

Food allergy: Diagnosis and treatment

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ABSTRACT

Immunoglobulin E-mediated food reactions usually develop within minutes of food ingestion. Although most reactions are not life-threatening, fatalities do occur. Risk factors for fatal food-induced anaphylaxis include the presence of asthma (a risk factor for anaphylaxis in general), failure to use epinephrine autoinjectors promptly, a history of severe reactions, known food allergy, denial of symptoms, and adolescent and young adult age. The most commonly implicated foods are cow's milk, egg, peanut, soy, tree nuts, fish, shellfish, and wheat. Peanut, tree nuts, and seafood are the most common food allergens in adults, whereas cow's milk, peanut, egg, soy, and wheat are more common in children. The major food allergens are glycoproteins, which are generally water soluble and stable to the effects of heat, proteases, and acids. Recent studies showed that natural tolerance can be acquired at a later age than previously thought, even during adolescence. Allergies to peanut, tree nuts, and seafood are frequently life-long. Patients and their caregivers should be taught when and how to administer injectable epinephrine. In terms of primary prevention, there is evidence that early introduction, followed by ongoing regular consumption of peanut has a protective effect on the development of peanut allergy.

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Food hypersensitivity is defined as an aberrant immune response induced by a food protein. Such responses may be immunoglobulin E (IgE) mediated, cell mediated, or mixed reactions. IgE-mediated (type I hypersensitivity) reactions account for the majority of immune-based food reactions. The overall prevalence of IgE-mediated food allergy in the general population is estimated to be between 2% and 10%.¹ Three million children (3.9%) under the age of 18 years are estimated to have food allergy, with an 18% increase over the previous decade noted in the 2008 National Center for Health Statistics assessment.² Analysis of the national survey data also indicates that the rate of peanut allergy has tripled since the late 1990s.^{1–3} Although any food may elicit an IgE-mediated reaction, the most commonly implicated foods are cow's milk, egg, peanut, soy, tree nuts, fish, shellfish, and wheat. In the United States, allergies to milk, egg, peanut, wheat, and soy are more common in children, whereas allergies to peanut, tree nuts, and seafood are common food allergens in adults. Food allergy is part of the atopic march, with atopic dermatitis that classically occurs

earliest in life, followed by food allergy, asthma, and, finally, allergic rhinitis.⁴

The major food allergens are glycoproteins that are generally water soluble and stable to the effects of heat, proteases, and acids. A failure to establish oral tolerance to these food proteins or a breakdown in existing tolerance allows for disproportionate production of food-specific IgE antibodies. Route of exposure, genetic susceptibility, patient age, and antigen properties (*e.g.*, solubility) are factors thought to contribute to the development of tolerance.^{5,6} Antigen dose, frequency of exposure, and preparation of the food also affect allergenicity and tolerance.⁷

IgE-mediated food reactions often are characterized by cutaneous manifestations, such as pruritis, rash, urticaria, or angioedema; however, these are not required for a diagnosis because anaphylactic reactions may occur without cutaneous findings in up to 20% of cases.⁸ Gastrointestinal manifestations, such as vomiting, diarrhea, and abdominal pain are common, especially in children. Oral symptoms may include tongue edema, lip or perioral edema, or pruritus of the palate or lips, and these also occur to a milder degree in patients with pollen-food allergy syndrome. Pollen-food allergy syndrome occurs when plant proteins, especially those in raw fruits and vegetables that are cross-reactive with those present in pollens, induce immediate symptoms on contact with the oral mucosa, which causes local mast cell activation.⁹ Isolated lower respiratory symptoms, such as bronchoconstriction and wheezing, are infrequent and more commonly occur as part of a generalized anaphylactic reaction. Similarly, sneezing, rhinorrhea, and nasal pruritus may occur in conjunction with the other symptoms noted

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above but are not suggestive of food allergy when they occur in isolation.

Food allergy is the most common cause of generalized anaphylaxis seen in hospital emergency departments.⁸ Peanut and tree nut ingestions account for the majority of food-induced anaphylaxis fatalities in the United States.¹⁰ Symptoms usually develop within minutes of food ingestion but may occur up to 2 hours later. Even after initial treatment, symptoms of anaphylaxis may recur 4–12 hours later. In the past, such “biphasic” reactions were reported to occur up to one-third of the time and to be just as severe as the initial reaction.^{8,10} Results of newer research indicate lower rates of biphasic reactions, of <1%.¹¹ In the context of positive results of oral food challenges, the rate of biphasic reaction was 0.6%, with these reactions being relatively mild.¹² It is important to note that food-induced anaphylaxis may be fatal. Risk factors for fatal food-induced anaphylaxis include the presence of asthma, failure to use epinephrine autoinjectors promptly, a history of severe reactions (known food allergy), denial of symptoms, and adolescent or young adult age.¹⁰

As emphasized in the National Institute of Allergy and Infectious Diseases sponsored food allergy guidelines,¹³ a thorough history is essential for proper assessment of IgE-mediated food allergy. The temporal association (typically within 2 hours of ingestion), reproducibility (symptoms occur on every exposure), and clinical features are important to ascertain. Diet history and ingredient labels should be carefully reviewed, although occult ingredients may be the cause. When the clinical history is suggestive of an IgE-mediated process, skin-prick tests (SPT) or *in vitro* tests to assess the presence of food-specific IgE should be performed to confirm the diagnosis. The positive predictive value of food SPT is <50%, but the negative predictive accuracy is >95%. Thus, a negative SPT result essentially rules out an IgE-mediated process. Intradermal tests should not be used in the assessment of food hypersensitivity due to a high false-positive rate and a risk of systemic allergic reaction.

In vitro measurement of serum food-specific IgE is sensitive but also has a high false-positive rate. Similar to SPT, food-specific IgE testing can be difficult to interpret, particularly when positive, with only a vague (or no) history of reaction and is more useful when yielding a negative result. For food-specific IgE, testing in the absence of a clinical history of reaction is generally not advised because of the high false-positive rate, which could lead to misdiagnosis and unnecessary dietary restriction. Both SPT wheal diameter and food-specific IgE levels do not correlate with the severity of food reactions, but rather, higher results are associated with a greater likelihood of clinical reactivity.¹⁴

Oral food challenges may be indicated for a diagnosis when the history and testing are inconclusive or when evaluating for the development of tolerance.¹⁵ Double-blind placebo controlled food challenges are considered to be the standard for a diagnosis because they are least susceptible to bias.¹⁵ However, because double-blind placebo controlled food challenges are labor and time intensive, open challenges often are used in the allergist’s office. Medications and supplies for emergency resuscitation must be immediately available to the supervising physician in such settings.

IgE-dependent food hypersensitivities are characterized as acute responses, but there are other subacute and chronic immunologic aberrancies that may affect the gastrointestinal tract or skin, particularly in children. Atopic dermatitis can be exacerbated by a food allergen; up to 35% of children with moderate-to-severe atopic dermatitis have been confirmed to have food allergy as a trigger.^{1,3,7} Eosinophilic gastroenteropathies occur *via* mixed IgE and non-IgE processes, and, in some patients, can be attributed to food allergens.¹⁶ Symptoms depend on the site of eosinophilic infiltration and can include dysphagia, gastroesophageal reflux, food impaction, gastric-outlet obstruction, postprandial emesis, weight loss, and failure to thrive. Non-IgE-mediated food reactions also exist. Food protein-induced enterocolitis syndrome has the most dramatic presentation of cell-mediated gastrointestinal food allergy in infants and is usually triggered by exposure to cow’s milk or soy. Patients present with delayed onset (>2 hours after ingestion) of profuse and persistent vomiting, abdominal cramps, and/or diarrhea, which results in dehydration, metabolic acidosis, and, sometimes, hypotension and shock.¹⁷ Some patients have chronic diarrhea and poor growth, which resolve on elimination of the antigen (chronic food protein-induced enterocolitis syndrome). Dietary protein-induced proctitis or proctocolitis, in contrast, is a relatively benign disorder of infancy, which results in bloody, mucous-containing stools due to cow’s milk exposure and usually resolves by 1 year of age. Dietary-protein enteropathy, also usually attributable to cow’s milk, is a malabsorptive disorder characterized by diarrhea and poor weight gain. This disorder is transient and does not require permanent elimination diets.

Current treatment of IgE-mediated food reactions focuses on food allergen avoidance and prompt treatment of reactions. Treatment of acute reactions is dependent on the severity of symptoms with isolated, nonprogressive cutaneous symptoms being treated with H₁ antihistamine and severe or multisystem anaphylactic reactions that require epinephrine. Autoinjectors that contain epinephrine should be prescribed to facilitate rapid administration, after which a call to emergency medical services or transport to the nearest

hospital should occur. Observation for a minimum of 4 hours after resolution of the immediate response is advisable due to the risk of a biphasic reaction.¹¹ Evaluation and regular follow-up with an allergy/immunology specialist, including periodic measurement of serum food-specific IgE should be performed to help determine if tolerance has developed and when food challenge can be recommended.¹⁵

Whereas analysis of older data suggests that the majority of children outgrow allergies to foods such as cow's milk and egg by age 5 years, results of more recent studies indicate that tolerance is often acquired later; although only 42% develop natural tolerance to cow's milk by age 8 years, 79% of children become tolerant by age 16 years.¹⁸ Egg allergy has been found to have a similar trajectory.¹⁹ More-rapid resolution rates have been shown for wheat (65% outgrow the allergy by age 12 years) and soy (69% outgrow the allergy by age 10 years).^{20,21} However, allergies to certain foods, such as peanuts, tree nuts, and seafood, are frequently life-long.

Recently, research initiatives have focused on the possibility of primary prevention. The Learning Early About Peanut Allergy study,²² the first randomized trial to evaluate early allergen introduction as a prevention strategy, demonstrated that early and regular feeding of peanut to infants at high risk of developing a peanut allergy led to an 86.1% relative reduction in the prevalence of peanut allergy at age 5 years.²² High risk was defined as history of either moderate-severe atopic dermatitis or egg allergy. Subsequently, the National Institute of Allergy and Infectious Diseases addendum guidelines for prevention of peanut allergy²³ were published. If an infant does not have atopic dermatitis or a history of food allergy, the recommendation is to introduce peanut at an age-appropriate time, in accordance with family preference and cultural practice.

If an infant has mild-to-moderate atopic dermatitis, then the recommendation is to introduce peanut-containing foods at approximately 6 months of age. If an infant has severe eczema, egg allergy, or both, then the recommendation is to highly consider evaluation with peanut-specific IgE or SPT, and, if necessary, oral food challenge. Based on results of this testing, peanut-containing foods should be introduced at 4–6 months of age.²³ The American Academy of Pediatrics recommendations for prevention of atopic disease in those infants with a strong family history include breast-feeding for at least 6 months or substituting extensively or partially hydrolyzed formulas for cow's milk-based formula in those infants who are not breast-fed.²⁴

Because no approved treatment for food allergy exists, there is much excitement over products that are currently in randomized clinical trials. Phase III clinical

trials of immunotherapy *via* oral and epicutaneous routes are evaluating the risks and benefits of desensitization, and studies of sublingual immunotherapy are also being performed. U.S. Food and Drug Administration approved therapies for food allergy are anticipated in the near future.

IMMUNOLOGY

- Food hypersensitivity develops due to a failure to establish oral tolerance or due to a breakdown in existing tolerance.
- The skin and gastrointestinal tract play major roles in achieving tolerance versus developing allergic sensitization.²⁵
- Food proteins that escape proteolysis are taken up by intestinal epithelial cells and presented to primed T cells. This process leads to the generation of T helper type 2 cells that produce IL-4, IL-5, and IL-13, which can lead to the responses of IgE-mediated hypersensitivity reactions.⁷
- The dose of antigen and frequency of ingestion are the primary factors in determining whether oral tolerance will be induced *via* active suppression by regulatory T cells (favored by low dose) or by clonal anergy or deletion (favored by high dose).⁶ To maintain desensitization, regular consumption of the allergen is needed.⁶

CLINICAL PEARLS

- Food-induced anaphylaxis may occur without skin manifestations, so health-care providers need to have a high index of suspicion for possible IgE-mediated food reactions when treating patients.
- Common food allergens in children include egg, peanut, cow's milk, soy, tree nuts, fish, shellfish, and wheat. Peanut, tree nut, fish, and shellfish represent the common food allergens in adults.
- Children may not outgrow allergies to cow's milk and egg until adolescence. Allergies to peanut, tree nuts, fish, and shellfish typically persist into adulthood.^{1,7,18,19}
- It is advisable that any patient with a food allergy carry an epinephrine autoinjector at all times and be instructed on its proper use.
- In accordance with the Learning Early About Peanut Allergy study guidelines,²² early introduction of peanut is now recommended to help prevent development of peanut allergy. An infant with severe eczema or a known egg allergy should be tested for the presence of IgE to peanut, and, it is advised, depending on the results, to introduce peanut at 4–6 months of age if able, with ongoing consumption thereafter.^{22,23}

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