

9. Food allergy

Hugh A. Sampson, MD *New York, NY*

Food allergies affect as many as 6% of young children, most of whom “outgrow” the sensitivity, and about 2% of the general population. Although any food may provoke a reaction, relatively few foods are responsible for the vast majority of food allergic reactions: milk, egg, peanuts, tree nuts, fish, and shellfish. Many of these food allergens have been characterized at a molecular level, which has increased our understanding of the immunopathogenesis of many responses and may soon lead to novel immunotherapeutic approaches. Food allergic reactions are responsible for a variety of symptoms involving the skin, gastrointestinal tract, and respiratory tract and may be due to IgE-mediated and non-IgE-mediated mechanisms. A systematic approach including history, laboratory studies, elimination diets, and often food challenges will lead to the correct diagnosis. Currently, management of food allergies consists of educating the patient to avoid ingesting the responsible allergen and to initiate therapy in case of an unintended ingestion. (*J Allergy Clin Immunol* 2003;111:S540-7.)

Key words: Food allergy (hypersensitivity), oral tolerance, atopic dermatitis, food-associated exercised-induced anaphylaxis, allergic eosinophilic gastroenteritis, dietary protein-induced enteropathy, dietary protein-induced enterocolitis, celiac disease, dietary protein-induced colitis, dermatitis herpetiformis

An adverse food reaction consists of any abnormal reaction after the ingestion of a food. It may be due to a food intolerance, which is an adverse physiologic response, or to a food hypersensitivity (allergy), which is an adverse immunologic reaction.¹ Food intolerances may be due to factors inherent in a food, such as toxic contaminants (eg, histamine in scombroid fish poisoning) or pharmacologic properties of the food (eg, tyramine in aged cheeses), or it may be due to characteristics of the host, such as metabolic disorders (eg, lactase deficiency), or idiosyncratic responses. Food aversions may mimic adverse food reactions but are not reproducible when the patient ingests the food in a blinded fashion. Food hypersensitivities (allergies) are most frequent in young children and may be due to IgE-mediated or non-IgE-mediated immune mechanisms.

Food allergies are most prevalent during the first years of life, affecting about 6% of infants younger than 3 years.² About 2.5% of newborn infants have hypersensitivity reactions to cow milk in the first year of life, with

Abbreviation used

DBPCFC: Double-blind, placebo-controlled food challenge

about 80% “outgrowing” the allergy by their fifth birthday.¹ IgE-mediated reactions account for about 60% of milk allergic reactions; about 25% of these infants retain their sensitivity into the second decade of life, and 35% go on to acquire other food allergies.³ About 1.5% of young children are allergic to eggs and 0.5% to peanuts. Some evidence suggests that the prevalence of peanut allergy has been increasing during the past 2 decades.⁴ Children with atopic disorders tend to have a higher prevalence of food allergy; about 35% of children with moderate to severe atopic dermatitis have IgE-mediated food allergy,⁵ and about 6% of children with asthma have food-induced wheezing.⁶ Adverse reactions to food additives also have been demonstrated to affect 0.5% to 1% of children.⁷ Food allergy appears to be less common in adults, although adequate epidemiologic studies are lacking. A survey in the United States indicated that peanut and tree nut allergies together affect 1.1% of American adults.⁸ Overall, it is estimated that about 2% of adults in the United States are affected by food allergies.¹

PATHOGENESIS

The gastrointestinal tract forms an extensive barrier to the outside environment and provides a surface to process and absorb ingested food and to discharge waste products. The immune system associated with this barrier, the gut-associated lymphoid tissue, is capable of discriminating among harmless foreign proteins or commensal organisms and dangerous pathogens. The mucosal immune system is composed of both the innate and adaptive immune systems. Unlike the systemic immune system, the adaptive mucosal immune system is specifically proficient at inhibiting responses to nondangerous antigens (oral tolerance) and yet mounting a rapid response to pathogens. However, developmental immaturity of various components of the gut barrier and immune system reduces the efficiency of the infant mucosal barrier and probably plays a major role in the increased prevalence of gastrointestinal infections and food allergy during the first few years of life.¹

Despite the evolution of an elegant barrier system, about 2% of ingested food antigens are absorbed and transported throughout the body in an “immunologically intact” form, even through the mature gut.⁹ In a classic series of experiments, Brunner and Walzer used serum from patients with food allergies to passively sensitize

From the Jaffe Food Allergy Institute, The Mount Sinai School of Medicine, New York.

Supported in part by National Institutes of Health (National Institute of Allergy and Infectious Diseases) grant.

Reprint requests: Hugh A. Sampson, MD, Department of Pediatrics, Box 1198, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574.

© 2003 Mosby, Inc. All rights reserved.

0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.134

volunteers and demonstrate the rapidity with which food antigens are absorbed and transported to cutaneous or intestinal mast cells.¹⁰

Although intact food antigens penetrate the gastrointestinal tract, they generally do not cause clinical symptoms because most individuals acquire tolerance. In mucosal tissues, soluble antigens, such as food antigens, are typically poor immunogens and induce a state of unresponsiveness known as *oral tolerance*. Unresponsiveness of T cells to ingested food proteins is believed to be the result of T-cell anergy or induction of regulatory T cells. Intestinal epithelial cells play a major role in tolerance induction to food antigens, acting as nonprofessional antigen-presenting cells.¹¹ In addition, dendritic cells residing within the noninflammatory environment of Peyer patches express IL-10 and IL-4, which favor generation of tolerance. Finally, T regulatory cells [T_H3 and Tr-1 cells], which are potent sources of transforming growth factor β ,¹² are generated in mucosal lymphoid tissue in response to low-dose antigen and mediate bystander tolerance within the gastrointestinal tract. The gut flora also play a significant role in oral tolerance induction, because animals raised in a germ-free environment from birth fail to acquire normal tolerance.¹³ In addition, studies indicate that exclusive breast-feeding may promote the development of oral tolerance and prevent some food allergy and atopic dermatitis.^{14,15}

Despite the enormous diversity of the human diet, relatively few foods account for most food allergies. Sensitization to food allergens may occur in the gastrointestinal tract after the ingestion of a food, considered a traditional or class 1 food allergy, or after inhalation of an airborne allergen that cross-reacts with a specific food, considered a class 2 food allergy.¹⁶ The major food allergens identified as Class 1 allergens are water-soluble glycoproteins, which are 10 to 70 kD and stable to treatment with heat, acid and proteases.¹ Most class 2 allergens are plant-derived proteins that are highly heat labile and difficult to isolate, often making standardized extracts for diagnostic purposes unsatisfactory. A limited number of the class 1 and 2 food allergens have been identified, cloned, sequenced, and expressed as recombinant proteins (Tables IA and IB). Many of the plant-related allergens are homologous with pathogen-related proteins, seed storage proteins, profilins, peroxidases, or protease inhibitors common to many plants.¹⁶ Animal-related allergens appear to be more limited in number and cross-reactivity. In children, cow milk, egg, peanut, soy, wheat, and fish account for more than 85% of documented food allergies, whereas in adults peanuts, tree nuts, fish, and shellfish are responsible for most allergic reactions.¹

Food hypersensitivities develop in genetically predisposed persons when oral tolerance fails to develop normally or breaks down. IgE-mediated reactions develop when food-specific IgE antibodies residing on mast cells and basophils bind circulating ingested food allergens and activate the cells to release a number of potent mediators and cytokines, as discussed elsewhere in this article. As depicted in Table II, a number of non-IgE-mediated

food hypersensitivity disorders have been described. There is little evidence to implicate antigen-antibody complex-mediated hypersensitivity in food-related disorders. Cell-mediated hypersensitivity reactions probably contribute to a number of gastrointestinal disorders, as noted in Table II.

DIAGNOSING FOOD HYPERSENSITIVITY DISORDERS

The diagnostic approach to adverse food reactions is similar to that for other medical problems.¹⁷ The medical history attempts to establish whether a food allergic reaction occurred and to obtain information to design an appropriate diagnostic challenge. The following information should be delineated: (1) the food responsible for the reaction, (2) the quantity of the suspected food ingested, (3) the length of time between ingestion and development of symptoms, (4) whether similar symptoms occurred when the food was eaten previously, (5) whether other factors (eg, exercise) are necessary, and (6) when the last reaction to the food occurred. Dietary diaries may be a useful adjunct to history, because such information is obtained prospectively and is less dependent on a patient's memory. Elimination diets are frequently used both in diagnosis and management of adverse food reactions. The success of elimination diets requires that the correct allergen be identified, that the patient maintain a diet completely devoid of all forms of the offending allergen, and that other factors not provoke similar symptoms during the period of study. Such conditions can be difficult to fulfill, and elimination diets alone are rarely diagnostic of food allergy.

For IgE-mediated disorders, skin prick tests are frequently used to screen patients for sensitivity to specific foods. Allergens eliciting a wheal at least 3 mm greater than the negative control are considered positive, indicating a possibility that the patient has symptomatic reactivity to the specific food (overall positive predictive accuracy is <50%), whereas negative skin test results essentially confirm the absence of IgE-mediated reactions (negative predictive accuracy >95%).¹⁷ In infants younger than 2 years, skin prick tests to milk, egg, or peanuts with wheal diameters of at least 8 mm are reportedly more than 95% predictive of reactivity.¹⁸ In general, negative skin prick test results are extremely useful for excluding IgE-mediated food allergies, but positive skin test results are only suggestive of the presence of clinical food allergies. When evaluating allergy to many fruits and vegetables (eg, apples, oranges, bananas, potatoes, carrots, and celery) commercially prepared extracts are generally inadequate because of the lability of the responsible allergen, so the fresh food must be used for skin testing.

Radioallergosorbent tests and similar in vitro assays may be used to identify food-specific IgE antibodies. More recently, the use of a quantitative measurement of food-specific IgE antibodies (CAP System FEIA; Pharmacia & Upjohn, Bridgewater, NJ) has been shown to be more predictive of symptomatic IgE-mediated food aller-

TABLE IA. Representative food allergens: Class 1 food allergens

Protein fraction	Approximate proportion of protein (%)	Molecular weight (kd)	Nomenclature
Cow milk			
Caseins	76%-86%	19-24	
Whey	14%-24%		
β -Lactoglobulin	7%-12%	36	Bos d 5
Chicken egg white			
Ovalbumin	54%	45	Gal d 1
Ovomucoid	11%	28	Gal d 2
Peanut			
Vicilin	—	63.5	Ara h 1
Conglutin	—	17/19	Ara h 2
Glycinin	—	64	Ara h 3
Fish			
Parvalbumin	—	12.3	Gad c 1
Lipid-transfer proteins (pathogen-related proteins group 14)			
Apple	—	9	Mal d 3
Corn	—	9	Zea m 14

TABLE IB. Representative food allergens: Class 2 food allergens

Protein fraction	Molecular weight (kd)	Nomenclature	Homology
Latex-fruit cross-reactivity			
Pathogen-related protein 2 group			
Latex	34/36	Hev b 2	1,3 glucanase
Banana			
Kiwi			
Pathogen-related protein 3 group			
Latex	5	Hev b 6.02	Chitinase
Avocado	32	Pers a 1	Endochitinase
Pathogen-related protein 5			
Apple	31	Mal d 2	Thaumatococcus homolog
Cherry	23.3	Pru av 2	Thaumatococcus
Birch Bet v 1 homologs (pathogen-related proteins 10)			
Apple		Mal d 1	Bet v 1 homolog
Carrot		Dau c 1	Bet v 1 homolog
Celery	16	Api g 1	Bet v 1 homolog
Birch Bet v 2 homologs (celery-mugwort-spice syndrome)			
Latex	14	Hev b 8	Profilin
Celery		Api g 4	Profilin
Potato			Profilin

gy.¹⁹ Food-specific IgE levels exceeding the diagnostic values indicate that the patient is more than 95% likely to have an allergic reaction if he or she ingests the specific food (Table III).

The double-blind, placebo-controlled food challenge (DBPCFC) is considered the gold standard for the diagnosis of food allergies.¹⁷ The foods evaluated by DBPCFCs are determined by history or skin test (radioallergen sorbent test) results. Foods unlikely to provoke food allergic reactions may be screened by open or single-blind challenges. Suspected foods should be eliminated for 7 to 14 days before challenge, longer for some non-IgE-mediated gastrointestinal disorders. Medications that might interfere with interpreting the challenge results (eg, antihistamines) must be discontinued. If results of the blinded challenge are negative, this must be confirmed by an open feeding under observation to rule out the rare false-negative result. In some non-IgE-mediated

food allergies (eg, dietary protein-induced enterocolitis), allergen challenges may require as much as 0.3 to 0.6 g food protein/kg body weight given in one or two doses.²⁰ In other non-IgE-mediated disorders (eg, allergic eosinophilic gastroenteritis), the patient may require several feedings during a 1- to 3-day period to elicit symptoms. The length of the observation period depends on the type of reaction suspected. Patients with histories of life-threatening anaphylaxis should undergo challenges only when the history and laboratory testing cannot conclusively determine the causative antigen (such challenges should be performed in an intensive care unit-like setting) or the patient is believed to have outgrown his or her sensitivity. Multiple food allergies are rare; if suspected, they must be confirmed by DBPCFC.

From a clinical and diagnostic standpoint, it is helpful to categorize food hypersensitivity disorders according to the predominant target organ and mechanism of

response. IgE-mediated reactions are typically rapid in onset, whereas non-IgE-mediated disorders become evident hours to days after allergen ingestion. Some disorders may involve both IgE-mediated and non-IgE-mediated mechanisms; these are variable in time of onset.

Gastrointestinal food hypersensitivity reactions

As depicted in Table IV, a number of gastrointestinal food hypersensitivities have been described. The oral allergy syndrome (or pollen-food allergy syndrome) is elicited by a variety of plant proteins that cross-react with airborne allergens, especially birch, ragweed, and mugwort pollens.¹⁶ Patients allergic to ragweed may react to fresh melons and bananas, and those allergic to birch pollen may show symptoms after the ingestion of raw potatoes, carrots, celery, apples, pears, hazelnuts, and kiwi. Immunotherapy for treating the pollen-induced rhinitis may eliminate oral allergy symptoms.²¹ Gastrointestinal anaphylaxis typically occurs with allergic manifestations in other target organs.¹

Most non-IgE-mediated gastrointestinal hypersensitivities have been described predominantly in infants and children. Allergic eosinophilic esophagitis and gastroenteritis are characterized by infiltration of the esophagus, stomach, or intestinal walls with eosinophils; by basal zone hyperplasia; by papillary elongation; by absence of vasculitis; and by peripheral eosinophilia in about 50% of patients.²² Allergic eosinophilic esophagitis is seen most frequently during infancy through adolescence and typically features chronic gastroesophageal reflux.²²⁻²⁴ Responsible food allergens may need to be eliminated from the diet for as long as 8 weeks to bring about resolution of symptoms and for as long as 12 weeks to bring about normalization of intestinal histologic state.²⁵ Allergic eosinophilic gastroenteritis may occur at any age, including in young infants, where it may be seen as pyloric stenosis with outlet obstruction and postprandial projectile emesis.²⁶ Weight loss or failure to thrive is a hallmark of this disorder.

Food protein-induced proctocolitis generally is seen in the first few months of life in response to food proteins passed in maternal breast milk or to milk- or soy-based formulas.^{27,28} Lesions are confined to the distal large bowel and consist of mucosal edema with infiltration of eosinophils in the epithelium and lamina propria. Food protein-induced enterocolitis syndrome is most commonly seen in infants before 3 months of age but may be delayed in breast-fed babies.²⁰ Symptoms are most commonly provoked by cow milk or soy protein-based formulas but may be due to other foods in older children (eg, various cereal grains).²⁰ In adults, shellfish (eg, shrimp, crab, and lobster) hypersensitivity may provoke a similar syndrome, with delayed onset of severe nausea, abdominal cramps, and protracted vomiting. Dietary protein-induced enteropathy (excluding celiac disease) generally is seen in the first several months of life with diarrhea (mild to moderate steatorrhea in about 80% of cases) and poor weight gain.²⁹ Biopsy reveals a patchy villous atrophy, a prominent mononuclear round cell

TABLE II. Food hypersensitivity disorders

Type	Disorders
<u>IgE mediated</u>	
Cutaneous	Urticaria Angioedema Morbilliform rashes Flushing
Gastrointestinal	Oral allergy syndrome Gastrointestinal anaphylaxis
Respiratory	Acute rhinoconjunctivitis Bronchospasm (wheezing)
Generalized	Anaphylactic shock
<u>Mixed IgE and cell mediated</u>	
Cutaneous	Atopic dermatitis
Gastrointestinal	Allergic eosinophilic esophagitis Allergic eosinophilic gastroenteritis
Respiratory	Asthma
<u>Cell mediated</u>	
Cutaneous	Contact dermatitis Dermatitis herpetiformis
Gastrointestinal	Food protein-induced enterocolitis Food protein-induced proctocolitis Food protein-induced enteropathy syndromes Celiac disease
Respiratory	Food-induced pulmonary hemosiderosis (Heiner syndrome)

infiltrate, and few eosinophils.²⁹ Celiac disease, a more extensive enteropathy leading to malabsorption, is associated with sensitivity to gliadin found in wheat, rye, and barley. Celiac disease is highly associated with HLA-DQ2 [$\alpha 1^*0501$, $\beta 1^*0201$], which is present in more than 90% of patients with celiac disease.³⁰ Once the diagnosis of celiac disease is established, lifelong elimination of gluten-containing foods is necessary to control symptoms and to avoid the increased risk of malignancy.

Infantile colic, an ill-defined syndrome of paroxysmal fussiness characterized by inconsolable, agonized crying, generally develops in the first 2 to 4 weeks of life and persists through the third to fourth month of life.³¹ Diagnosis can be established by the implementation of several brief trials of hypoallergenic formula.

Cutaneous food hypersensitivity reactions

As listed in Table V, acute urticaria and angioedema are among the most common symptoms of food allergic reactions, although the exact prevalence of these reactions is unknown. Acute urticaria due to contact with food (eg, meats, vegetables, and fruits) is also common. Food allergy is infrequently the cause of chronic urticaria and angioedema (symptoms lasting greater than 6 weeks). Atopic dermatitis is one form of eczema that generally begins in early infancy and is characterized by typical distribution, extreme pruritus, and a chronically relapsing course.³² Allergen-specific IgE antibodies bound to Langerhans cells play a unique role as nontraditional receptors.³³ DBPCFCs generally provoke a markedly pruritic, erythematous, morbilliform rash. Urticarial lesions are rarely seen, but gastrointestinal and

TABLE III. Food-specific IgE concentrations predictive of clinical reactivity

Allergen	Decision point [kU _A /L]	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Egg	7	61	95	98	38
Infants ≤2 y*	2			95	
Milk	15	57	94	95	53
Infants ≤2 y†	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‡	~15	—	—	~95	

Adapted from Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-6. Used with permission.

*Boyano MT, et al. Validity of specific IgE in children with egg allergy. *Clin Exp Allergy* 2001;31:1464-9.

†Garcia-Ara C, et al. Specific IgE levels in the diagnosis of immediate hypersensitivity to cow's milk protein in infants. *J Allergy Clin Immunol* 2001;107:185-90.

‡Tentative values.

TABLE IV. Gastrointestinal food hypersensitivities

Disorder	Mechanism	Symptoms	Diagnosis
Oral allergy syndrome	IgE mediated	Mild pruritus, tingling and/or angioedema of the lips, palate, tongue or oropharynx; occasional sensation of tightness in the throat and rarely systemic symptoms	Clinical history and positive skin prick test responses to relevant food proteins (prick plus prick method), oral challenge, positive with fresh food, negative with cooked food
Gastrointestinal anaphylaxis	IgE mediated	Rapid onset of nausea, abdominal pain, cramps, vomiting, and/or diarrhea; other target organ responses (eg, skin, respiratory tract) often involved	Clinical history and positive results of skin prick test or radioallergen sorbent tests, positive or negative oral challenge
Allergic eosinophilic esophagitis	IgE mediated and/or cell mediated	Gastroesophageal reflux or excessive spitting up or emesis, dysphagia, intermittent abdominal pain, irritability, sleep disturbance, failure to respond to conventional reflux medications	Clinical history, skin prick tests, endoscopy and biopsy, elimination diet and challenge
Allergic eosinophilic gastroenteritis	IgE mediated and/or cell mediated	Recurrent abdominal pain, irritability, early satiety, intermittent vomiting, failure to thrive and/or weight loss	Clinical history, skin prick tests, endoscopy and biopsy, elimination diet and challenge
Food protein–induced proctocolitis	Cell mediated	Gross or occult blood in stool, typically thriving, usually seen in first few months of life	Skin prick test results negative, elimination of food protein leads to clearing of most bleeding in 72 h, positive or negative results of endoscopy and biopsy, challenge induces bleeding within 72 h
Food protein–induced enterocolitis	Cell mediated	Protracted vomiting and diarrhea (may or may not be bloody) not infrequently with dehydration, abdominal distention, failure to thrive, vomiting typically delayed 1-3 h after feeding	Skin prick test results negative, elimination of food protein leads to clearing of symptoms in 24-72 h, challenge leads to recurrent vomiting within 1-2 h, ~15% have hypotension develop
Food protein–induced enteropathy, celiac disease (gluten-sensitive enteropathy)	Cell mediated	Diarrhea or steatorrhea, abdominal distention and flatulence, weight loss or failure to thrive, ± nausea and vomiting, oral ulcers	Endoscopy and biopsy show IgA, elimination diet with resolution of symptoms and food challenge, celiac IgA antigliadin and anti-transglutaminase antibodies

respiratory symptoms frequently develop. Food-induced contact dermatitis is seen frequently among food handlers, especially among those handling raw fish, shellfish, meats, and eggs.³⁴ Dermatitis herpetiformis is a

chronic blistering skin disorder associated with a gluten-sensitive enteropathy and characterized by a chronic, intensely pruritic papulovesicular rash symmetrically distributed over the extensor surfaces and buttocks.³⁵

TABLE V. Cutaneous food hypersensitivities

Disorder	Mechanism	Symptoms	Diagnosis
Acute urticaria and angioedema	IgE mediated	Pruritus, hives, and/or swelling	Clinical history, skin prick tests or radioallergosorbent test, positive or negative challenge
Chronic urticaria and angioedema	IgE mediated	Pruritus, hives, and/or swelling of > 6 weeks duration	Clinical history, skin prick tests or radioallergosorbent test, elimination diet, challenge
Atopic dermatitis	IgE and cell mediated	Marked pruritus; eczematous rash in "classic" distribution	Clinical history, skin prick tests; CAP-System FEIA (quantitative IgE), elimination diet and food challenges
Contact dermatitis	Cell mediated	Marked pruritus; eczematous rash	Clinical history, patch test
Dermatitis herpetiformis	Cell mediated	Marked pruritus; papulovesicular rash over extensor surfaces and buttocks	Skin biopsy (IgA deposition), IgA antigliadin and antitransglutaminase antibodies, positive or negative endoscopy

TABLE VI. Respiratory food hypersensitivities

Disorder	Mechanism	Symptoms	Diagnosis
Allergic rhinoconjunctivitis	IgE mediated	Periocular pruritus, tearing, and conjunctival erythema, nasal congestion, rhinorrhea, sneezing	Clinical history, skin prick tests, elimination diet, food challenge
Asthma	IgE and cell mediated	Cough, dyspnea, wheezing	Clinical history, skin prick tests, elimination diet, food challenge
Heiner syndrome	Uncertain	Recurrent pneumonia, pulmonary infiltrates, hemosiderosis, iron-deficiency anemia, failure to thrive	Clinical history, peripheral eosinophilia, milk precipitins (if caused by milk), positive or negative lung biopsy, elimination diet

Respiratory food hypersensitivity reactions

Acute respiratory symptoms secondary to food allergy represent pure IgE-mediated reactions, whereas chronic respiratory symptoms represent a mix of IgE-mediated symptoms (Table VI). Rhinoconjunctivitis alone is infrequently a manifestation of food allergy, although it commonly accompanies other food allergic symptoms. Asthma is an uncommon manifestation of food allergy, although acute bronchospasm is usually seen with other food-induced symptoms.³⁶ However, airway hyperreactivity and worsening of asthma also may be induced.³⁷ Vapors or steam emitted from cooking food (eg, fish)³⁸ may induce asthmatic reactions. Food-induced asthmatic symptoms should be suspected in patients with refractory asthma and a history of atopic dermatitis, gastroesophageal reflux, food allergy or feeding problems as an infant, or a history of positive skin test results or reactions to a food. Heiner syndrome is a rare form of food-induced pulmonary hemosiderosis typically caused by cow milk.³⁹ Generalized anaphylaxis, as a result of food allergies, accounts for at least a third of all patients with anaphylaxis seen in hospital emergency departments.⁴⁰ In addition to variable expression of cutaneous, respiratory, and gastrointestinal symptoms, patients may have cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias. Curiously, serum β -tryptase is rarely (<10% of the time) elevated in food-induced anaphylaxis.^{41,42} In a recent survey of 32 fatal food-induced anaphylactic cases,⁴⁰ a number of fac-

tors were evident: most patients were adolescents or young adults, virtually all were known to have food allergy with a previous history of reaction to the implicated food, virtually all had asthma, only 10% had epinephrine available for use at the time of the reaction, about 10% of those who received epinephrine in a timely fashion did not survive, and peanuts or tree nuts were responsible for the vast majority (94%) of the fatalities in the United States. Diagnosis depends on a history of typical symptoms after the isolated ingestion of a specific food and the demonstration of food-specific IgE antibodies. Lacking this evidence, a physician-supervised food challenge is generally warranted to ensure that the suspected food is truly responsible for the anaphylactic reaction. Such challenges should be done in a hospital setting by a physician experienced in the treatment of anaphylactic reactions.

Food-associated exercise-induced anaphylaxis is an unusual form of anaphylaxis that occurs only when the patient exercises within 2 to 4 hours after ingesting a food, whereas in the absence of exercise, the patient can ingest the food without any apparent reaction.⁴³ It is most common in women 15 to 35 years old. Diagnosis is based on patient history and the demonstration of food-specific IgE antibodies.

THERAPY OF FOOD ALLERGIC DISORDERS

Once the diagnosis of food hypersensitivity has been established, the only proven therapy is strict elimination of the offending allergen. Patients and their families must

be educated to avoid accidentally ingesting food allergens (eg, by reading food labels), to recognize early symptoms of an allergic reaction, and to initiate early management of an anaphylactic reaction.¹⁷ A wealth of educational material is available through such organizations as the Food Allergy and Anaphylaxis Network (Fairfax, Va, 1-800-929-4040 or <http://www.foodallergy.org>). Most symptomatic reactivity to food allergens is lost with time, except for peanuts, nuts, and seafood.^{17,44} Children with low levels of peanut-specific IgE should be reevaluated to determine whether they have outgrown their allergy. Symptomatic reactivity to food allergens is generally extremely specific, and patients with IgE-mediated food allergies rarely react to more than one member of a botanic family or animal species.⁴⁵

Antihistamines may partially relieve symptoms of oral allergy syndrome⁴⁶ and IgE-mediated skin symptoms but do not block systemic reactions. Oral corticosteroids are generally effective in treating chronic IgE-mediated disorders (eg, atopic dermatitis or asthma), or non-IgE-mediated gastrointestinal disorders (eg, allergic eosinophilic esophagitis or gastroenteritis and dietary-induced enteropathy), but the side effects of protracted corticosteroid use are unacceptable. Anti-IgE and novel forms of immunotherapy are being explored for the treatment of IgE-mediated food allergy.^{47,48} For more than 50 years, allergists have debated whether food allergy can be prevented. Meta-analyses of existing studies suggest a beneficial effect,^{49,50} and the American Academy of Pediatrics recommends that "high-risk" infants be exclusively breast-fed, that lactating mothers avoid peanuts and nuts (to avoid sensitization through breast milk), that the introduction of solid food be delayed until 6 months of age, and that major allergens, such as peanuts, nuts, and seafood, be introduced after 3 years of age.

In summary, food hypersensitivities affect as many as 6% of children younger than 3 years and approximately 2% of the general population. Investigations in the past have fairly well characterized the food hypersensitivity disorders, but our understanding of the basic immunopathologic mechanisms remains incomplete. Current studies of allergen characterization and the rigorous scientific methods now being applied to this field by many investigators provide hope that new information regarding the pathogenesis of these disorders and new forms of therapy will soon become available.

REFERENCES

- Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999;103:717-28.
- Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79:683-8.
- Host A, Halken S, Jacobsen HP, Eastmann A, Mortensen S, Mygil S. The natural course of cow's milk protein allergy/intolerance [abstract]. *J Allergy Clin Immunol* 1997;99:S490.
- Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;110:784-9.
- Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BD, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:e8.
- Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy. *J Allergy Clin Immunol* 1988;81:1059-65.
- Fuglsang G, Madsen C, Saval P, Osterballe O. Prevalence of intolerance to food additives among Danish school children. *Pediatr Allergy Immunol* 1993;4:123-9.
- Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the United States of America. *J Allergy Clin Immunol* 1999;103:559-62.
- Husby S, Foged N, Host A, Svehag SE. Passage of dietary antigens into the blood of children with coeliac disease: quantification and size distribution of absorbed antigens. *Gut* 1987;28:1062-72.
- Brunner M, Walzer M. Absorption of undigested proteins in human beings: the absorption of unaltered fish protein in adults. *Arch Intern Med* 1928;42:173-9.
- Mayer L. Mucosal immunity and gastrointestinal antigen processing. *J Pediatr Gastroenterol Nutr* 2000;30 Suppl:S4-12.
- Smith KM, Eaton AD, Finlayson LM, Garside P. Oral tolerance. *Am J Respir Crit Care Med* 2000;162:S175-8.
- Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1997;159:1739-45.
- Zeiger R. Breast-feeding and dietary avoidance. In: de Weck A, Sampson H, editors. *Intestinal immunology and food allergy*. New York: Raven Press; 1995. p. 203-22.
- Jarvinen KM, Suomalainen H. Development of cow's milk allergy in breast-fed infants. *Clin Exp Allergy* 2001;31:978-87.
- Breiteneder H, Ebner C. Molecular and biochemical classification of plant-derived food allergens. *J Allergy Clin Immunol* 2000;106:27-36.
- Sampson HA. Food allergy. Part 2: diagnosis and management. *J Allergy Clin Immunol* 1999;103:981-99.
- Hill DJ, Hosking CS, Reyes-Benito LV. Reducing the need for food allergen challenges in young children: a comparison of in vitro with in vivo tests. *Clin Exp Allergy* 2001;31:1031-5.
- Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-6.
- Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998;214-9.
- Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy* 1998;28:1368-73.
- Sampson HA, Sicherer SH, Birnbaum AH. AGA technical review on the evaluation of food allergy in gastrointestinal disorders. *American Gastroenterological Association. Gastroenterol* 2001;120:1026-40.
- Liacouras CA, Markowitz JE. Eosinophilic esophagitis: a subset of eosinophilic gastroenteritis. *Curr Gastroenterol Rep* 1999;1:253-8.
- Ruchelli E, Wenner W, Voytek T, Brown K, Liacouras C. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. *Pediatr Dev Pathol* 1999;2:15-8.
- Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino-acid based formula. *Gastroenterology* 1995;109:1503-12.
- Snyder JD, Rosenblum N, Wershil B, Goldman M, Winter HS. Pyloric stenosis and eosinophilic gastroenteritis in infants. *J Pediatr Gastroenterol Nutr* 1987;6:543-7.
- Machida H, Smith A, Gall D, Trevenen C, Scott RB. Allergic colitis in infancy: clinical and pathologic aspects. *J Pediatr Gastroenterol Nutr* 1994;19:22-6.
- Lake AM. Food-induced eosinophilic proctocolitis. *J Pediatr Gastroenterol Nutr* 2000;30 Suppl:S58-60.
- Savilahti E. Food-induced malabsorption syndromes. *J Pediatr Gastroenterol Nutr* 2000;30 Suppl:S61-6.
- Sollid LM, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. *Gastroenterology* 1993;105:910-22.
- Hill DJ, Hosking CS. Infantile colic and food hypersensitivity. *J Pediatr Gastroenterol Nutr* 2000;30 Suppl:S67-76.
- Sampson HA, Sicherer SH. Eczema and food hypersensitivity. *Immunol Allergy Clin North Am* 1999;19:495-518.
- Bieber T, Kraft S, Jugend M, Strobel I, Haberkost J, Tomov H, et al. New insights in the structure and biology of the high affinity receptor for IgE (Fc epsilon RI) on human epidermal Langerhans cells. *J Dermatol Sci* 1996;13:71-5.

34. Judd L. A descriptive study of occupational skin disease. *N Z Med J* 1994;107:147-9.
35. Hall RP. Dermatitis herpetiformis. *J Invest Dermatol* 1992;99:873-81.
36. James JM, Bernhisel-Broadbent J, Sampson HA. Respiratory reactions provoked by double-blind food challenges in children. *Am J Respir Crit Care Med* 1994;149:59-64.
37. James JM, Eigenmann PA, Eggleston PA, Sampson HA. Airway reactivity changes in food-allergic, asthmatic children undergoing double-blind placebo-controlled food challenges. *Am J Respir Crit Care Med* 1996;153:597-603.
38. Crespo JF, Pascual C, Dominguez C, Ojeda I, Munoz FM, Estaban MM. Allergic reactions associated with airborne fish particles in IgE-mediated fish hypersensitive patients. *Allergy* 1995;50:257-61.
39. Lee SK, Kniker WT, Cook CD, Heiner DC. Cow's milk-induced pulmonary disease in children. *Adv Pediatr* 1978;25:39-57.
40. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107:191-3.
41. Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
42. Lin RY, Schwartz LB, Curry A, Pesola GR, Knight RJ, Lee HS, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. *J Allergy Clin Immunol* 2000;106:65-71.
43. Varjonen E, Vainio E, Kalimo K. Life-threatening, recurrent anaphylaxis caused by allergy to gliadin and exercise. *Clin Exp Allergy* 1997;27:162-6.
44. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol* 2001;107:367-74.
45. Sicherer SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 2001;108:881-90.
46. Bindslev-Jensen C, Vibits A, Stahl Skov P, Weeke B. Oral allergy syndrome: the effect of astemizole. *Allergy* 1991;46:610-3.
47. Leung DY, Sampson HA, Yunginger JW, Burks AW, Schneider L, Wortel CH, et al. Effect of anti-IgE therapy (TNX-901) in patients with severe peanut allergy. *N Engl J Med*. In press 2003.
48. Sampson HA. Immunological approaches to the treatment of food allergy. *Pediatr Allergy Immunol* 2001;12:91-6.
49. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001;45:520-7.
50. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001;139:261-6.