

Food Allergy in Children

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Food allergic reactions have generated increasing concern in the United States, with approximately one fourth of American households altering their dietary habits because a member of the family is perceived to suffer from food allergies [1]. Scientific, prospective studies, however, have indicated that only 6% to 8% of children younger than 5 years experience IgE-mediated food allergic reactions, with about 1.5% of young children reacting to cow's milk, about 1.3% to hen's egg, and 1.0% to peanut [2–4]. There is some evidence to suggest that certain food allergies, such as peanut allergy, have been increasing during the past 2 decades [4]. Both in a cohort of American children and in a population-based study of young children, the prevalence of sensitivity to peanuts at least doubled in the last 10 years [4]. Food hypersensitivity is reportedly less common in adults, but a recent survey in the United States found that 1.3% of adults are allergic to peanuts or tree nuts [4,5]. Given the estimated frequency of allergy to fish, shellfish, and other sensitivities, it is likely that about 4% of the adult population, or about 5.5 million Americans, are affected by food allergies [6].

In spite of increased recognition and understanding of food allergies, food-induced anaphylaxis is the single most common cause of anaphylaxis seen in hospital emergency departments, accounting for about one third of anaphylaxis cases seen [7]. It is estimated that about 30,000 food-induced anaphylactic

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events are seen in emergency departments in the United States each year and that about 200 fatal cases occur in the United States each year. Peanuts or tree nuts cause more than 80% of these reactions [7].

Food hypersensitivity is a common clinical allergic problem. Adverse reactions to foods are classified as either food allergy or food intolerance [8,9]. The use 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) (Fig. 1) 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 IgE mechanism, of which anaphylaxis is the classic example.

Food intolerance (Table 1) 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 (eg, histamine in scombroid fish poisoning, toxins secreted by Salmonella, Shigella, and Campylobacter organisms)
- Pharmacologic properties of the food (eg, caffeine in coffee, tyramine in aged cheeses)
- Host characteristics such as metabolic disorders (eg, lactase deficiency)
- 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 most well-characterized food

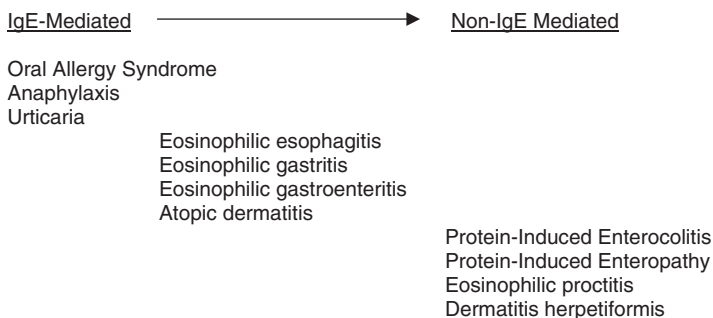


Fig. 1. Food hypersensitivity (allergy) immunologic spectrum.

Table 1
Food intolerance: non-immunologic adverse reactions

Toxic/pharmacologic	Nontoxic/intolerance
Bacterial food poisoning	Lactase deficiency
Heavy metal poisoning	Galactosemia
Scombroid fish poisoning	Pancreatic insufficiency
Caffeine	Gallbladder/liver disease
Tyramine	Hiatal hernia
Histamine	Gustatory rhinitis
	Anorexia nervosa

allergic reactions, although non-IgE-mediated immune mechanisms are believed to be responsible for a variety of hypersensitivity disorders. This article examines adverse food reactions that are IgE-mediated, non-IgE-mediated, and those entities that have characteristics of both.

Pathophysiology

IgE-mediated responses

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 the gastrointestinal tract. Either a failure to develop or a breakdown in oral tolerance results in excessive production of food-specific IgE antibodies [10]. These food-specific antibodies bind high-affinity Fc ϵ I receptors on mast cells and basophils and low-affinity Fc ϵ II receptors on macrophages, monocytes, lymphocytes, eosinophils, and platelets [9,11]. After the food allergen binds to 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 [12–14]. A rise in plasma histamine has been associated with IgE-mediated allergic symptoms after blinded food challenges [15]. In IgE-mediated gastrointestinal reactions, endoscopic observation has revealed local vasodilatation, edema, mucus secretion, and petechial hemorrhaging. Increased stool and serum prostaglandin E₂ and prostaglandin F₂ have been seen after food challenges causing diarrhea.

Non-IgE-mediated responses

Although a variety of reports have discussed other immune mechanisms causing food allergic reactions, the scientific evidence supporting these mechanisms is limited. Several studies have examined type III (antigen-antibody complex-mediated) hypersensitivity reactions [9,16]. Although 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 in which 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 (ie, enterocolitis), but significant supporting evidence of a specific cell-mediated hypersensitivity disorder is lacking.

Clinical manifestations of food hypersensitivity

IgE-mediated hypersensitivity

Gastrointestinal food hypersensitivity reactions

The signs and symptoms of food-induced IgE-mediated gastrointestinal allergy in humans may be secondary to a variety of syndromes including the oral allergy syndrome, immediate gastrointestinal hypersensitivity, and, in a small subgroup of patients, allergic eosinophilic gastroenteritis [16].

The oral allergy syndrome (pollen-associated food allergy) (Box 1) [17,18] is considered a form of contact urticaria that is confined almost exclusively to the oropharynx and rarely involves other target organs.

The symptoms include rapid onset of pruritus and angioedema of the lips, tongue, palate, and throat. The symptoms generally resolve quite rapidly. This syndrome is most commonly associated with the ingestion of fresh fruits and vegetables, not processed foods. Patients with allergic rhinitis secondary to certain airborne pollens (especially ragweed and birch pollens) are frequently afflicted with this syndrome. Patients with ragweed sensitivity may experience these symptoms following contact with certain melons (eg, watermelons, cantaloupe, honeydew) and bananas. Patients with birch sensitivity often have symptoms following the ingestion of raw potatoes, carrots, celery, apples, and hazelnuts. The diagnosis of this syndrome is made after a suggestive history and positive skin-prick tests with the implicated fresh fruits or vegetables [17]. The caveat in this syndrome is that the commercially available allergen extracts for fruits and vegetables may be heat labile and often do not have the reliability of an allergen from the fresh food. It may be necessary to use the prick-by-prick method, in which the device used for introducing the allergen into the skin must first be pricked into the food.

Immediate gastrointestinal hypersensitivity (Box 2) is a form of IgE-mediated gastrointestinal hypersensitivity that may accompany allergic manifestations in

Box 1. Oral allergy syndrome (pollen-associated food allergy)*Oral manifestations*

- Burning
- Swelling
- Itching
- Erythema
- Immediate onset of symptoms

Age of onset

- Beyond infancy
- Typically younger than 5 years

Proteins implicated

- Heat-labile fresh fruit and vegetable allergens
- Pollen and latex cross-reactivity

Pathology

- IgE antibodies

Treatment

- Avoidance
- Cooking the food

Natural history

- Unknown

From Sampson HA, Anderson JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. *J Pediatr Gastroenterol Nutr* 2000;30(Suppl 1):S87–94; with permission.

other target organs [2,16]. The symptoms vary but may include nausea, abdominal pain, abdominal cramping, vomiting, or diarrhea. In studies of children with atopic dermatitis and food allergy, the frequent ingestion of a food allergen seems to induce partial desensitization of gastrointestinal mast cells resulting in less-pronounced symptoms.

Box 2. Immediate gastrointestinal hypersensitivity*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 findings: gastric hypotonia and pylorospasm

Age of onset

- Infancy, childhood

Proteins implicated

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

Pathology

- IgE-mediated

Treatment

- Protein elimination

Natural history

- 80% of cases (except for cases of peanut and fish allergy) resolve after protein elimination diet

From Sampson HA, Anderson JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. *J Pediatr Gastroenterol Nutr* 2000;30(Suppl 1):S87–94; with permission.

The diagnosis of these symptoms is made by a suggestive clinical history, positive skin-prick tests, complete elimination of the suspected food allergen for up to 2 weeks with resolution of symptoms, and oral food challenges. After avoidance of a particular food for 10 to 14 days, vomiting may occur during a challenge even though the patient previously was able to ingest the food without having vomiting.

Respiratory and skin hypersensitivity reactions to food

Respiratory and ocular symptoms are common concurrent manifestations of IgE-mediated reactions to foods [16,19]. Symptoms may include periocular erythema, pruritus, and tearing; nasal congestion, pruritus, sneezing, and rhinorrhea; and coughing, voice changes, and wheezing. Isolated naso-ocular 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 lead to immediate cutaneous symptoms or can aggravate 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 fish, shellfish, tree nuts, and peanuts.

Atopic dermatitis is a chronic skin disorder that generally begins in early infancy and is characterized by typical distribution, extreme pruritus, a chronically relapsing course, and association with asthma and allergic rhinitis [20,21]. Up to one third of children with atopic dermatitis have at least one food allergic reaction [20]. The foods to which these children have reactions are primarily milk, egg, peanut, soy, wheat, fish, and tree nuts. Food challenges may be needed to help with the diagnosis of food allergy in these children.

Mixed IgE-mediated and non-IgE-mediated reactions

Allergic eosinophilic gastroenteropathy (Box 3) is a disorder characterized by infiltration of the gastric or intestinal walls with eosinophils, absence of vasculitis, and, frequently, peripheral eosinophils [2,22,23]. Patients presenting with this syndrome frequently have postprandial nausea and vomiting, abdominal pain, diarrhea, occasionally steatorrhea, and failure to thrive in young infants or weight loss in adults. There seems 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 serum IgE concentrations, positive skin-prick 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. As many as eight biopsy sites may be required to 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-prick tests or radioallergen sorbent tests (RASTs), and peripheral eosinophilia. Other laboratory studies consistent with this disease include Charcot-Leyden crystals in the stool, anemia,

Box 3. Allergic eosinophilic gastroenterocolitis*Manifestations*

- Abdominal pain
- Anorexia
- Early satiety
- Failure to thrive
- Gastric outlet obstruction
- Gastric or colonic bleeding
- Atopic in $\pm$ 70% of cases
- Elevated IgE
- $\pm$ Food-specific IgE
- 50% of cases with peripheral eosinophilia
- Radiographic findings: antral obstruction, Menetrier's disease, gastroesophageal reflux, bowel 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; gastric antrum, esophagus, 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

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hypoalbuminemia, and abnormal D-xylose tests. An elimination diet lasting to 12 weeks may be necessary before complete resolution of symptoms and normalization of intestinal histology.

Non-IgE-mediated food hypersensitivity

Dietary protein enterocolitis (also known as protein intolerance) (Box 4) [16] is a disorder that presents most commonly in infants between 1 day and 1 year of age. The typical symptoms are isolated to the gastrointestinal tract and typically consist of recurrent vomiting or diarrhea. The symptoms can be severe enough to cause dehydration. Cow's milk or soy protein (particularly in infant formulas) is most often responsible for this syndrome, although egg sensitivity has been reported in older patients. The children often have stools that contain occult blood, polymorphonuclear neutrophils, and eosinophils and are frequently positive for reducing substances (indicating malabsorbed sugars). Skin-prick tests for the putative food protein are characteristically negative. 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 or diarrhea within minutes to several hours, occasionally leading to shock [22]. It is common to find children who are intolerant to both cow's milk and soy protein. This disorder tends to subside by 18 to 24 months of age. Elimination of the offending allergen generally results in improvement or resolution of the symptoms within 72 hours, 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 g/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 [24]. Infants with this disorder often do not appear ill, have normally formed stools, and generally are discovered because of the presence of gross or occult blood in the stool. 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 leukocytes are also prominent [24]. It is thought, but has not been supported by well-controlled studies, that cow's milk- and soy protein-induced colitis resolves after 6 months to 2 years of allergen avoidance. Elimination of the offending food allergen leads to resolution of hematochezia within 72 hours, but the mucosal lesions, which range from patchy mucosal injection to severe friability with small aphthous ulcerations and bleeding, may take up to 1 month to disappear.

Celiac disease is an extensive enteropathy leading to malabsorption. Total villous atrophy and an extensive cellular infiltrate are associated with sensitivity to gliadin, the alcohol-soluble portion of gluten found in wheat oat, rye, and

Box 4. Dietary protein enterocolitis*Manifestations*

- Diarrhea with bleeding
- Anemia
- Emesis
- Abdominal distension
- Failure to thrive
- Hypotension
- Fecal leukocytes
- Normal IgE
- 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

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barley [16]. The general incidence is thought to be 1:4000 but has 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. Oral ulcers and other extra-intestinal symptoms secondary to malabsorption are not common.

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 (Box 5) [25].

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 from other causes. The history may be directly useful in diagnosing food allergy in acute events (eg, systemic anaphylaxis following the ingestion of fish). In many cases, however, less than 50% of reported allergic reactions to food could be substantiated by double-blind, placebo-controlled, food challenge (DBPCFC) [19,26,27]. Several pieces of information are important to establish that a food allergic reaction occurred:

1. The food suspected to have provoked the reaction
2. The quantity of the food ingested
3. The length of time between ingestion and development of symptoms
4. A description of the symptoms provoked
5. Whether similar symptoms developed on other occasions when the food was eaten
6. Whether additional factors (e.g. exercise) are necessary to induce the reaction
7. 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). In chronic disorders like atopic dermatitis, the history is often an unreliable indicator of the offending allergen.

A diet diary frequently has been used as an adjunct to the medical history. Patients are asked to keep a chronologic record of all foods ingested during a specified period 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. This method rarely detects an unrecognized association between a food and a patient's symptoms. In contrast to the medical history, one can collect infor-

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

Medical history

Diet diary

- Elimination diet
- Skin-prick testing
- RAST
- Basophil histamine release assay (research only)
- Intestinal mast cell histamine release (research only)
- Double-blind, placebo-controlled food challenge (DBPCFC) (Open or single-blind challenge)

mation on a prospective basis that is not so dependent on a patient's or parent's memory.

An elimination diet frequently is used in diagnosis and management of adverse food reactions. Foods suspected of provoking a reaction are eliminated completely from the diet. The success of an elimination diet depends on several factors, including the correct identification of the allergens 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 meeting all these requirements 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 (Alimentum, Ross Products, Columbus, OH; Nutramigen, Mead Johnson Nutritionals, Evansville, IN) is highly suggestive of cow's milk allergy, but the symptoms also could be caused by lactose intolerance. Avoidance of suspected food allergens before 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.

Allergy skin-prick tests are highly reproducible [28] and often are used to screen patients with suspected IgE-mediated food allergies. 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. The allergy skin-prick test provides two important pieces of information. First, a positive skin test to a food indicates the possibility that the patient has symptomatic reactivity to that specific food (overall, the positive predictive accuracy is less than 50%). Second, a negative skin test confirms the absence of an IgE-mediated reaction (overall negative predictive accuracy is greater than 95%). Both of these statements are justified if appropriate and good-quality food extracts are used.

The skin-prick test is an excellent means of excluding IgE-mediated food allergies but should be considered only suggestive of the presence of clinical food allergies. There are some minor exceptions to the general statement [16]:

1. IgE-mediated sensitivity to several fruits and vegetables (apples, oranges, bananas, pears, melons, potatoes, carrots, celery, among others) frequently are not detected with commercial reagents, presumably because of the instability of the responsible allergen in the food.
2. 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 because of the lack of skin reactivity.
3. Conversely, a positive skin test to a food ingested in isolation that provokes a serious systemic anaphylactic reaction may be considered diagnostic.

An intradermal skin test is a more sensitive tool than the skin-prick test but is much less specific than a DBPCFC. In one study, no patient who had a negative skin-prick test but a positive intradermal skin test to a specific food had a positive DBPCFC to that food [28]. In addition, intradermal skin testing increases the risk of inducing a systemic reaction compared with skin-prick testing.

RASTs and similar in vitro assays (including ELISA) are used to identify food-specific IgE antibodies. These tests often are used to screen for IgE-mediated food allergies. Although they are generally considered slightly less sensitive than skin tests, one study comparing Phadebos RAST (Pharmacia, Uppsala, Sweden) with DBPCFCs found skin-prick tests and RASTs to have similar sensitivity and specificity when a Phadebos score of three or greater was considered positive [29]. In this study, if a score of two was considered positive, there was a slight improvement in sensitivity, but the specificity decreased significantly. In general, in vitro measurements of serum food-specific IgE performed in high-quality laboratories provide information similar to skin-prick tests. The newest generation of in vitro studies for specific IgE include the CAP-RAST (CAP-FEI [Pharmacia, Uppsala, Sweden]). For patients with suspected food allergy, there are now accepted levels of specific IgE that are greater than 95% predictive of a patient's being allergic to that food [30,31]. This test is best used for patients with possible allergic reactions to milk, eggs, and peanuts (and possibly to wheat, soy, and fish)(Table 2).

The DBPCFC is the reference standard for the diagnosis of food allergy [16]. This test has been used successfully by many investigators in both children and adults for the last several years to examine a wide variety of food-related complaints. The foods to be tested in the oral challenge are based on history, skin-prick test, or RAST results.

A DBPCFC is the best means of controlling for the variability of chronic disorders (eg, chronic urticaria, atopic dermatitis), any potential temporal effects, and acute exacerbations secondary to reducing or discontinuing medications [16]. In particular, psychogenic factors and observer bias are eliminated. False-negative challenges are rare in a DBPCFC but may occur when a patient receives

Table 2

Food-specific IgE concentrations predictive of clinical reactivity

Allergen	Decision point (kU/L)	Sensitivity	Specificity	Positive predictive value (%)	Negative predictive value (%)
Egg	7	61	95	98	38
Infants $\leq$ 2yrs	2			95	
Milk	15	57	94	95	53
Infants $\leq$ 2yrs	5			95	
Peanut	14	57	100	100	36
Fish	20	25	100	100	89
Soybean	30	44	94	73	82
Wheat	26	61	92	74	87
Tree nuts ^a	~ 15	—	—	~ 95	

^a Tentative values.

Data from Boyano MT, Garcia-Ara C, Diaz-Pena JM, et al. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;31:1464–9 (egg); and Garcia-Ara C, Boyano-Martinez T, Diaz-Pena JM, et al. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol* 2001;107:185–90 (milk).

insufficient material during the challenge to provoke the reaction or the lyophilization of the food antigen has altered the relevant allergenic epitopes (eg, fish). Overall, the DBPCFC has proven to be the most accurate means of diagnosing food allergy now available.

Open food challenges (or single-blind challenges) may be used in many cases to diagnose patients with food allergy (Table 3). Many different schemes are available for the administration of food for an oral challenge.

Practical approach to diagnosing food allergy

The diagnosis of food allergy remains a clinical exercise that uses a careful history, selective skin-prick tests or RASTs (if an IgE-mediated disorder is sus-

Table 3

Example of open oral peanut challenge with peanut butter

Time (min)	Sequence (dose)	Peanut butter administered
0	1	1/32 t ^a , touch lip
15	2	1/32 t, inside buccal
25	3	1/32 t, on tongue
35	4	1/16 t ^b , ingested
45	5	1/4 t, ingested
55	6	1/4 t, ingested
65	7	1 t, ingested
75	8	Remaining up to a total of 2 peanut butter/T

Abbreviations: t, teaspoon; T, tablespoon.

^a 1/32 teaspoon is the size of three kernels of rice.

^b 1/16 teaspoon is the size of kernel of corn.

Box 6. Diagnostic approach to non-IgE-mediated disease

- Includes disease with unknown mechanisms
 - Food additive allergy
- Elimination diets (may need elemental diet)
- Oral challenges
 - Timing/dose/approach individualized for disorder
 - Enterocolitis syndrome can elicit shock
 - Enteropathy/eosinophilic gastroenteritis-prolonged feedings to develop symptoms
- DBPCFCs preferred
- May require ancillary testing (endoscopy/biopsy)

pected), appropriate exclusion diet, and blinded provocation (Boxes 6 and 7 and Table 4) [16,32]. Other diagnostic tests that do not seem to be of significant value include food-specific IgG or IgG₄ antibody levels, food-antigen-antibody complexes, evidence of lymphocyte activation (H₃ uptake, interleukin-2 production, leukocyte inhibitory factor, among others.), and sublingual or intra-cutaneous provocation. Blinded challenges may not be necessary in suspected gastrointestinal disorders, in which pre- and postchallenge laboratory values and biopsies are often used.

An exclusion diet eliminating all foods suspected by history or skin-prick testing (or RASTs) for IgE-mediated disorders should be followed for at least 2 weeks. Some gastrointestinal disorders may need to have the exclusion diet extended for as long as 12 weeks following appropriate biopsies. If no improvement is noted following the exclusion 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 provocative factors.

Box 7. Diagnostic approach to IgE-mediated food allergy

- Test for specific-IgE antibody
 - Negative: reintroduce food^a
 - Positive: start elimination diet
- Elimination diet
 - No resolution: reintroduce food^a
 - Resolution
 - Open/single-blind challenges for screening
 - DBPCFC for equivocal open challenges

^a Unless convincing history warrants supervised challenge

Table 4
Allergen cross-reactivity summary

Sensitivity	Possible cross-reaction	Risk (%)
A legume	Other legumes	5–10
A tree nut	Other tree nuts	40
A fish	Other fish	50
A shellfish	Other shellfish	50–75
A grain	Other grains	20
Egg	Chicken	5
Cow's milk	Beef	10
Cow's milk	Goat's milk	>90
Cow's milk	Mare's milk	4
Pollen	Fruits/vegetables	50
Melon	Other fruits (melon, banana, avocado)	90
Latex	Fruits	35
Fruits	Latex	10

Open or single-blind challenges in a clinic setting may be helpful to screen for suspected food allergens. The presumptive diagnosis of food allergy based on a patient's history and skin-prick tests or RAST results is no longer acceptable. There are exceptions, 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, more than one quarter of the population will continue to alter their eating habits based on misconception of food allergy.

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 [16,33]. Elimination diets may lead to malnutrition or eating disorders, especially if these diets include a large number of foods or are used for extended periods. Studies have shown that symptomatic food sensitivity generally is lost over time except for sensitivity to peanuts, tree nuts, and seafood.

Symptomatic food sensitivity is usually very specific, so patients rarely react to more than one member of a botanical family or animal species. Certain factors place some individuals at increased risk for more severe anaphylactic reactions:

1. History of a previous anaphylactic reaction
2. History of asthma, especially if poorly controlled
3. Allergy to peanuts, nuts, fish, and shellfish
4. Patients taking β -blockers or angiotensin-converting enzyme inhibitors
5. Possibly, female gender

Medications

Several medications have been used in an attempt to protect patients with food hypersensitivity, including oral cromolyn, H₁ and H₂ antihistamines, ketotifen, corticosteroids, and prostaglandin synthetase inhibitors.

Some of these medications may modify food allergy symptoms, but overall they have minimal efficacy or unacceptable side effects. The use of epinephrine is vitally important in acute anaphylaxis. The importance of prompt epinephrine administration when symptoms of systemic reactions to foods develop cannot be overemphasized. Epi-Pen (0.3 mg; Dey L.P., Napa, CA) and Epi-Pen, Jr. (0.15 mg; Dey L.P., Napa, CA) can be given intramuscularly or subcutaneously (most recent studies suggest intramuscular administration is better) at a dose of 0.01 mg/kg.

Immunotherapy

Recent blinded, placebo-controlled studies of rush immunotherapy for the treatment of peanut hypersensitivity demonstrated efficacy in a small number of patients [34]. The adverse reaction rates were significant and preclude general clinical application at this time.

Newer types of vaccines for immunotherapy specifically for food-induced anaphylaxis being developed include [35,36]

1. Humanized anti-IgE monoclonal antibody therapy [37]
2. Plasmid-DNA immunotherapy
3. Peptide fragments (overlapping peptides)
4. Cytokine-modulated immunotherapy
5. Immunostimulatory sequence-modulated immunotherapy
6. Bacterial-encapsulated allergen immunotherapy
7. Engineered recombinant protein immunotherapy [38,39].

Additionally, recent studies with humanized, monoclonal antibody anti-IgE have been used in phase I trials for patients with peanut allergy [37]. This type of therapy seems to be a promising future option for patients with a history of food-induced anaphylaxis or with a food allergy that places the patient at risk for a future systemic, anaphylactic reaction.

Patient education

Patient education and support are essential for patients with food allergies. In particular, adults and older children prone to anaphylaxis (and the parents of these children) 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 in requesting 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, consider the need to eliminate the incriminated allergen; if doing so is not practical, warning stickers can 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 (10,400 Easton Place, Suite 107, Fairfax, VA 22030-5647; www.foodallergy.org).

Prognosis

There is a good possibility that many young children diagnosed with anaphylaxis to foods such as milk, egg, wheat, and soybeans may outgrow the clinical sensitivity after several years [2,16,40–43]. Children who develop a food sensitivity after 3 years of age are less likely to lose the food reactions over a several-year period. Patients who develop very mild reactions (skin symptoms only) to peanuts early in life (ie, during the first 12–24 months) may outgrow their symptoms [40,41]. Allergies to foods such as tree nuts, fish, and seafood generally are not outgrown no matter at what age they develop. These individuals seem likely to retain their allergic sensitivity for a lifetime. Consequently, several groups are evaluating new strategies to desensitize patients to these foods.

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