



Food allergy: manifestations, diagnosis and management

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Adverse reactions to food are common but only a fraction of them are due to hypersensitivity (or allergy). Of the latter, immunoglobulin (Ig)E-mediated reactions appear to be the most common and best understood. A wide variety of manifestations may affect various body systems, particularly the gastrointestinal tract, skin and respiratory tract. Diagnosis depends primarily on thorough medical history, often supplemented by skin testing or specific serum IgE antibody measurement. Verification would require appropriately designed challenge testing. At present, treatment is primarily strict avoidance of the offending food, together with crossreacting other foods. Several immunomodulatory therapeutic agents are being explored. A few studies demonstrated a potential benefit of probiotics for prophylaxis and treatment. A multicenter study is currently investigating the efficacy and safety of anti-IgE in subjects with peanut allergy. Experimental studies in mice revealed preliminary findings that promise vaccine development using novel approaches, such as modified food allergen epitopes, immunostimulatory sequence-conjugated allergens and chimeric proteins capable of complexing with IgE or its receptors.

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Food allergy (FA) has been gaining increasing popularity among the public, out of proportion to reality. According to questionnaire surveys, up to 25–30% of the general population claim to have a food allergy [1,2]. On the other hand, well-designed studies estimated a prevalence of 3–6% in children [3] and 1–2% in adults [4,5].

Adverse food reactions can be caused by a variety of mechanisms (TABLE 1). The term intolerance is vague and its use should be minimized [7]. One adverse food reaction that is most commonly misdiagnosed as allergy is lactose intolerance [8]. Whereas milk protein allergy can affect various body systems, including life-threatening systemic anaphylaxis, the manifestation of lactose intolerance is benign and is limited to the gastrointestinal (GI) tract. Scromboid food poisoning is another condition that can be frequently misdiagnosed as allergy [9]. Bacterial spoiling of fish that has a high histidine content (e.g., tuna and mackerel) can produce histamine that may result in manifestations mimicking allergy. Strictly speaking, FA is an adverse reaction to food that is immunologically mediated.

Pathogenesis

FA may involve any or multiple of the four basic immunologic mechanisms. Immunoglobulin (Ig)E-mediated mechanisms are the best understood. Any food can act as an allergen, with proteins being the primary immunogens. According to a recent concept, food allergens can be classified into two classes [10]. Class I comprise the major food allergens whose primary interaction with the immune system occurs in the GI tract and the manifestations may involve remote body systems (TABLE 2). Class II food allergens are those that crossreact with aeroallergens. Subjects with respiratory aeroallergens may show allergic reactions to the relevant crossreacting foods (TABLE 3) [11,12].

The host defense in the GI tract comprises of innate and adaptive immunologic mechanisms. Ingested antigens are digested by a series of agents: salivary lysozymes, gastric acidity, gastric pepsins, pancreatic enzymes, intestinal enzymes and intestinal epithelial cell lysozymes. Physical barriers of the healthy

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mucosa include a mucus layer that traps antigens and epithelial cells joined by tight junctions that exclude macromolecule absorption [13]. During infancy, the chemical and adaptive GI barriers are not fully developed, which predispose, at least partly, to the development of FA.

The mucosal adaptive immune system has two mechanisms of defense [14]. The first consists of secretory IgA and IgM that bind to soluble luminal antigens and prevent their absorption. The second mechanism suppresses the over-reaction to antigens and results in tolerance. With oral tolerance, the immune response is downregulated and mature lymphocytes become hyporesponsive to dietary antigens [15]. Active suppression, clonal deletion and clonal anergy may be responsible for oral tolerance. Perhaps FA is the consequence of a break in oral tolerance mechanisms or of a failure of induction of oral tolerance [16].

By far, most ingested proteins are not absorbed intact. More than 98% are either eliminated or are absorbed as free amino acids, or as small di- or tripeptides [17]. The remaining 2% are absorbed intact. Intestinal epithelial cells (IEC) sample antigens from the lumen of the gut and can function as an antigen-processing cell, and present the antigen to T-cells in the lamina propria via major histocompatibility complex molecules. The interaction of the naive T-cell and the IEC-presented antigen results in the selective activation of CD8⁺ suppressor T-cells [18]. Mucosa-associated lymphoid tissue, found on many mucosal surfaces (such as the gut, respiratory and genitourinary), as well as in the mammary glands and skin, functions as the site of immune system interaction with the

external environment [19]. Gut-associated lymphoid tissue includes Peyer's patches (PP) in the small intestine and to a lesser extent in the rectum. A specialized cell (M-cell) in the epithelial layer overlaying the PP uptakes antigens and transports them into the PP [20]. Antigens are then processed by dendritic cells and presented to naive T-cells which differentiate into at least four regulatory T-cells [18]. In addition to CD8⁺ suppressor cells, there are: CD4⁺ T-regulatory (Tr)1 cells, CD4⁺ T-helper (Th)3 cells, CD4⁺/25⁺ cells and natural killer (NK) cells. CD4⁺ Tr1 secretes interleukin (IL)-10 and Th3 secretes transforming growth factor (TGF)- β ; both cytokines have a suppressive effect. CD4⁺/25⁺ cells also have a suppressive effect, possibly through surface-bound TGF- β . TGF- β also promotes B-cell isotype switching to IgA. After being activated, the T-cell migrates to the B-cell area of the PP and stimulates B-cells. Both types of cells are then directed by a special homing process to migrate to specific target organs (e.g., gut, skin and lung) [17]. Although the activated lymphocytes can migrate to any lymphoid tissue, they preferentially migrate to the organ where they were initially activated.

In a murine model, oral tolerance can occur in two forms: a single high dose or repeated low doses [16]. High-dose tolerance occurs through T-cell receptor ligation in the absence of costimulatory signals resulting in lymphocyte anergy. Low-dose tolerance is mediated by CD4⁺ Th3 cells, Tr1 cells and CD4⁺/25⁺ cells. Oral tolerance may also occur by the mechanism of portal tolerance, in which liver-associated NK1.1 lymphocytes mediate tolerance to antigens that reach the liver via the portal vein.

Antibodies to food antigens of the IgG, A and M isotypes are normally produced with titers that are highest during infancy and decline with age [15]. Certain genetically predisposed individuals have an abnormal immune response to food allergens. For example, antigliadin IgA antibody is found in excessive quantities in patients with celiac disease [15]. Any disruption in the chemical, physical, cellular or adaptive immunity could alter the response to antigen and increase the production of antibodies. In individuals with a genetic predisposition for atopy, an increase in antibody production is usually directed to IgE and subsequent food allergy.

Immunologic mechanisms

Any of the four types of Gell and Coombs immune reactions may be involved in FA [21], and more than one type can be involved in some reactions.

- Type I or immediate hypersensitivity reactions are frequently induced by small quantities of allergen and are predominantly IgE mediated. This type is the best understood and is primarily manifested as urticaria, angioedema, bronchospasm, GI upset and systemic anaphylaxis.
- Type II or cytotoxic reactions involve antibodies (primarily of the IgM or IgG isotypes) that bind to cell-bound antigens and result in complement activation and cell lysis. This reaction appears to be rare in FA and can be the underlying mechanism in a few reported cases of severe thrombocytopenia to milk ingestion.

Table 1. Adverse reactions to food.

Mechanism	Offending food
Hypersensitivity	Various food proteins
Gastrointestinal irritation	Spices, unripe fruits or vegetables, chemical contaminants
Toxicity	Poisonous plants, mushrooms or fish; contamination with chemicals, bacterial or bacterial toxin
Enzyme deficiency	
Lactase deficiency	Lactose
Phenylketonuria	Phenylalanine
Glucose-6-phosphate dehydrogenase	Fava beans
Diabetes mellitus	Sugar
Pharmacologic	
Scromboid poisoning	Histamine in spoiled fish
Ergotamine	Mushrooms
Caffeine	Coffee, tea
Vasoactive amines	
- Serotonin	Banana, pineapple, tomato, avocado
- Theobromine	Chocolate
- Tyramine	Cheese
Psychologic	Any food

Modified from [6].

Table 2. Major allergens of common foods (Class I).

Protein	Molecular weight (kDa)	Nomenclature
<i>Chicken egg white</i>		
Ovomucoid	28	Gal d 1
Ovalbumin	44	Gal d 2
Conalbumin	78	Gal d 3
Lysozyme	14	Gal d 4
Serum albumin	69	Gal d 5
<i>Cow's milk</i>		
Whey		
- α -lactalbumin	14.2	Bos d 4
- β -lactoglobulin	18.3	Bos d 5
- Serum albumin	67	Bos d 6
- Immunoglobulin	160	Bos d 7
Caseins (α , β , κ)	20–30	Bos d 8
<i>Cod</i>		
Parvalbumin	12	Gad c 1
<i>Shrimp</i>		
Tropomyosin	36	Pen a 1
<i>Peanut</i>		
Vicilin	63.5	Ara h 1
Conglutin	17	Ara h 2
Glycinin	60	Ara h 3
<i>Wheat</i>		
Agglutinin	-	Tri a 18
Omega-5 gliadin	65	Tri a 19
<i>Soybean</i>		
Hydrophobic protein	7	Gly m 1
Profilin	14	Gly m 3
PR-10 protein	17	Gly m 4

- Type III or immune complex reactions result when antigens are bound to their specific antibodies (mainly IgG and IgM). These complexes together with complement are usually cleared from the circulation by the phagocytic system. However, if excessive quantities are formed, the deposition of these complexes in the small blood vessels of specific shock organs initiates chemotaxis of inflammatory cells, for example neutrophils and monocytes. The degree of inflammatory process determines the extent of local tissue damage. This type of reaction appears to be rare and may be manifested as vasculitis, arthropathy or nephropathy.

- Type IV or cell-mediated/delayed type hypersensitivity requires sensitized T-lymphocytes. When bound to a specific antigen, sensitized T-lymphocytes proliferate, produce and release cytokines (e.g., IL-2 and interferon [IFN]- γ) that attract other inflammatory cells and result in local tissue damage. This type of reaction is typically manifested in allergic contact dermatitis and can be involved to various degrees in atopic dermatitis [22,23].

Effect of food processing

Various methods of food processing may increase or decrease its allergenicity [24,25]. Protein epitopes (antigenic determinates) can be sequential or conformational. Heat treatment or partial hydrolysis can alter conformational but not sequential epitopes; alteration of the latter requires extensive hydrolysis. In any particular patient, production of IgE antibodies may be directed to one type of epitope. It is worth noting that processing, particularly heat, may expose certain epitopes that were not accessible to the immune system in the native form of the food. For example, IgE from peanut-allergic individuals binds 90-fold stronger to extracts of roasted peanut than extracts of raw peanut [26]. Preparation by peeling or storage may reduce or alter allergenicity. Mechanical processing such as cutting or grinding can cause surface denaturing of protein aggregation, allowing for oxidation to occur. Isolation and purification (e.g., melting, pressing, distillation, extraction, refining, filtration, decanting, sieving or polishing) may separate certain protein fractions from the basic food. Thermal procedures (e.g., heating, evaporation, cooling or freezing) might cause protein denaturation, side-chain amino acid alteration or reaction with other molecules. Biochemical procedures (e.g., fermentation or enzyme addition) alter the structure of food protein. Hypoallergenic food (e.g., extensively hydrolyzed milk, soy or wheat) can be produced by this procedure. Genes can be altered using genetic technology which may induce new protein structures.

Route of exposure

By far, the primary route of sensitization to food is ingestion. Inhalation, skin contact and non-GI mucosal contact probably play more of a role than is recognized. Through the process of homing, activated lymphocytes can migrate to distant organ systems. Once the sensitized lymphocytes are present in a tissue, allergic reactions may occur via different routes of exposure. IgE sensitization can take place through lipophilic allergens entering the dermis through hair follicles or damaged skin [27,28]. Exposure by skin contact or inhalation can be substantial in certain occupations. However, severe reactions may occur through trivial exposure [29]. During the process of cooking, particularly during frying or boiling, allergens become airborne in excessive quantities. A woman with chronic GI symptoms experienced anaphylaxis to carrageenan in barium enema solution [30]. Another milk-sensitive woman had an anaphylactic reaction during artificial insemination caused by bovine serum albumin in the sperm medium [31].

Table 3. Food allergens that crossreact with aeroallergens (Class II).

Inhalant allergen	Protein classification	Crossreacting food allergen
Birch (Bev v 1)	Bev v 1 homolog	Apple (Mal d 1), cherry (Pru av 1), apricot (Pru ar 1), pear (Pyr c 1), carrot (Dau c 1), celery (Api g 1), hazelnut (Cor a 1)
Birch (Bev v 2) and Mugwort (Art v 4)	Profilin	Celery (Api g 4), cherry (Pru av 4), pear (Pyr c 4), carrot (Dau c 4), apple (Mal d 4)
Ragweed	Profilin	Banana (Mus xp 1), melon
Grass	Profilin	Melon, tomato (Lyc e 1)
Latex (Hev b 2)	1,3 gluconase	Banana, chestnut, fig, kiwi, avocado
Latex (Hev b 6.02)	Chitinase	Avocado (Pers a 1), chestnut,
Latex	Thaumatococcus-like proteins	Apple (Mal d 2), cherry (Pru av 2)

Manifestations

FA can affect any of several body systems and have a variety of manifestations; the most common of which are presented in TABLE 4.

Gastrointestinal

The GI tract is the first organ to come into contact with food. During infancy and early childhood, the immaturity of the GI tract predisposes it to be the most affected organ. Symptoms of GI food hypersensitivity often manifest as hypermotility, but hypomotility (constipation) can occur [32].

In some patients, the symptoms can be limited to the oral cavity (such as itching, burning sensation and mild swelling). This entity is referred to as oral allergy syndrome (OAS) and occurs from eating certain fresh fruit or vegetables that cross-react with specific pollens causing respiratory allergy in that individual (TABLE 3) [11,12]. The crossreacting proteins are heat-labile, hence the offending food is usually tolerated when cooked. However, celery, which crossreacts with birch and mugwort pollens, contains both heat-labile and -stable proteins, and may cause symptoms even when cooked. Birch pollen immunotherapy has been shown to eliminate the symptoms that are caused by crossreacting food allergens in the OAS [33].

In recent years, primary eosinophilic GI disorders (EGID) have been increasingly identified [34]. This group of disorders includes eosinophilic esophagitis (EE), eosinophilic gastritis and eosinophilic gastroenteritis. It appears that both IgE- and non-IgE-mediated reactions are involved to various degrees. Approximately 75% of patients with EGID are atopic, and 10% have a family member with an EGID. The disorders are characterized by infiltration of the esophageal, gastric or intestinal mucosa with eosinophils. In more than 50% of cases, local infiltration of eosinophils occurs without an increase of circulating eosinophils.

EE typically develops during infancy through early adolescence [35]. Symptoms include gastroesophageal reflux (GER), abdominal pain, chest pain, nausea and vomiting. It may persist for many years, resulting in chronic inflammation and

subsequent narrowing of the esophagus causing significant dysphagia. In contrast to simple GER, the inflammatory process involves the mucosa, submucosa and in some patients the muscular layer. Normally, the esophageal mucosa does not contain eosinophils. Up to seven eosinophils per high power field can be seen in the presence of GER from any cause, but more than 20–24 are indicative of EE. Although the etiology of EE is not well elucidated, food and aeroallergen sensitivities were noted in most patients, suggesting that perhaps both the oral and inhalation routes are involved.

Eosinophilic gastritis and eosinophilic gastroenteritis can present at any age [34]. Manifestations include vomiting, abdominal pain, early satiety, failure to thrive, gastric bleeding and gastric outlet obstruction. Eosinophilic infiltration can involve the mucosa, serosa or muscular layers. Therefore, the absence of eosinophils in a routine mucosal biopsy should not exclude the disease.

Food protein-induced enteropathy, colitis, proctitis or a combination thereof, typically presents during the first few months of life, and are mostly non-IgE mediated [35]. Primary symptoms are vomiting, hematochezia, nausea, abdominal pain and failure to thrive. The GI bleeding is usually occult and may continue unidentified for prolonged periods. Gross GI bleeding is rare but very alarming. The stools may contain excessive leukocytes, Charcot-Leyden crystals and eosinophils. Peripheral eosinophilia is usually mild. Protein loss is common and results in significant hypoalbuminemia. Cow's milk and soy are the most common offending allergens in children, even in exclusively breast-fed infants since food allergens ingested by the mother can cross from the maternal circulation to the mammary gland. Mucosal biopsy usually shows patchy villous atrophy, eosinophils and infiltrates of mononuclear cells [36].

Celiac disease, a gluten-induced enteropathy, is sometimes included among food hypersensitivity disorders. However, the exact underlying mechanism remains unclear [37,38]. Celiac disease is a permanent disorder and is associated with significant malabsorption and failure to thrive. Infantile colic can result from a wide variety of causes, including food protein allergy [39].

Cutaneous

The skin is probably second to the GI tract as the most frequently affected organ by FA. Although food ingestion is the major route, skin contact can play a significant role in both sensitization and provocation of FA.

Several studies have demonstrated the role of food in skin allergies, particularly atopic dermatitis and acute urticaria/angioedema [40,41]. FA has been demonstrated to play a role in a third to a half of children with atopic dermatitis. In contrast, FA plays a minor role in adult-onset atopic dermatitis. Whereas FA is frequently implicated in acute urticaria/angioedema, it is rarely involved in chronic cases.

Gluten-induced enteropathy, even asymptomatic cases, can be associated with dermatitis herpetiformis manifested as a papulovesicular rash on the extensor surfaces and the buttocks [42].

Exposure to FA by skin contact is evolving as having a significant role, both in local and systemic reactions [43,44]. Such an exposure is major in certain food industries but can occur at home and other places. In addition to local irritant effects, immunologically mediated reactions may occur at the site of contact, a remote organ, or even as systemic anaphylaxis (TABLE 5). Severe reactions from trivial skin contact or hidden food allergen in a topical dermatologic medication have been reported [29,44].

Respiratory

The role of food in causing respiratory allergy is less than in GI and cutaneous allergies, but is probably being frequently unrecognized [6,36,45]. Food-induced upper and lower respiratory

tract symptoms are much more common in young children than in adults. Eustachian tube dysfunction secondary to chronic rhinitis may be a cause of chronic serous otitis media or the middle ear may be the primary shock organ. In some patients, the manifestations of FA can be limited to subclinical bronchial hyper-reactivity, which would be difficult to recognize [46,47]. Respiratory symptoms may develop from inhaling, touching or ingesting food proteins in sensitized individuals. Occupational asthma has been reported in crab-processing workers, bakery workers to inhaled egg or flour, and harbor workers unloading soybeans. Interestingly, patients with baker's asthma caused by inhaled wheat flour can eat wheat without symptoms [48]. Another condition that is probably being frequently unrecognized is milk-induced pulmonary disease (Heiner syndrome) [49]. Typically, the disease starts during infancy and is manifested by coughing, wheezing and recurrent or persistent pulmonary infiltrate. The underlying mechanism is predominately a Type III reaction in which immune complexes cause an inflammatory reaction in the alveolar capillaries. In some cases, the vasculitis is severe, leading to bleeding and causing pulmonary hemosiderosis.

Systemic anaphylaxis

In highly allergic subjects, FA can involve multiple organ systems simultaneously and can be life threatening. In the USA, systemic anaphylaxis to foods accounts for a third to a half of all cases of anaphylaxis seen in the emergency department [36]. Peanut is the most common cause of fatal cases, followed by tree nuts, shellfish and fish. In some patients, food-induced anaphylaxis occurs only when the patient

Table 4. Immunologically mediated adverse reactions to food.

System	Immunoglobulin E mediated	Non-immunoglobulin E mediated	Mixed
Gastrointestinal	Immediate gastrointestinal hypersensitivity	Food protein-induced enteropathies	Eosinophilic gastrointestinal disorders
	Oral allergy syndrome	Celiac disease	
	Vomiting	Bleeding (occult, gross)	
	Infantile colic		
	Diarrhea		
	Gastroesophageal reflux		
Cutaneous	Acute urticaria	Contact dermatitis	
	Acute angioedema	Dermatitis herpetiformis	Atopic dermatitis
Respiratory	Rhinoconjunctivitis	Milk-induced pulmonary disease (Heiner syndrome)	
	Bronchospasm		
Generalized	Anaphylaxis	Postprandial exercise-induced anaphylaxis	
		Headache/migraine	

Table 5. Manifestations of reactions to food by skin contact.

Limited to skin	Systemic manifestations
Immediate reactions	Bronchospasm
- Urticaria/angioedema	Laryngeal edema
- Irritant dermatitis	Systemic anaphylaxis
- Phototoxic dermatitis	
- Protein contact dermatitis	
Delayed reactions	
- Allergic contact dermatitis	

Modified from [43].

exercises within a few hours of ingesting the offending food (postprandial exercise-induced anaphylaxis), with wheat being the most commonly implicated.

Diagnosis

An outline for the diagnosis of FA is presented in TABLE 6. Since FA has no pathognomic clinical features, a thorough medical history, careful physical examination and selected laboratory tests are of great importance for the differential diagnosis. Although patients are usually not completely aware of their offending allergens, the medical history alone can be convincing enough in some patients to make or exclude the diagnosis without any further evaluation. When FA is suspected, identification of the offending food(s) may be pursued through specific tests [36,50].

Although the food symptom diary appears simple, the patient's compliance with accurate recording is usually poor and often difficult to deduce meaningful correlation from. Its usefulness is more in patients with intermittent or infrequent symptoms, where recording of foods and events can be limited to the preceding 6–12 h of appearance of symptoms.

Trials of elimination diets are most useful if there are only a few suspected foods that can be avoided for a short period, otherwise compliance would be poor. The duration of elimination should be at least equal to the symptom-free periods the patient has had. If the symptoms markedly improve with minimal or no medication, each food is reintroduced at intervals ranging from a few to several days, depending on the anticipated symptoms. In some cases, particularly in children, limiting the diet to an elemental formula might be necessary. In patients with anticipated severe reactions, the reintroduction of suspected foods should take place under supervision in a medical facility.

Percutaneous skin testing is the most commonly used screening method for IgE-mediated reactions. Glycerinated extracts (concentrations of 1:10 or 1:20 wt/vol), histamine (positive control) and diluent (negative control) are applied by the prick or puncture technique. Currently available extracts are not standardized and their potency varies widely, which partly explains the suboptimal degree of reliability of skin testing for FA. Intradermal skin testing for FA is not recommended due to

an unacceptable rate of false-positive results and the risk of systemic reactions. In fact, in exquisitely sensitive patients, particularly those who react to food by skin contact or inhalation, skin testing should be avoided and *in vitro* testing should be used. The reliability of percutaneous skin testing may be improved by using fresh or native foods particularly for fruits and vegetables (prick-to-prick technique).

Atopy patch testing is useful in the diagnosis of cell-mediated food allergies (e.g., allergic contact dermatitis) or those with combined reactions, for example, atopic dermatitis [51] and eosinophilic gastroenteropathies [34,52].

Food-specific IgE antibodies can be measured in the serum by a variety of methods. The enzyme immunoassays are more popular than the radioimmunoassays [53–55]. At present, the ImmunoCap® system (Pharmacia–Upjohn Diagnostics, MI, USA) appears to be the most sensitive and reproducible assay. Determining the serum total IgE level can be helpful, not only in assessing the atopic status of the patient but also in the interpretation of the potential relevance of a positive food-specific IgE level. If the total serum IgE level is high, low levels of specific antibodies are usually not clinically relevant, but the same levels can be relevant when the serum IgE is low [50].

Serum IgE antibody testing is considered a counterpart of skin testing. The former detects the antibody in the circulation whereas the latter reflects the presence of antibodies on the cutaneous mast cells and releasability of mediators. Therefore,

Table 6. Diagnostic approach to food allergy.

Procedure	Specific items
Medical history	Age of onset Nature, severity, duration and frequency of symptoms Time of onset in relation to food or other factors Personal history of allergy, particularly of atopic dermatitis
Physical findings	Manifestations of allergy Manifestations suggestive of nonallergic disease
Laboratory tests to support allergy	Serum total immunoglobulin E level Eosinophilia
Selected tests to exclude or verify nonallergic disease	
Specific screening tests	Trials of elimination diets Food/symptom diary Allergy skin testing Specific immunoglobulin E antibodies in serum
Confirmation by challenge testing	

Modified from [49].

skin testing is a biologic test mimicking the immediate-type hypersensitivity reaction *in vivo*. However, in certain situations, *in vitro* testing is preferred over skin testing, such as in the presence of dermographism, generalized dermatitis, the need for continuous intake of antihistamines, or in exquisitely sensitive subjects. For several reasons, neither skin testing nor *in vitro* testing should be expected to be of a high degree of reliability. It is worth noting also that the concentration of specific IgE antibodies is highest in the shock organ and may not be present in sufficient quantities in the skin or circulation.

Elimination–challenge testing is the definitive procedure to document a cause-and-effect relationship of a particular food to the patient's symptoms [56]. Double-blind, placebo-controlled oral challenge allows removal of bias from the procedure. However, in clinical practice, single-blind, placebo-controlled challenge is adequate in most cases. Open challenge can be a valid testing modality in young children, where the symptoms are objective and bias is unlikely [50].

All suspected foods (by history, diary, percutaneous skin testing or serum IgE antibodies) should be simultaneously and strictly eliminated from the diet. If the symptoms markedly improve, each food should be reintroduced individually. To avoid severe reactions, the test should be started with a safe dose – depending on the degree of sensitivity of the patient and the anticipated reaction. Every 20–30 min the dose can be increased by 50–100% as long as no reaction develops. The total cumulative dose should be at least equal to the quantity normally ingested. Observation of the patient should continue for at least 1 h after the last dose and can be longer, depending upon the anticipated reaction and the timing of its onset. Challenges should be avoided in patients with life-threatening anaphylaxis to a specific food, particularly on more than one occasion [50]. If confirmation is still required, skin contact or application of a very small quantity to the inside of the lower lip may be performed and if negative, a titrated oral challenge may follow. Therefore, the choice of the types of challenge should be individualized.

Challenge may not be necessary when only one food out of many tested is strongly positive (by percutaneous skin testing or specific IgE antibody testing) and the symptoms improve on elimination. Although certain levels of specific IgE antibody can be of high reliability in predicting the challenge results, it may not be applicable on dealing with an individual patient in clinical practice. Using the ImmunoCap system, one study reported that a peanut-specific IgE level of 14 kU/l had a 100% predictive value of a positive challenge [57]. However, a large study showed that only 30% of patients with severe reactions to peanut and/or tree nut had CAP IgE of 15 kU/l or greater [58]. The test was falsely negative in 22% of allergic subjects and falsely positive in 40% of nonallergic subjects. In the same group, the percutaneous skin testing was positive to a tolerated nut in 46%, including 3% who had a wheal of 8 mm diameter or greater.

There are many limitations for oral food challenges. Choosing a placebo that can completely mask the challenge food, especially if large quantities are involved, can be difficult. Reproducing the natural exposure regarding route, quantity

and form may not be attained in blind challenges. Using dry/powdered food poses two problems: possible alteration of allergenicity and estimation of the weight equivalence to the natural food. Furthermore, the possible involvement of concomitant factors (e.g., exercise, hormonal changes and multiple allergens) can result in a negative challenge unless such factors are recognized and incorporated.

Additional studies may be required to fully investigate the diagnosis of certain manifestations of FA. In addition to obtaining mucosal biopsies, evaluation of patients with suspected EGID may include stool analysis or serologic tests for intestinal parasites [34].

Management

At present, the only proven effective method for the treatment of FA is elimination of the offending food(s). Young children with multiple offending foods or with EGID often require an amino acid-based diet or another hypoallergenic formula prior to resolution of symptoms. Elimination of the causative allergen can be difficult and requires education on reading labels of commercial food products, particularly regarding unfamiliar terms (e.g., whey and casein for milk and ovalbumin and ovomucoid for egg). When eating out, extra caution needs to be practiced by highly allergic subjects. Inquiry about the ingredients in food served in restaurants cannot be overemphasized. Buffet-style prepared food should be avoided due to the high risk of food cross contamination. The Food Allergy and Anaphylaxis Network is a lay organization that has material to assist in educating patients on dietary elimination [101].

Patients with a history of a severe systemic reaction should have self-injectable epinephrine available at all times. Intramuscular injection into the lateral side of the thigh provides the best route of absorption [59]. Antihistamines may be useful in symptomatic treatment but should not be relied upon for prophylaxis. Systemic corticosteroids may be needed for acute severe reactions and are effective in treating chronic disorders (e.g., EGID or atopic dermatitis), but their long-term use is associated with significant side effects. Swallowed fluticasone dipropionate solution has been shown to provide long-term control in EE, but occasionally is complicated with esophageal candidiasis [34]. In refractory cases of EGID, immunosuppressive antimetabolite therapy (e.g., azathioprine) can be an alternative [34].

Prognosis

Uncontrolled FA can be associated with substantial degrees of morbidity and a high risk of sudden fatality. The prognosis of FA depends on several factors, such as age of onset, type and severity of manifestations, type and multiplicity of offending foods, and degree of avoidance. Favorable prognostic criteria include early age of onset, symptoms limited to the GI tract, low degree of sensitivity (skin test reactivity, specific IgE level and total IgE level), and certain foods such as milk, soy, cereals and fruit. FA can last for many years in patients who had systemic anaphylaxis, reactions by trivial exposure such as hidden food, inhalation or skin contact, multiple food allergens, and highly allergenic foods such as peanut, tree nuts, crustaceans, mollusks and finfish.

Expert opinion

In recent years, numerous well-designed clinical and laboratory investigations have significantly enhanced our understanding of FA. Substantial improvement has occurred in the diagnosis, and promising new modalities of treatment are anticipated within the next few years.

The spectrum of FA presentations has been broadened by the inclusion of an increasing number of uncommon manifestations that have been well documented by critical investigators. By the same token, inhalation and contact with the skin or with the mucosa of the genital and lower GI tracts can be significant routes of exposure in some patients. Studies on the crossreactivity between certain pollens and certain foods have explained the mechanism of the OAS. They also demonstrated that an allergy to an individual member of a food family (e.g., legumes or fish) does not necessarily indicate allergy to all family members.

Screening for FA has been improved by emphasizing the importance of a thorough medical history, by a modest improvement in the quality of the diagnostic material for skin testing, and in the procedures for specific IgE antibody measurement in the serum. Verification still depends on performing an appropriately designed challenge test. The reliability of the percutaneous skin test and patch tests would be enhanced by developing standardized material with optimal sensitivity and specificity. The clinical and laboratory diagnosis of non-IgE immunologic reactions are in need of improvement.

Laboratory investigations have led to the identification and characterization of the major allergens in several commonly allergenic foods. Such work has paved the road towards better diagnostic procedures and several potential therapeutic modalities. At present, there is a large multicenter study on the use of anti-IgE for peanut allergy, which is expected to be of protective value against accidental exposures. Certain Chinese herbal formulae have demonstrated a prophylactic effect against experimental food-induced anaphylaxis in mice. However, their specific active ingredients have not been elucidated and their application to human subjects may be hindered by several logistic factors and safety concerns.

A major step forward towards a vaccine has been the successful modification of major food allergen epitopes, by means of a single amino acid substitution, that resulted in marked reduction in their IgE-binding capacity. The rectal administration in mice of heat-killed *Escherichia coli* containing such mutated recombinant epitopes reduced the Th2 response and the production of specific IgE antibodies.

Other attempted approaches in experimental animals include the use of synthetic immunostimulatory sequence-conjugated allergen and the use of a chimeric protein that could complex with the specific IgE or with the receptors on mast cells and basophils. Additional approaches are being explored and some novel effective and safe modalities for prophylaxis and/or treatment of FA are expected to develop within the next few years.

Five-year view

In the past few years, advances have been made in allergen characterization and sequence determination by chemical and molecular biologic approaches. Many food allergen epitopes have been identified and are compiled by the International Union of Immunological Societies Allergen Nomenclature Sub-Committee [102]. Better diagnostic materials based on known allergenic protein sequences and epitopes are expected to be available in the near future.

Multiple immunomodulatory approaches to FA treatment are being investigated, with promising results [60]. A preliminary investigation demonstrated that administration of monoclonal anti-IgE (TNX-901) to peanut-allergic subjects significantly increased the tolerance threshold to peanuts [61]. Currently, a Phase II trial is underway, investigating the use of humanized murine anti-IgE antibodies (omalizumab) in peanut-allergic patients. Omalizumab blocks IgE-mediated reactions by binding to the circulating IgE and reducing the expression of the high-affinity IgE receptors on mast cells and basophils. Recent studies on anti-IL-5 (mepolizumab) have shown promising results in patients with EE and hypereosinophilic syndrome [62].

Several years ago, a trial of traditional immunotherapy with peanut extract resulted in serious adverse reactions and the procedure was abandoned [63]. Recently, engineered recombinant proteins that differ by a single amino acid in the IgE-binding epitope failed to bind IgE but retained the ability to interact with T-cells [64]. Mice treated with engineered recombinant peanut allergen had a significant decrease of symptoms upon oral challenge to peanut [65]. In a later investigation, an engineered recombinant peanut protein was administered together with heat-killed *Listeria monocytogenes*, to peanut-sensitized mice with a far greater protective effect compared with using only the engineered recombinant peanut protein [66]. Heat-killed bacterial adjuvant induce IL-12 production, which leads to a Th1 cytokine response with increased production of IFN- γ and IgG2a antibody and suppression of the Th2 response with decreased production of IL-4 and IgE antibody [67]. To avoid the risk of using potentially pathogenic bacteria, heat-killed *E. coli* of nonpathogenic strains is being used instead of *L. monocytogenes* [68].

In animal experiments, immunostimulatory sequences (e.g., CpG oligodeoxynucleotide) covalently linked to allergens have been shown to reduce the IgE-mediated allergic response in humans with ragweed allergy and in peanut-allergic mice [36].

Clinical trials of probiotics have demonstrated promising prophylactic and therapeutic values [69]. However, more studies are needed to standardize the type and quantity of organisms used.

In recent trials, certain Chinese herbal medicine, Food Allergy Herbal Formula-2, caused downregulation of the Th2 response and eliminated anaphylaxis in peanut-allergic mice for as long as 5 weeks post therapy [70].

Key issues

- Awareness of the manifestations and risk of food allergy has been constantly increasing among the public as well as among medical professionals.
- Proper diagnosis and identification of the offending food(s) are essential for appropriate management.
- Exquisitely sensitive subjects should wear Medi-Alert identification and have self-injectable epinephrine readily available.
- Basic research studies have significantly clarified the underlying immunologic mechanisms and identified the epitopes of several major food allergens.
- Novel approaches for prophylaxis and/or treatment are being investigated and their potential application is anticipated in the near future.

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