vaccines from natural allergen sources.³⁸ However, based on the knowledge of the structure of the disease-causing allergens, it has become possible to produce new forms of allergy vaccines based on purified allergen molecules (Figure 6).

Oral immunotherapy (OIT) provides effective desensitization allowing the majority of subjects to pass a full food challenge after 2–4 years of treatment. Other routes of immunotherapy, including the sublingual and

epicutaneous routes, demonstrate increased safety in comparison to OIT, but at a cost of lower efficacy³⁹. Recent advances in food immunotherapy research have given many patients and practitioners hope for a widely available treatment for food allergy. The studies presented in this review demonstrate that desensitization can be achieved in many patients undergoing either OIT or SLIT. Whereas individuals on OIT appear to reach higher challenge thresholds, have greater changes in immunologic measures of desensitization, and have a higher chance of achieving sustained unresponsiveness than those on SLIT, this is accompanied by an increase in the risk of both systemic reactions and intolerable gastrointestinal symptoms during treatment. While the studies conducted to date are promising, many risks need to be addressed before food immunotherapy should be used in clinical practice. Systemic reactions are known to occur unpredictably during treatment, and at present, it does not appear that food immunotherapy decreases the risk of systemic reactions compared to those practicing food avoidance. It is also unclear whether food immunotherapy, which requires frequent visits.⁴¹

The mechanisms by which allergen immunotherapy leads to clinical protection involves the production of blocking antibodies such as IgA and IgG⁴⁰, reduction in basophil and mast cell reactivity, generation of regulatory T cells⁴¹ and an altered DC phenotype facilitating increased Treg generation and reduced Th2 skewing.^{42,43}

Adjuvants and Immunomodulation

To date, immunotherapy has primarily been administered as allergen in the absence of other immunomodulation. Bacterial vectors carrying peanut allergens failed in human trials due to reactions to the therapy⁴³, despite many strategies to improve safety.

Microbial therapies

The finding that Clostridia strains can suppress allergy in mice^{44,45} suggests the potential use of microbial therapeutics to enhance the development of tolerance when given with allergen immunotherapy. There is currently a great interest in the potential of microbial therapeutics to prevent or treat allergic diseases.

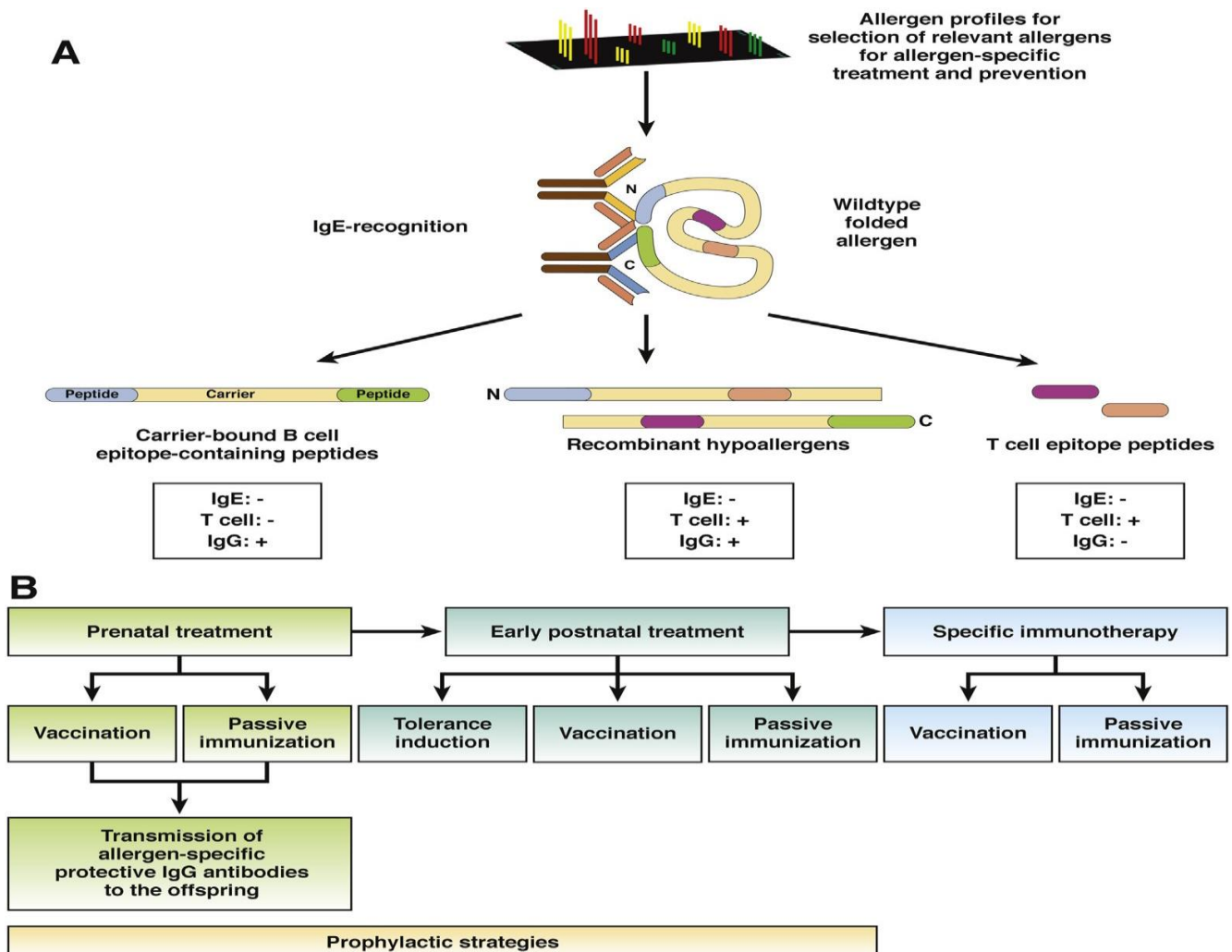


Figure 7. Allergen-specific forms of prophylaxis and treatment.⁴⁵

Future directions

Diet and composition of the microbiota are two major inter-related factors that can modify susceptibility to food allergy. Future studies focusing on the intestinal microbiota are needed in human subjects and mouse models to develop rational microbial therapeutics (next-generation probiotics) for the prevention of food allergy. Allergen immunotherapy by the oral, sublingual, or epicutaneous routes show differing levels of efficacy and safety. Studies are needed to test the feasibility of adjuvants (or microbial therapeutics) to optimize the tolerogenic potential of allergen immunotherapy, as well as novel delivery vehicles or allergen modifications to improve safety.

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