

CHAPTER 14

Food allergy

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DEFINITIONS

Standardized nomenclature has facilitated research in the study of reactions to foods and food additives. Adverse food reaction is a generic term referring to any untoward reaction after the ingestion of a food or food additive. Adverse food reactions can be categorized into two types: food allergy (food hypersensitivity) and food intolerance. A food hypersensitivity reaction is an abnormal immunologic response, whereas food intolerance is the result of nonimmunologic mechanisms. Such mechanisms include responses to the pharmacologic properties of the food (e.g., caffeine in irritable bowel, tyramine in the induction of nausea, vomiting, and headache); to toxins contained in the food, often from improper handling (e.g., histamine in scombroid fish poisoning and gastroenteritis secondary to *Salmonella*, *Shigella*, and *Campylobacter* toxins), and to metabolic disorders (e.g., abdominal pain and diarrhea secondary to lactase and other disaccharidase deficiencies, phenylketonuria).

PREVALENCE

No satisfactory epidemiologic studies have been conducted to determine the prevalence of adverse food reactions in adults. A recent survey indicated that about one third of adults reported experiencing adverse food reactions. Two studies in children have addressed the prevalence of adverse food reactions: one study examined Finnish children 6 years of age or less and the other studied American children 3 years of age or less. Parents in both studies reported that about one quarter of their children less than 4 years of age had adverse food reactions. Interestingly, both studies were able to confirm adverse food reactions by blinded challenge in 8% of the populations studied. Overall, 1% to 3% of the pediatric population is believed to have food allergic reactions. However, food allergy may be as high as 30% in some groups, such as children with atopic dermatitis.¹

PATHOPHYSIOLOGY

Food allergy develops as a result of interactions between food allergens, the gastrointestinal tract, and the immune system. Foods consist of protein, carbohydrate, and fat. The glycoprotein portion of the food is generally implicated in allergic responses. These glycoproteins are generally water soluble, largely heat resistant and acid stable, and commonly in the range of 14 to 40 kilodaltons in molecular weight. A few foods cause most allergic reactions: in adults, fish, shellfish, tree nuts, and peanuts are the main causes, whereas in children, eggs, peanuts, milk, soy, and wheat are the main culprits.

The gastrointestinal tract consists of a series of barrier networks that largely prevent foreign proteins (such as food antigens) from entering the body. Various intestinal and pancreatic enzymes break proteins into amino acids and small peptides. The gut enterocyte selectively absorbs small peptides and amino acids, and further breaks down small peptides to non-antigenic fragments. Secretory IgA molecules in the gut lumen complex with foreign protein, blocking their absorption, while circulatory IgA may bind foreign protein, thus allowing access to the circulation and leading to its clearing in the bile.²

Despite the intricate barrier network to prevent the entry of foreign protein into the body, Walzer et al.³ unequivocally established that food proteins readily gain access to the circulation and are transported to distal target organs. In normal volunteers in a series of experiments utilizing P-K tests with serum from highly food-allergic individuals, Walzer et al. demonstrated that food antigens gain access to the body at all levels of the gastrointestinal tract. Other investigators have presented evidence to suggest that antigen permeability is increased after gastroenteritis and in young infants.

CLINICAL SYMPTOMS

A variety of symptoms have been documented to be secondary to food hypersensitivity reactions. Fatal anaphylactic reactions were reported⁴ in seven patients, and several reports of anaphylactic shock secondary to food hypersensitivity have appeared in the

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literature. Anaphylactic shock secondary to exercise after the ingestion of certain foods also has been reported in some individuals.

Several claims have been made for the use of fasting or hypoallergenic diets in treating rheumatoid arthritis. However, only two cases are reported in which the investigators documented a cause and effect by double-blind, placebo-controlled oral food challenges. Oligoantigenic diets also have been claimed to be successful in treating seizure disorders in some children. A study identified 16 children with epilepsy and migraine who had exacerbation of seizures during double-blind, placebo-controlled oral food challenges.⁵ Reports since the turn of the century have suggested a role for elimination diets in the treatment of migraine headaches. Vaughn et al.⁶ found that headache cleared in 15% of 80 adult patients with migraine while following an elimination diet, and their symptoms were exacerbated during double-blind challenge with a single food.

Acute urticaria/angioedema secondary to ingestion or contact with food is common, although the actual prevalence of this disorder is not known. Chronic urticaria/angioedema secondary to food allergy is believed to be rare. The development of atopic dermatitis has been associated with food hypersensitivity in children. During blinded food challenges a pruritic, erythematous morbilliform rash develops within 10 to 90 minutes of allergen ingestion.⁷ Repeated ingestion of the offending allergen leads to activation of cutaneous mast cells and induction of the late-phase IgE inflammatory response, both of which result in pruritus, consequent scratching, and the development of eczematous lesions.⁸ Dermatitis herpetiformis is a highly pruritic skin rash associated with gluten-sensitive enteropathy that is sometimes misdiagnosed as eczema.⁹

Both upper and lower respiratory symptoms have been demonstrated secondary to food allergy. In one study of 300 patients attending a pulmonary clinic, double-blind oral food challenges indicated six patients (2%) had significant food allergy.¹⁰ Heiner syndrome is a non-IgE-mediated form of pulmonary hemosiderosis that is reportedly due to food (predominantly milk) hypersensitivity.

Symptoms involving the oropharynx may occur within minutes of ingesting a food allergen. Such symptoms include pruritus of the lips, tongue, and soft palate and swelling of the lips and tongue. Oral allergy syndrome consists of symptoms confined primarily to the oropharynx and is most commonly reported secondary to a variety of fresh fruits and vegetables. Patients with respiratory allergy to birch pol-

len reportedly develop oral symptoms secondary to eating potatoes, carrots, celery, hazelnuts, and apples. Similarly, patients allergic to ragweed may develop oral symptoms to melons and bananas.

A variety of gastrointestinal disorders have been described. Protein-losing enteropathy syndrome has been described secondary to ingesting cow's milk. Gastrointestinal symptoms are minimal (occasional diarrhea and vomiting) and children manifest edema secondary to hypoalbuminemia. Intestinal biopsies reveal infiltration of eosinophils, suggesting a form of eosinophilic gastroenteropathy syndrome. Eosinophilic gastroenteropathy syndrome often manifests as postprandial nausea with vomiting, abdominal pain, diarrhea with or without steatorrhea, and weight loss in the adult and failure to thrive in the infant. Patients often have atopic disease, elevated serum IgE levels, positive skin test results, peripheral eosinophilia, iron deficiency anemia, and hypoalbuminemia. In some patients, symptoms are associated with specific foods.

Patients with food-induced enterocolitis generally are between 1 week and 3 months old and have vomiting and diarrhea severe enough to produce dehydration. Stools contain gross or occult blood and are often watery and positive for carbohydrate (reducing substances). The syndrome is most commonly associated with ingestion of cow's milk or soy, but also has occurred with eggs. Some patients only have diarrhea containing gross or occult blood and lesions confined to the distal bowel (i.e., food-induced colitis). Both disorders clear clinically within 72 hours of allergen elimination.

Malabsorption syndrome includes a spectrum of disorders that generally come to medical attention because of diarrhea and carbohydrate malabsorption. This syndrome has been described secondary to the ingestion of cow's milk, soy, egg, and wheat and often leads to patchy villous atrophy. A more extensive enteropathy with total villous atrophy is associated with sensitivity to gliadin, a component of gluten (coeliac disease). Patients with coeliac disease have a high prevalence of the major histocompatibility antigens HLA-8 and HLA-Dw3.

Infantile colic has been associated with the ingestion of foreign food proteins (most frequently cow's milk) in some breast-fed and formula-fed infants.¹¹ Many more subjective symptoms have been attributed to food allergy, but convincing proof of association is lacking.

DIAGNOSTIC TESTS

Several laboratory tests have evolved for use in the diagnosis of IgE-mediated food hypersensitivity re-

actions. When compared with the double-blind, placebo-controlled, oral food challenge—the current “gold standard” for diagnosing food allergy—the skin puncture and skin prick tests have had excellent negative predictive accuracies for IgE-mediated food allergy, but poor positive predictive accuracies. Intradermal skin tests are even less specific than skin prick tests. IgE RASTs performed in a reliable laboratory provide predictive information that does not significantly differ from that provided by skin prick tests.

Kemeny et al.¹² demonstrated that IgG and IgG subclass responses to different food antigens varied, but they were not able to demonstrate any predictive value for subclass determination in food-allergic individuals. Other investigators have reached similar conclusions. IgA antibodies to gliadin and reticulin have been shown to correlate with the presence of coeliac disease. Approximately 93% of children and adults with untreated coeliac disease have IgA anti-gliadin antibodies and 44% have IgA antireticulin antibodies. However, biopsy confirmation of the diagnosis is required.

Malabsorption syndromes and eosinophilic gastroenteritis require endoscopy while the patient ingests the suspected allergen and after beginning an elimination diet. In the malabsorption syndromes, villous atrophy may be partial or complete and is often patchy. Consequently, multiple biopsies are required to exclude this diagnosis, especially in young children. Breath hydrogen and D-xylose absorption may be abnormal due to secondary disaccharidase deficiency.

Food-induced enterocolitis and colitis syndromes require an allergen challenge (0.6 gm of protein/kg body weight) in an office or hospital setting. A positive challenge will provoke occult or grossly apparent blood in the stools, an increase in polymorphonuclear cells and eosinophils over baseline in the stools, and an increase in the total peripheral blood polymorphonuclear cell count of 3500 cells/mm³ over baseline 6 to 8 hours after challenge.

No good laboratory test has emerged to assist in the diagnosis of slow-onset food hypersensitivity disorders. In disorders in which cell-mediated reactions are important, the stimulation of peripheral blood mononuclear cells *in vitro* with food antigens has been investigated for ³H thymidine uptake, leukocyte inhibitory factor production, and interleukin-2 generation. Although many patients with food hypersensitivity have increased activity compared with normal patients, these tests are not discriminatory. Other tests (e.g., cytotoxic tests, oral and intradermal provocation tests) have been suggested for diagnosing food allergy, but their diagnostic efficiencies have never been validated.

PATIENT EVALUATION

The initial evaluation of a patient with suspected food allergy should focus on a careful history and physical examination. The history should emphasize the following points: food suspected and the approximate quantity ingested, time between ingestion and the development of symptoms, description of the symptoms, frequency and reproducibility of symptoms, the most recent occurrence, and whether other factors (i.e., exercise) are necessary for the reaction to occur. Although the history is extremely important, the history is validated by blinded challenge in only 30% to 40% of cases. The physical examination is important for ruling out other causes of the patient's symptoms.

At this point, laboratory studies should be initiated based on the information gathered. If an IgE-mediated reaction is suspected, skin prick tests or RASTs are an appropriate first step. If non-IgE-mediated disorders are suspected, appropriate studies should be undertaken.

Many structural and enzymatic abnormalities in both children and adults can result in gastrointestinal symptoms that closely mimic food-allergic reactions. The differential diagnosis must be carefully considered in all patients undergoing evaluation because many of these other disorders can also be life threatening.¹³ Foods may contain a variety of preservatives, dyes, and other chemicals that are implicated in adverse reactions. Many foods also have endogenous pharmacologic agents that can trigger symptoms in highly susceptible individuals. Occasionally, improper handling of food (scombroid poisoning) or ingestion of a toxin by an animal (ciguatera poisoning) will result in symptoms that closely mimic an allergic reaction.

When a limited number of foods is suspected, a trial elimination diet may be instituted for a 1- to 2-week period. If a food is solely responsible for the patient's symptoms, the patient should show unequivocal improvement within this time. Assuming a patient has carefully maintained the prescribed elimination diet for 7 to 14 days, some conclusion may be drawn about the probability of the patient having a food allergy. If eliminating a single food has led to symptom resolution, the restricted diet may be continued, although confirmation with a challenge may still be desirable in some instances. If the diet required the elimination of several foods, results were not unequivocal, or no significant change occurred but food allergy is still suspected, a food challenge is necessary. In cases in which food allergy is suspected but no specific food is clearly indicated, or if many food allergens are suspected, a highly restricted diet may

be attempted first. Food challenges may be conducted in the allergist's office or in a hospital.¹⁴ In some circumstances (e.g., behavioral disorders) challenges may be conducted in the patient's home. However, *challenges should never be conducted outside the physician's office or hospital if any possibility of an anaphylactic reaction exists.*

Studies using blinded challenges rarely find individuals clinically symptomatic to more than one or two foods regardless of the number of positive skin tests or RASTs. Similarly, patients are rarely clinically symptomatic to more than one member of a botanical family (e.g., legume¹⁵). If a patient appears to be allergic to a variety of foods by single-blind challenge, double-blind, placebo-controlled food challenges are necessary to clarify the situation.

THERAPY

Once the diagnosis has been established, the only proved form of therapy is strict elimination of the offending food. This requires considerable time (and ideally a dietitian) to educate the patient on spotting all forms of "hidden foods" and assuring a nutritionally sound diet. Teaching patients to read food labels is necessary to assure good compliance with an elimination diet.¹⁶

In the protein-losing enteropathy syndrome and food-induced enterocolitis, a short course of corticosteroids can be life saving. However, long-term management involves identification and removal of the responsible food. Eosinophilic gastroenteropathy syndrome often requires treatment with corticosteroids, especially if no food is implicated. Although several other treatment modalities are frequently recommended, they have not been shown to be effective in controlled trials in which the diagnosis of food allergy has been unequivocally established.

NATURAL HISTORY

Experience and follow-up challenge studies in individuals with food allergy indicate that food allergies do not necessarily last throughout one's lifetime. Sampson and Scanlon¹⁷ have demonstrated the loss of food allergy in up to 40% of children in 1 to 3 years, even though results of skin tests and RASTs may not change. A recent report by Pastorello¹⁸ indicates that adults also may lose food allergies after a period of elimination. Evidence suggests that the likelihood of losing a food allergy depends somewhat on the food provoking symptoms. Allergies to peanut, tree nuts, fish, and other seafood appear to last longer. Consequently, allergic individuals should be rechallenged to most foods every 1 to 2 years and to peanuts, tree nuts, and seafood every 3 to 6 years to determine

whether their clinical hypersensitivity persists. There are no challenge-confirmed reports of individuals who have lost a food allergy and then redeveloped it after ingesting the food for a period.

Some patients with coeliac disease can tolerate gluten-containing products after many years of avoidance. However, the risk of gastrointestinal tract malignancy is increased in patients with coeliac disease who ingest gluten regardless of the presence of clinical symptoms. In symptomatic coeliac patients ingesting gluten, intestinal malignancy is reportedly as high as 20%.

PREVENTION

The role of breast-feeding and food allergen avoidance in the prevention of atopy and food allergy remains highly controversial. Breast-feeding (especially with maternal avoidance of major allergens such as milk, egg, peanut, and fish during lactation) can postpone atopic disease in high-risk infants, but there is no evidence that it actually prevents this disorder. Zeiger et al.¹⁹ suggest that such a regimen may be successful in preventing milk allergy in some high-risk infants. Until our understanding of immunologic sensitization to food allergens is more complete, investigators recommend exclusive breast-feeding with hydrolyzed formula supplements if necessary for the first 6 months of life and withholding highly allergenic foods (milk, egg, peanuts and peanut butter, and fish) for 2 to 3 years in children at high risk of allergic disease.

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Food allergy

Prospective studies on the prevalence of adverse food reactions indicate:

- a. 30% to 40% of children less than 6 years of age have adverse food reactions
- b. 8% of children less than 6 years of age have adverse food reactions
- c. 2% of adults experience food-allergic reactions
- d. Many "confirmed" food reactions in infants are "outgrown" by 1 year of age

Explanation: Although parents reported that 30% of their children experienced adverse reactions to foods, reactions could be confirmed in only 8% by blinded challenge. Follow-up challenges revealed that many adverse reactions, especially to fruit juices, were short lived and had resolved by 1 year of age. No good information is available on the adult population.

Answer: b and d.

References: Kajosaari M. Food allergy in Finnish children aged 1 to 6 years. *Acta Paediatr Scand* 1982;71:815; Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683.

The patient who has been diagnosed with food hypersensitivity should:

- a. Eat the food on a rotational basis once every 2 to 3 weeks
- b. Never eat the food again
- c. Begin oral cromolyn sodium therapy
- d. Be rechallenged in 2 to 3 years to see if clinical tolerance has developed

Explanation: Follow-up studies in patients diagnosed by double-blind, placebo-controlled, oral food challenges suggest that about one third will develop clinical tolerance in 2 to 3 years if maintained on an appropriate allergen avoidance diet. Stocchi et al. suggest this may work for adults, too.

Answer: d.

References: Bock SA. The natural history of food sensitivity. *J ALLERGY CLIN IMMUNOL* 1982;69:173-7; Sampson HA. IgE mediated food intolerance. *J ALLERGY CLIN IMMUNOL* 1988;81:495-504; Stocchi L, Pastorello EA, Schilke ML, et al. Role of the elimination diet in adults with food allergy. *J ALLERGY CLIN IMMUNOL* 1988;81:187.

The foods listed below are most commonly implicated in food allergic reactions except:

- a. Peanuts
- b. Fish
- c. Egg
- d. Strawberries

Explanation: Although strawberries frequently are implicated as a cause of urticaria, published blinded challenge studies have failed to confirm these reports. Allergic reactions to egg, milk, and peanut are most common in children, whereas allergic reactions to tree nuts, fish, and various seafood are most common in adults.

Answer: d.

References: Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adults. II. A detailed analysis of reaction patterns during oral food challenge. *J ALLERGY CLIN IMMUNOL* 1985;75:356-63; Bock SA, Lee Y, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. *J ALLERGY CLIN IMMUNOL* 1978;62:327-34.

The best laboratory tests to exclude immediate food hypersensitivity include:

- a. Skin prick test
- b. IgG₄ RAST
- c. IgE RAST
- d. Food antigen-IgE immune complexes

Explanation: Although the “gold standard” for diagnosing food hypersensitivity is the double-blind, placebo-controlled, oral food challenge, the skin prick test and the IgE RAST have excellent negative predictive values for IgE-mediated hypersensitivity reactions.

Answer: a and c.

References: Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind placebo-controlled food challenges in children with atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 1984;74:26-33; Paganelli R, Quinti I, D’Offizi GP, et al. Immune complexes in food allergy: a critical reappraisal. *Ann Allergy* 1987;59:157-61.

In the patient who develops life-threatening reactions to peanuts, the best course of management includes:

- a. Desensitizing the patient to peanuts with immunotherapy
- b. Prescribing adrenalin to be carried at all times
- c. Prescribing cromolyn sodium to be taken before ingesting a food containing peanuts
- d. Recommending careful avoidance of all peanut-containing products and providing lists of potential hidden sources

Explanation: No good evidence indicates that immunotherapy or cromolyn sodium plays any role in preventing severe life-threatening allergic reactions. Preventative measures are the only modalities currently available to deal with these disorders.

Answer: b and d.

Reference: Sampson HA. IgE mediated food intolerance. *J ALLERGY CLIN IMMUNOL* 1988;81:495-504.

IgE-mediated allergic reactions to foods have been implicated in which of the following?

- a. Eczema
- b. Allergic rhinitis
- c. “Idiopathic” anaphylaxis
- d. Cows’ milk-induced colitis

Explanation: Although cow’s milk-induced colitis is believed to be secondary to a hypersensitivity reaction to cow’s milk protein, there is no evidence that an IgE-mediated reaction is involved. In the study by Stricker et al., 7% of patients (7 of 102) labeled as “idiopathic” were found to have symptoms secondary to food-allergic reactions.

Answer: a, b, and c.

References: Sampson HA. IgE mediated food intolerance. *J ALLERGY CLIN IMMUNOL* 1988;81:495-504; Stricker WE, Anorve-Lopez E, Reed CE. Food skin testing in patients with idiopathic anaphylaxis. *J ALLERGY CLIN IMMUNOL* 1986;77:516-9.