Review

Food allergy

Wesley Burks[1] and Barbara K. Ballmer-Weber[2]

[1] Pediatric Allergy and Immunology, Duke University Medical Center, Durham, NC, USA
[2] Allergy Unit, Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

This article reviews the classification of food allergies, their prevalence, pathophysiology, diagnosis, treatment and prognosis.

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1 Disease definition

Critical to any discussion of food allergy and food intolerance is a basic understanding of the classification of adverse reactions to foods [1]. The utilization of these terms has allowed better communication regarding various reactions to food components. An adverse food reaction is a general term that can be applied to a clinically abnormal response to an ingested food or food additive. Adverse food reactions may be secondary to food hypersensitivity (allergy) or food intolerance.

Food hypersensitivity (allergy) is an immunologic reaction resulting from the ingestion of a food or food additive. This reaction occurs only in some patients, may occur after only a small amount of the substance is ingested, and is unrelated to any physiologic effect of the food or food additive. To most physicians, the term is synonymous with reactions that involve the immunoglobulin E (IgE) mechanism, of which anaphylaxis is the classic example.

Food intolerance is a general term describing an abnormal physiologic response to an ingested food or food additive. This reaction has not been proven to be immunologic in nature, and may be caused by many factors including toxic contaminants (*e.g.*, histamine in scombroid fish poisoning, toxins secreted by *Salmonella, Shigella*, and *Campylobacter*), pharmacologic properties of the food (*e.g.,* caffeine in coffee, tyramine in aged cheeses), characteristics of the host such as metabolic disorders (*e.g.*, lactase deficiency), and idiosyncratic responses.

The term "food intolerance" has often been overused and, like the term food allergy, has been applied incorrectly to all adverse reactions to foods. IgE-mediated (Type I) hypersensitivity accounts for the majority of well-characterized food allergic reactions; however, non-IgE-mediated immune mechanisms are believed to be responsible for a variety of hypersensitivity disorders. For this discussion we will examine adverse food reactions that are IgE-mediated, non-IgE-mediated, and those entities that have characteristics of both.

2 Prevalence

The true prevalence of adverse food reactions is still unknown. Up to 15% of the general population believes that they may be allergic to some food. The actual prevalence, however, of food allergy appears by the best available studies to be about 3% of the adult population [2]. The prevalence of adverse food reactions in young children is estimated at between 6 and 8%. Several well-controlled studies have revealed that the vast majority of food allergic reactions present in the first year of life.

3 Pathophysiology

3.1 IgE-mediated hypersensitivity

A variety of hypersensitivity responses to an ingested food antigen may result from the genetically predisposed patient's lack of development of oral tolerance or a breakdown of oral tolerance in their gastrointestinal tract. Either a failure to develop or a breakdown in oral tolerance results in excessive production of food-specific IgE antibodies.

Correspondence: Dr. Wesley Burks, Pediatric Allergy and Immunology, Box 3530, Duke University Medical Center, Durham, NC 27710, USA
E-mail: Wesley.Burks@duke.edu
Fax: +1-919-681-2949

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; **OAS**, oral allergy syndrome; **RAST**, radioallergosorbent test

These food-specific antibodies bind high-affinity FcεI receptors on mast cells and basophils and low-affinity FcεII receptors on macrophages, monocytes, lymphocytes, eosinophils, and platelets [1]. After the food allergen reaches the food-specific antibodies on mast cells or basophils, mediators such as histamine, prostaglandins, and leukotrienes are released. These mediators then promote vasodilatation, smooth muscle contraction, and mucus secretion resulting in the symptoms of immediate hypersensitivity. The activated mast cells also may release various cytokines that play a part in the IgE-mediated late-phase response. With repeated ingestion of a specific food allergen, mononuclear cells are stimulated to secrete histamine-releasing factors. The "spontaneous" generation of histamine-releasing factors by the activated mononuclear cells *in vitro* has been associated with increased cutaneous irritability in children with atopic dermatitis. A rise in plasma histamine has been associated with IgE-mediated allergic symptoms after blinded food challenges. In IgE-mediated gastrointestinal reactions, endoscopic observation has revealed local vasodilatation, edema, mucus secretion, and petechial hemorrhaging. Increased stool and serum PGE_2 and PGF_2 have been seen after food challenges causing diarrhea.

3.2 Non-IgE-mediated hypersensitivity

Although a variety of reports have discussed other immune mechanisms causing food allergic reactions, the scientific evidence supporting these mechanisms is limited. Type III (antigen-antibody complex-mediated) hypersensitivity reactions have been examined in several studies. While IgE-food antigen complexes are seen more commonly in patients with food hypersensitivity, there is little support for food antigen-immune complex-mediated disease. Type IV (cell-mediated) hypersensitivity has been discussed in several disorders where the clinical symptoms do not appear until several hours after the ingestion of the suspected food. This type of immune response may contribute to some adverse food reactions (*i.e.*, enterocolitis), but significant, supporting evidence of a specific cell-mediated hypersensitivity disorder is lacking.

4 Diagnosis

4.1 Clinical manifestations of food hypersensitivity

4.1.1 IgE-mediated hypersensitivity

4.1.1.1 Gastrointestinal food hypersensitivity reactions

The signs and symptoms of food-induced IgE-mediated gastrointestinal allergy in man may be secondary to a variety of syndromes including the oral allergy syndrome (OAS), immediate gastrointestinal hypersensitivity, and a small subgroup of allergic eosinophilic gastroenteritis [3].

The OAS is considered a form of contact urticaria induced by exposure of the oral and pharyngeal mucosa to food allergens. Affected subjects may report rapid onset of symptoms with increasing severity, from mild itching of the lips, mouth and throat, to lip and tongue swelling, to severe angioedema of the pharyngeal mucosa up to life-threatening emergencies [4]. The OAS is the most common food allergy-related manifestation and can be present either isolated or in association with systemic cutaneous or respiratory symptoms, and may even result in anaphylaxis [5, 6]. OAS may be the first manifestation of food allergy in the natural course of the disease towards more severe reactions, and it may be an important alarm manifestation in subjects at risk for severe food-induced allergic symptoms. OAS is generally thought to be related to plant-derived foods only; however, severe reactions to animal-derived foods may also be preceded and accompanied by local oral symptoms [7]. The triggering food may be dependent on geographically different nutritional habits and may thus vary from place to place. In contrast to food-dependent allergic reactions induced by gastric or intestinal absorption, where digestion may affect allergen structure, OAS is most likely induced by exposure to native non-modified allergens. As a consequence, even unstable or rapidly degradable allergens are able to cause OAS. Patients with allergic rhinitis secondary to certain airborne pollens (especially birch, mugwort, and ragweed pollens) are frequently afflicted with this syndrome (Table 1). Patients with birch pollen sensitization often have symptoms following the ingestion of stone fruits and pip fruits, but also after ingesting vegetables such as carrots or celery [5, 8], nuts, or legumes [9, 10]. Patients with ragweed pollen sensitization may experience allergic symptoms including OAS following contact with certain melons (watermelons, cantaloupe, honeydew, *etc.*) and bananas [11]. The diagnosis of this syndrome is made after a suggestive history and positive prick skin tests with the implicated fresh fruits or vegetables [12]. The convert in this syndrome is that the commercially available allergen extracts for fresh fruits and vegetables often do not have the reliability of the other food extracts. It may be necessary to use the "prick-by-prick" method, where the device used for introducing the allergen into the skin may initially have to be "pricked" into the food.

Immediate gastrointestinal hypersensitivity (Table 2) is a form of IgE-mediated gastrointestinal hypersensitivity, which may accompany allergic manifestations in other target organs [13]. The symptoms vary but may include nausea, abdominal pain, abdominal cramping, vomiting, and/or diarrhea. In studies of children with atopic dermatitis and food allergy, the frequent ingestion of a food allergen

Table 1. Pollen-associated food allergy syndrome [42, 43]

Oral Manifestations
- Burning
- Swelling
- Itching
- Erythema
- Blistering
- Immediate Onset of symptoms

Systemic Manifestations (less frequent than oral manifestations)
- Rhinitis/conjunctivitis
- Bronchospasm
- Diarrhea, vomiting, abdominal pain
- Flush, urticaria, angioedema anaphylaxis

Age of Onset
- Beyond Infancy
- Mainly but not exclusively after the onset of pollinosis symptoms

Proteins implicated
- Cross-reactive allergens in pollen and plant food Heateat-lability of some fresh fruit,nut, and vegetable allergens
- Combined pollen and latex cross-reactivity

Pathology
- Immunoglobulin E antibodies

Treatment
- Avoidance
- Cooking, but not for all patients effective

Natural history
- Unknown

Table 2. Immediate gastointestinal hypersensitivity [44]

Manifestations
- Nausea, abdominal pain and vomiting within 1 to 2 hours
- Diarrhea within 2 to 6 hours
- Frequently associated with atopic disease
- Food-specific IgE antibodies
- Radiographic: gastric hypotonia and pylorospasm

Age of onset
- Infancy, childhood

Proteins implicated
- Milk, egg, peanut, soy, cereal, fish

Pathology
- Immunoglobulin E-mediated

Treatment
- Protein elimination

Natural history
- 80% of cases resolve after protein elimination diet (except in the case of peanut and fish allergy)

appears to induce partial desensitization of gastrointestinal mast cells resulting in less pronounced symptoms.

The diagnosis of these symptoms is made by a suggestive clinical history, positive prick skin tests, complete elimination of the suspected food allergen for up to 2 wk with resolution of symptoms, and oral food challenges. After avoidance of a particular food for 10 – 14 days it is not unusual for symptoms of vomiting to occur during a challenge, even though the patient was previously ingesting the food without vomiting each time they ate it.

4.1.1.2 Respiratory and skin food hypersensitivity reactions

Respiratory and ocular symptoms are common manifestations of IgE-mediated reactions to foods [1, 12, 14]. Symptoms may include periocular erythema, pruritus, and tearing; nasal congestion, pruritus, sneezing, and rhinorrhea; and coughing, voice changes, and wheezing. Isolated nasoocular symptoms are an uncommon manifestation of food hypersensitivity reactions.

The skin is a frequent target organ in IgE-mediated food hypersensitivity reactions. The ingestion of food allergens can either lead to immediate cutaneous symptoms or aggravate more chronic symptoms. Acute urticaria and angioedema are probably the most common cutaneous manifestation of food hypersensitivity reactions, generally appearing within minutes of ingestion of the food allergen. The foods commonly causing these reactions in children include eggs, milk, peanuts, and tree nuts. In adults, this list includes for the USA fish, shellfish, tree nuts, and peanuts, whereas in Europe fruits, nuts, and vegetables are the most prevalent elicitors.

Atopic dermatitis is a chronic skin disorder that generally begins in early infancy and is characterized by typical distribution, extreme pruritus, chronically relapsing course, and association with asthma and allergic rhinitis [15, 16].

4.1.2 Mixed IgE-mediated and non-IgE-mediated hypersensitivity

Allergic eosinophilic gastroenteropathy (Table 3) is a disorder characterized by infiltration of the gastric and/or intestinal walls with eosinophils, absence of vasculitis, and frequently peripheral eosinophils [3, 17]. Patients presenting with this syndrome frequently have post-prandial nausea and vomiting, abdominal pain, diarrhea, occasionally steatorrhea, and failure to thrive in young infants or weight loss in adults. There appears to be a subset of patients with allergic eosinophilic gastroenteritis who have symptoms secondary to food. These patients generally have the mucosal form of this disease with IgE-staining cells in jejunal tissue, elevated IgE in duodenal fluids, atopic disease, elevated

Table 3. Allergic eosinophilic gastroenterocolitis [44]

Manifestations
- Abdominal pain
- Anorexia
- Early satiety
- Failure to thrive
- Gastric outlet obstruction
- Gastric or colonic bleeding
- ± 70% of cases atopic
- Elevated immunoglobulin E
- ± Food-specific immunoglobulin E
- 50% of cases with peripheral eosinophilia
- Radiographic: antral obstruction, Menetrier's Disease, gastroesophageal reflux, bowl wall edema, vomiting, diarrhea, protein-losing enteropathy, decreased albumin

Age at onset
- Neonate to adolescent

Proteins implicated
- Cow's milk, egg, fish, soy, cereals
- Less than 50% skin test specificity

Pathology
- Marked eosinophilic infiltration of mucosa and submucosa; gastic antrum, esophagus, and duodenum; and colon

Treatment
- 50% of patients respond to dietary elimination of documented allergen
- Excellent response to hydrolyzed protein formula in patients less than 2 years of age
- Excellent response to L-amino acid formula
- Responsive to steroids

Natural history
- Disorder is typically prolonged

Table 4. Dietary protein enterocolitis [44]

Manifestations
- Diarrhea with bleeding
- Anemia
- Emesis
- Abdominal distension
- Failure to thrive
- Hypotension
- Fecal leukocytes
- Normal immunoglobulin E
- Food challenge: vomiting in 3 to 4 hours; diarrhea in 5 to 8 hours

Age at onset
- 1 day to 1 year

Implicated proteins
- Cow's milk, soy, rice, poultry, fish

Pathology
- Patchy villous injury and colitis

Treatment
- 80% or more of cases respond to hydrolyzed casein formula and symptoms clear in 3 to 10 days
- Up to 20% of cases require L-amino acid formula or temporary intravenous therapy

Natural history
- In general: with treatment 50% of cases resolve by 18 months; 90% of cases resolve by 36 months
- Cow's milk: with treatment 50% of cases resolve by 18 months; 90% of cases resolve by 36 months
- Soy: illness is often more persistent

serum IgE concentrations, positive prick skin tests to a variety of foods and inhalants, peripheral blood eosinophils, iron-deficiency anemia, and hypoalbuminemia.

The diagnosis of this entity is based on an appropriate history and a gastrointestinal biopsy demonstrating a characteristic eosinophilic infiltration. Multiple sites (up to eight) may need to be biopsied to effectively exclude eosinophilic gastroenteritis because the eosinophilic infiltrates may be quite patchy. Patients with the mucosal form of the disease may have atopic symptoms, including food allergy, elevated serum IgE concentrations, positive skin tests or radioallergosorbent tests (RASTs), and peripheral eosinophilia. Other laboratory studies consistent with this disease include Charcot-Leyden crystals in the stool, anemia, hypoalbuminemia, and abnormal D-xylose test results. An elimination diet of up to 12 wk may be necessary before complete resolution of symptoms and normalization of intestinal histology.

4.1.3 Non-IgE-mediated food hypersensitivity

Dietary protein enterocolitis (also known as protein intolerance) (Table 4) is a disorder which presents most commonly in young adults between 1 wk and 3 months of age. The typical symptoms are isolated to the gastrointestinal tract and consist of typically recurrent vomiting and/or diarrhea. The symptoms can be severe enough to cause dehydration. Cow's milk and/or soy protein (particularly in infant formulas) are most often responsible for this syndrome, although egg sensitivity has been reported in older patients. The children will often have stools which contain occult blood, polymorphonuclear neutrophils, and eosinophils, and are frequently positive for reducing substances (indicating malabsorbed sugars). Prick skin tests for the putative food protein characteristically yield negative results. Jejunal biopsies classically reveal flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells. A food challenge with the responsible protein generally results in vomiting and/or diarrhea within minutes to several hours, occasionally lead to shock [3, 18]. It is not uncommon to find children who are sensitive to both cow's milk and soy protein. This disorder also tends to be lost by 18 – 24 months of age. Elimination of the offending allergen

generally will result in improvement or resolution of the symptoms within 72 h, although secondary disaccharidase deficiency may persist longer. Oral food challenges, which should be done in a medical setting because they can induce severe vomiting, diarrhea, dehydration, or hypotension, consist of administering 0.6 gm/kg body weight of the suspected food allergen.

Dietary protein proctitis generally presents in the first few months of life and is often secondary to cow's milk or soy protein hypersensitivity [19]. Infants with this disorder often do not appear ill, have normally formed stools, and generally are discovered because of the presence of blood (gross or occult) in their stools. Gastrointestinal lesions are confined to the small bowel and consist of mucosal edema with eosinophils in the epithelium and lumina propria. If lesions are severe with crypt destruction, polymorphonuclear leukocyte are also prominent [19]. It is thought, without a lot of well-controlled studies, that cow's milk and soy protein-induced colitis resolves by 6 months to 2 years of allergen avoidance. Elimination of the offending food allergen leads to resolution of hematochezia within 72 h, but the mucosa lesions may take up to 1 month to disappear and range from patchy mucosal injection to severe friability with small aphthoid ulcerations and bleeding.

Celiac disease is an extensive enteropathy leading to malabsorption. Total villous atrophy and an extensive cellular infiltrate are associated with sensitivity to gliardia, the alcohol-soluble portion of gluten found in wheat oat, rye, and barley. The general incidence is thought to be 1 : 4000 but has been reported to be as high as 1 : 500 in Ireland. Patients have an apparent genetic predisposition to this disease because approximately 90% of patients are HLA-B8 positive and nearly 80% have the HLA-DW3 antigen. Patients often have presenting symptoms of diarrhea or frank steatorrhea, abdominal distention and flatulence, weight loss, and occasionally nausea and vomiting. Other extra-intestinal symptoms and oral ulcers secondary to malabsorption are not common.

4.2 Geographic aspects of food allergy

In Central and Northern Europe allergy to food of plant origin is in most instances mediated by a sensitization to birch pollen, and up to 80% of birch pollen allergic patients suffer from an associated food allergy. Birch pollen sensitized patients are mainly affected by allergic reactions to foods of the *Rosaceae* family such as apple, pear, cherry, peach and nectarine, but also to kiwi and various vegetables or nuts. The immunological basis of this phenomenon is IgE cross-reactivity due to highly homologous amino acid sequences resulting in homologous structures of pollen and food allergens of plant origin (reviewed in [20]). Bet v 1, the major allergen of birch pollen, and its homologous proteins in food of plant origin were identified as the most important mediators of cross-reactivity. In addition, profilin, first identified as the birch pollen allergen Bet v 2, the birch pollen allergens Bet v 6, a phenyl coumaran benzylic ether reductase, and Bet v 8, a pectin esterase, may also be involved in this kind of cross-reactivity. It is a common misbelief that patients with pollen-related food allergies always have mild oropharyngeal symptoms, *i. e.*, an OAS. Recent double-blind placebo-controlled food challenge (DBPCFC) studies on hazelnut, apple, and cherry allergy support this view [21]. However, other studies, in particular on celery, carrot, or soy allergy in pollen-allergic subjects, reported systemic reactions in approximately 50% of the patients according to case histories. Furthermore, up to 50% of the patients experienced systemic reactions under challenge even when DBPCFC was performed by a careful protocol starting with mucosal challenges which were abrogated at the lowest dose of food reproducibly causing symptoms [5, 8, 9, 22]. In conclusion, these studies showed that symptoms of pollen-related allergy to certain foods can be more severe than commonly assumed.

The general view, that allergy to fruits, especially fruits of the Rosaceae family, and to nuts is mainly birch pollen mediated was challenged by the first publications from the Mediterranean area mentioning a small 9 – 10-kDa allergen, later identified as a non-specific lipid transfer protein (LTP), as a major allergen for patients sensitized to members of the Rosaceae subfamily of Prunoideae. In several studies from Italy and Spain, IgEs from Mediterranean patients allergic to different fruits, nuts, or vegetables recognized LTP but not birch pollen allergens [23, 24].

The observation that allergy to Rosaceae fruits in the Mediterranean area may be acquired independent of any pollen sensitization suggests that sensitization to LTP may occur by the oral route. The fact that LTPs are very stable allergens, mirrored for instance by their extreme resistance to pepsin digestion, supports this hypothesis. As shown in different studies, LTP sensitization seems to be a special hallmark of the Mediterranean area. More importantly, sensitization to LTP may be accompanied by a higher prevalence of systemic symptoms than sensitization to the Bet v 1 homologous allergens in plant food [21, 24 – 26].

Apart from geographic differences in the sensitization pattern to the individual allergens of one food, the lists of the most prevalent triggering foods leading to allergic reactions in different geographic areas show important differences which may be most likely explained by different nutritional habits. Whereas in the USA, UK, and Scandinavian countries peanuts and nuts are the most prevalent elicitors of anaphylaxis to foods, this is not the case in other regions. The top culprit foods for potentially life-threatening aller-

gic reactions to foods are, for instance, egg and seafood in France, in Switzerland celery (a pollen-related food), in Singapore bird's nest, and in Australia seafood [27].

4.3 Diagnosing adverse food reactions

As with all medical disorders, the diagnostic approach to the patient with a suspected adverse food reaction begins with the medical history and physical examination. Based on the information derived from these initial steps, various laboratory studies may be helpful [28, 29] (Table 5).

The true value of the medical history is largely dependent on the patient's recollection of symptoms and the examiner's ability to differentiate disorders provoked by food hypersensitivity and other etiologies. The history may be directly useful in diagnosing food allergy in acute events (*e.g.*, systemic anaphylaxis following the ingestion of fish). In many series in children with atopic dermatitis, less than 50% of reported food allergic reactions could be substantiated by DBPCFC [12]. In adults, however, this figure is substantially higher, *i.e.*, about 80%. Several pieces of information are important to establish that a food allergic reaction occurred: (i) the food suspected to have provoked the reaction, (ii) the quantity of the food ingested, (iii) the length of time between ingestion and development of symptoms, (iv) a description of the symptoms provoked, (v) whether similar symptoms developed on other occasions when the food was eaten, (vi) whether other factors (*e.g.*, exercise) are necessary, and (vii) the length of time since the last reaction. Any food may cause an allergic reaction, although only a few foods account for 90% of the reactions. In children these foods are egg, milk, peanuts, soy, and wheat (fish in Scandinavian countries), whereas in adults fruits, nuts, vegetables, and legumes are the most prevalent elicitors of food allergy. In chronic disorders like atopic dermatitis the history is often an unreliable indicator of the offending allergen.

A diet diary has been frequently used as an adjunct to the medical history. Patients are asked to keep a chronological record of all foods ingested over a specified period of time and to record any symptoms they experience during this time. The diary can then be reviewed at a patient visit to determine if there is any relationship between the foods ingested and the symptoms experienced. It is uncommon that this method will detect an unrecognized association between a food and a patient's symptoms. However, as opposed to the medical history, you can collect information on a prospective basis that is not so dependent on a patient's or parent's memory.

An elimination diet is frequently used both in diagnosis and management of adverse food reactions. If a certain food or foods are suspected of provoking the reaction, they are completely eliminated from the diet. The success of an elimination diet depends on several factors, including the correct identification of the allergen(s) involved, the ability of the patient to maintain a diet completely free of all forms of the possible offending allergen, and the assumption that other factors will not provoke similar symptoms during the study period. The likelihood of all of these conditions being met is often slim. For example, in a young infant reacting to cow's milk formula, resolution of symptoms following substitution of cow's milk formula with a soy formula or casein hydrolysate (Alimentumâ, Nutramigenâ) is highly suggestive of cow's milk allergy, but it could also be due to lactose intolerance. Avoidance of suspected food allergens prior to blinded challenge is recommended so the reactions may be heightened. Elimination diets, however, are rarely diagnostic of food allergy, particularly in chronic disorders such as atopic dermatitis or asthma.

Table 5. Methods used in the evaluation of food allergic reactions

Medical history
Diet diary
Elimination diet
Prick skin testing (PST)
In vitro determination of specific IgE (CAP-FEIA, RAST)
Double-blind placebo-controlled food challenge (DBPCFC) (open or single-blind challenge)

Allergy prick skin tests are highly reproducible and often used to screen patients with suspected IgE-mediated food allergies [30]. The glycerinated food extracts (1 : 10 or 1 : 20) and appropriate positive (histamine) and negative (saline) controls are applied by either the prick or puncture technique. A food allergen eliciting a wheal (not including erythema) at least 3 mm greater than the negative control is considered positive; anything else is considered negative. There are two important pieces of information gained from allergy prick skin tests. First, a positive skin test to a food merely indicates the possibility that the patient has symptomatic reactivity to that specific food but is not proof (overall the positive predictive accuracy is less than 50%). Second, a negative skin test may confirm the absence of an IgE-mediated reaction (overall negative predictive accuracy is greater than 95%). Both of these statements are justified if appropriately standardized and good-quality food extracts are used.

The prick skin test can be considered an excellent means of excluding IgE-mediated food allergies, but is only “suggestive” of the presence of clinical food allergies. There are some minor exceptions to the general statement: (i) IgE-mediated sensitivity to several fruits and vegetables (apples, bananas, kiwi, pears, melons, carrots, celery, *etc.*) is frequently not detected with commercial reagents, presumably

secondary to the liability of the responsible allergen in the food; (ii) children less than 1 year of age may have IgE-mediated food allergy without a positive skin test, and children less than 2 years of age may have smaller wheals, possibly due to the lack of skin reactivity, and conversely, (iii) a positive skin test to a food ingested in isolation which provokes a serious systemic anaphylactic reaction may be considered diagnostic.

An intradermal skin test is a more sensitive tool than the prick skin test but is much less specific than a DBPCFC [31]. In Bock's study [31], no patient who had a negative prick skin test but rather a positive intradermal skin to a specific food had a positive DBPCFC to that food. In addition, intradermal skin testing increases the risk of inducing a systemic reaction compared with prick skin testing.

RASTs and similar *in vitro* assays (including ELISAs) are utilized for the identification of food-specific IgE antibodies. These tests are often used to screen for IgE-mediated food allergies. While generally considered slightly less sensitive than skin tests, one study comparing Phadebos RASTâ with DBPCFCs found prick skin tests and RASTs to have similar sensitivity and specificity when a Phadebos score of 3 or greater was considered positive [32]. In this study, if a 2 was considered positive there was a slight improvement in sensitivity while the specificity decreased significantly. In general, *in vitro* measurements of serum food-specific IgE performed in high-quality laboratories provide information similar to prick skin tests. The newest generation of *in vitro* studies for specific IgE includes the CAP-FEIAâ. For children with atopic dermatitis and suspected food allergy, levels of specific IgE that are greater than 95% predictive of a patient being allergic to that food (so-called decision points) have been suggested for milk, egg, or peanut [29]. However, in similar studies performed in other centers different decision points have been determined, indicating that further studies are warranted to establish more reliable data [33]. The DBPCFC has been labeled the "gold standard" for the diagnosis of food allergy [5, 34]. This test has been used successfully by many investigators in both children and adults for the last few years to examine a wide variety of food-related complaints. The foods to be tested in the oral challenge are based on history and/or prick skin test (RAST) results.

A DBPCFC is the best means of controlling for the variability of chronic disorders (*e.g.*, chronic urticaria, atopic dermatitis, *etc.*), any potential temporal effects, and acute exacerbations secondary to reducing or discontinuing medications. In particular, psychogenic factors and observer bias are eliminated. These are the rare false-negative challenges in a DBPCFC. This may occur when a patient receives insufficient challenge material during the challenge to provoke the reaction or the lyophilization of the food antigen has altered the relevant allergenic epitopes (*e.g.*, fish). Therefore, the use of native fresh food for challenges is the most reliable way. Overall, the DBPCFC has proven to be the most accurate means of diagnosing food allergy at the present time.

4.4 Practical approach to diagnosing food allergy

The diagnosis of food allergy remains a clinical exercise that uses a careful history, selective prick skin tests or RASTs (if an IgE-mediated disorder is suspected), appropriate exclusion diet, and blinded provocation. Other diagnostic tests which do not appear to be of significant value include food-specific IgG or IgG4 antibody levels, food-antigen-antibody complexes, evidence of lymphocyte activation (^{3}H uptake, IL-2 production, leukocyte inhibitory factor, *etc.*), and intracutaneous provocation. Blinded challenges may not be necessary in suspected gastrointestinal disorders where pre- and post-challenge laboratory values and biopsies are often used.

An exclusion diet eliminating all foods suspected by history and/or prick skin testing (or RASTs) for IgE-mediated disorders should be conducted for at least 1 – 2 wk. Some gastrointestinal disorders may need to have the exclusion diet extended for up to 12 wk following appropriate biopsies. If no improvement is noted following the diet it is unlikely that food allergy is involved. In the case of some chronic diseases, such as atopic dermatitis or chronic asthma, other precipitating factors may make it difficult to discriminate the effects of the food allergen from other provoking factors.

Open or single-blind challenges in a clinic setting may be helpful to screen suspected food allergens. The presumptive diagnosis of food allergy based on a patient's history and prick skin tests or RAST results is no longer acceptable. There are exceptions to this, such as patients with severe anaphylaxis following the isolated ingestion of a specific food. It is important that the medical care provider make an unequivocal diagnosis of food allergy. If the present practice continues, over one-quarter of the population will continue to alter their eating habits based on a misconception of food allergy.

5 Treatment

Once the diagnosis of food allergy is established, the only proven therapy is the strict elimination of the food from the patient's diet. Elimination diets may lead to malnutrition and/or eating disorders, especially if they include a large number of foods and/or are followed for extended periods of time. Studies have shown that symptomatic food sensi-

tivity generally is lost in children over time except for sensitivity to peanuts, tree nuts, and seafood. In adults, however, the prognosis of food allergy is less favorable.

Whereas symptomatic food sensitivity is very specific in some patients, *i. e.*, they do not react to more than one member of a botanical family or animal species, this is not the case in other patients and in particularly not in pollen-related food allergy. Here, cross-reactions can even occur between phylogenetically distantly related species such as birch and kiwi or soy.

Certain factors place some individuals at increased risk for more severe anaphylactic reactions: (i) history of a previous anaphylactic reaction, (ii) history of asthma, especially if poorly controlled, (iii) allergy to peanuts, nuts, fish, and shellfish, (iv) patients on β-blockers or acetylcholinesterase inhibitors, and (v), possibly, being female.

5.1 Medications

Several medications have been used in an attempt to protect patients with food hypersensitivity, including oral cromolyn, H_1 and H_2 antihistamines, ketotifin, corticosteroids, and prostaglandin synthetase inhibitors.

Some of these medications do modify food allergy symptoms in a therapeutic approach, but overall they have minimal efficacy or unacceptable side effects in a prophylactic approach. The use of epinephrine is vitally important in acute anaphylaxis. The prompt administration of epinephrine when symptoms of systemic reactions to foods develop cannot be overemphasized. Epi-Penâ (0.3 mg) and Epi-Pen, Jr. â (0.15 mg) should be given IM at a dose of 0.01 mg/kg.

5.2 Immunotherapy

Recent blinded, placebo-controlled studies of rush immunotherapy for the treatment of peanut hypersensitivity demonstrated efficacy in a small number of patients [35]. The adverse reaction rates were significant and preclude any general clinical application at this time.

Newer types of vaccines for immunotherapy specifically for food-induced anaphylaxis being developed include: (i) humanized anti-IgE monoclonal antibody therapy, (ii) plasmid-DNA immunotherapy, (iii) peptide fragments: "overlapping" peptides, (iv) cytokine-modulated immunotherapy, (v) immunostimulatory sequence-modulated immunotherapy, (vi) bacterial-encapsulated allergen immunotherapy, and (vii) "engineered" recombinant protein immunotherapy [36].

5.3 Patient education

Patient education and support are essential for food allergic patients. In particular, adults and older children prone to anaphylaxis (and their parents) must be informed in a direct but sympathetic way that these reactions are potentially fatal.

When eating away from home, food-sensitive individuals should feel comfortable to request information about the contents of prepared foods. For the school-aged child, the American Academy of Pediatrics Committee of School Health has recommended that schools be equipped to treat anaphylaxis in allergic students. Children over the age of 7 years can usually be taught to inject themselves with epinephrine. The physician must be willing to explain and, with the parents, help instruct school personnel about these issues. In the home, one must consider the need to eliminate the incriminating allergen should be considered, or if this is not practical, warning stickers should be placed on foods with the offending antigens.

A variety of groups can help provide support, advocacy, and education, including The Food Allergy and Anaphylaxis Network (10400 Easton Place, Suite 107, Fairfax, VA 22030-5647, USA; www.foodallergy.org).

6 Prognosis

For many young children diagnosed with anaphylaxis to foods such as milk, egg, wheat, and soybeans, there is a good possibility that the clinical sensitivity may be outgrown after several years [13, 37]. Children who develop their food sensitivity after 3 years of age are less likely to lose their food reactions over a period of several years. Patients who develop very mild reactions to peanuts early in life (first 12 – 24 months) may outgrow their symptoms (up to 20%) [38 – 40]. Allergies to foods such as tree nuts, fish, and seafood are generally not outgrown no matter at what age they develop. These individuals appear likely to retain their allergic sensitivity for a lifetime. Consequently several groups are evaluating new strategies to "desensitize" patients to these foods [36, 41].

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