

Current reviews of allergy and clinical immunology

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Update on food allergy

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

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Tremendous progress has been made in our understanding of food-based allergic disorders over the past 5 years. Recent epidemiologic studies suggest that nearly 4% of Americans are afflicted with food allergies, a prevalence much higher than appreciated in the past. In addition, the prevalence of peanut allergy was found to have doubled in American children less than 5 years of age in the past 5 years. Many food allergens have been characterized at the molecular level, which has contributed to our increased understanding of the immunopathogenesis of many allergic disorders and might soon lead to novel diagnostic and immunotherapeutic approaches. The management of food allergies continues to consist of educating patients on how to avoid relevant allergens, to recognize early symptoms of an allergic reaction in case of an accidental ingestion, and to initiate the appropriate emergency therapy. However, the recent successful clinical trial of anti-IgE therapy in patients with peanut allergy and the number of immunomodulatory therapies in the pipeline provide real hope that we will soon be able to treat patients with food allergy. (*J Allergy Clin Immunol* 2004;113:805-19.)

Key words: Food allergy (hypersensitivity), food intolerance, clinical tolerance, mucosal immunity, food allergens

IMMUNOPATHOGENESIS AND CLINICAL DISORDERS

In the 5 years since the Journal's previous review on food allergy,^{1,2} our understanding of food-induced allergic reactions has increased dramatically, especially in the area of diagnosis and management. Investigation of allergenic food proteins and immunologic responses has moved to the molecular level, and this newfound knowledge now

Abbreviations used

AEE: Allergic eosinophilic esophagitis

AEG: allergic eosinophilic gastroenteritis

DBPCFC: Double-blind, placebo-controlled food challenge

provides novel strategies for the laboratory diagnosis and immunomodulatory control of IgE-mediated food hypersensitivity. Food allergy is now recognized as a worldwide problem in westernized nations, and like other atopic disorders, it appears to be on the increase. Recent estimates suggest that IgE-mediated food allergies affect 3.5% to 4% of Americans.³ Food allergy remains a leading cause of anaphylaxis treated in emergency departments in a number of countries, and the public has become increasingly aware of the problem. This review is meant to complement and update the 2-part series that was published previously in the Journal.^{1,2}

Recently, a European Academy of Allergy and Clinical Immunology task force published a revised nomenclature for allergy,⁴ which will be noted here in italics but not used in this review because the current nomenclature is well accepted in the United States. Adverse food reactions (*food hypersensitivities*) include any abnormal reaction resulting from the ingestion of a food and might be the result of food intolerances (*nonallergic food hypersensitivities*) or food hypersensitivity/allergy (*food allergy*).¹ Food intolerances (*nonallergic food hypersensitivities*) are adverse responses caused by some unique physiologic characteristic of the host, such as metabolic disorders (eg, lactase deficiency). Food hypersensitivities/allergies are adverse immunologic reactions that might be due to IgE- or non-IgE-mediated immune mechanisms. Toxic reactions might mimic food hypersensitivities and typically are due to factors inherent in a food, such as toxic contaminants (eg, histamine in scombroid fish poisoning) or pharmacologic substances within the food (eg, tyramine in aged cheeses), which can affect most healthy individuals when given in appropriate doses. Food aversions also might mimic adverse food reactions but are not

From the Department of Pediatrics and Immunobiology and the Jaffe Food Allergy Institute, The Mount Sinai School of Medicine.

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Reprint requests: Hugh A. Sampson, MD, Department of Pediatrics, Box 1198, The Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: hugh.sampson@mssm.edu.

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TABLE I. Prevalence of food allergies in the United States

Food	Young children	adults
Milk	2.5%	0.3%
Egg	1.3%	0.2%
Peanut	0.8%	0.6%
Tree nuts	0.2%	0.5%
Fish	0.1%	0.4%
Shellfish	0.1%	2.0%
Overall	6%	3.7%

reproducible when the patient ingests the food in a blinded fashion.

PREVALENCE OF FOOD HYPERSENSITIVITY

The prevalence of food hypersensitivities is greatest in the first few years of life, affecting about 6% of infants less than 3 years of age⁵ and decreasing over the first decade. Virtually all infants who have cow's milk allergy have it in the first year of life, with clinical tolerance developing in about 80% by their fifth birthday.¹ About 60% of infants with cow's milk allergy experience IgE-mediated reactions, and about 25% of these infants retain their sensitivity into the second decade of life, with 35% going on to have other food allergies.⁶ Table I lists the prevalence of various food allergies in the United States on the basis of the most recent studies. Although it was once thought that peanut, nut, and seafood allergies were never outgrown, it has become apparent that clinical tolerance develops in about 20% of young children with peanut allergy.^{7,8} Recent studies from the United Kingdom and the United States indicate that the prevalence of peanut allergy has doubled in young children during the past decade.^{9,10} 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,¹¹ and about 6% to 8% of asthmatic children have food-induced wheezing.¹² On the basis of these more recent surveys, 3.5% to 4% of the US population are believed to have IgE-mediated food allergy.³

PATHOGENESIS OF FOOD HYPERSENSITIVITY REACTIONS

Gut barrier

Food allergy represents an abnormal response of the mucosal immune system to antigens delivered through the oral route. Unlike the systemic immune system, which sees relatively small quantities of antigen and mounts a brisk inflammatory response, the mucosal immune system encounters enormous quantities of antigen on a daily basis and generally suppresses immune reactivity to harmless foreign antigens (eg, food proteins and commensal organisms), although it is fully capable of

mounting a brisk protective response to dangerous pathogens. The gastrointestinal mucosal barrier is a complex structure that provides an enormous surface area for processing and absorbing ingested food and discharging waste products.¹³ This barrier uses both physicochemical and cellular factors to prevent the penetration of foreign antigens. The physical barrier is comprised of the epithelial cells joined by tight junctions and covered with a thick mucus layer that traps particles, bacteria, and viruses, trefoil factors that help strengthen and promote restoration of the barrier, and luminal and brush border enzymes, bile salts, and extremes of pH, which all serve to destroy pathogens and render antigens nonimmunogenic. Innate (natural killer cells, polymorphonuclear leukocytes, macrophages, epithelial cells, and toll-like receptors) and adaptive immune (intraepithelial and lamina propria lymphocytes, Peyer's patches, sIgA, and cytokines) responses provide an active barrier to foreign antigens. However, developmental immaturity of various components of the gut barrier and immune system reduces the efficiency of the infant mucosal barrier.¹⁴ For example, enzymatic activity is suboptimal in the newborn period, and the sIgA system is not fully mature until 4 years of age.¹³ Consequently, this immature state of the mucosal barrier might play a role in the increased prevalence of gastrointestinal infections and food allergy seen in the first few years of life.¹

Despite the evolution of this complex mucosal barrier, about 2% of ingested food antigens are absorbed and transported throughout the body in an immunologically intact form, even through the normal mature gut.¹⁵ In an elegant series of experiments more than 75 years ago, Walzer and colleagues¹⁶⁻¹⁸ used sera from patients with food allergy to passively sensitize volunteers and demonstrate that immunologically intact antigens cross the mucosal barrier and disseminate rapidly throughout the body.

Oral tolerance induction

Even though intact foreign food antigens routinely penetrate the gastrointestinal tract, they infrequently induce clinical symptoms because tolerance develops in most individuals. Husby et al^{19,20} demonstrated that oral feeding leads to immunologic tolerance induction in human subjects. The underlying immunologic mechanisms involved in oral tolerance induction have not been fully elucidated, but recent studies suggest that various antigen-presenting cells, especially intestinal epithelial cells and various dendritic cells, and regulatory T cells play a central role.²¹ Five different regulatory T cells have been identified in conjunction with intestinal immunity: T_H3 cells, a population of CD4⁺ cells that secrete TGF- β ; T_R1 cells, CD4⁺ cells that secrete IL-10; CD4⁺CD25⁺ regulatory T cells; CD8⁺ suppressor T cells; and $\gamma\delta$ T cells.²¹ Intestinal epithelial cells have been shown to be nonprofessional antigen-presenting cells.²² Intestinal epithelial cells can process luminal antigen and present it to T cells on an MHC class II complex but lack a second

signal, thus suggesting their potential to play a major role in tolerance induction to food antigens. In addition, dendritic cells residing within the lamina propria and the noninflammatory environment of Peyer's patches express IL-10 and IL-4, which favor the generation of tolerance. It has been suggested that T cells primed in the local mucosal environment lead to tolerance induction, whereas T cells primed in the mesenteric lymph nodes, either from antigen reaching the node in the lymph or carried there by circulating dendritic cells, differentiate and travel to the mucosa, where they induce local immune responses.²¹

In the last several years, there has been increased interest in the role of the commensal gut flora in shaping the mucosal immune response. It is estimated that there are 10^{12} to 10^{14} bacteria per gram of colonic tissue, suggesting that there are more bacteria in the colon than cells in the body.¹³ Gut flora is largely established in the first 24 hours after birth, is relatively stable throughout life, and is dependent on maternal flora, genetics, and the local environment. The importance of gut flora in the development of oral tolerance induction is suggested by the fact that mice raised in a germ-free environment from birth fail to have normal tolerance.²³ Recent studies feeding lactating mothers and their offspring *Lactobacillus GG* suggest that probiotics might be of benefit in preventing atopic dermatitis,^{24,25} but whether they will be useful for preventing food allergy remains to be demonstrated.

Food allergens

The diversity of the human diet is enormous, and yet relatively few foods account for the majority of food allergies around the world. Milk, egg, and peanut account for the vast majority of food-induced allergic reactions in American children, whereas peanut, tree nuts, fish, and shellfish account for most of the food-induced allergic reactions in American adults. The regional dietary habits and methods of food preparation clearly play a role in the prevalence of specific food allergies in various countries around the world. For example, the per capita consumption of peanuts in China and the United States is essentially the same, but there is virtually no peanut allergy in China.²⁶ The Chinese eat predominantly boiled or fried peanuts, and Americans eat almost exclusively dry-roasted peanuts. The higher heat of dry roasting (180°C) and the process of maturation and curing have been shown to increase the allergenicity of peanut proteins.²⁷⁻³⁰ Other regional dietary habits also might play a role in sensitization to foods, as suggested by the fact that young Israeli children commonly receive a peanut-containing snack, and yet sesame seed allergy appears to be the major food allergy in this population.³¹

Sensitization to food allergens can occur in the gastrointestinal tract (considered traditional or class 1 food allergy) or as a consequence of an allergic sensitization to inhalant allergens (class 2 food allergy).³² The major food allergens identified as class 1 allergens are water-soluble glycoproteins that are 10 to 70 kd in size and

fairly stable to heat, acid, and proteases.¹ As increasing numbers of allergenic proteins have been identified, isolated, and characterized, it has become apparent that similar types of animal and plant proteins make up the vast majority of food allergens. As reviewed by Breiteneder and Radauer³³ in this issue of the Journal, plant allergens are found predominantly in the cupin and prolamin superfamilies and the protein families of the plant defense system. The cupin superfamily consists of the 7S (vicilins, such as Ara h 1, Jug r 2, Ses i 3) and 11S (legumins, such as Ara h 3, Cor a 9, and Ber e 2) seed storage proteins. The prolamin superfamily consists of cysteine-rich 2S albumin storage proteins (eg, Ara h 2, Jug r 1, Ber e 1, and Ses i 2), nonspecific lipid transfer proteins (eg, Cor a 8, Mal d 3, and Pru av 3), and cereal α -amylase and protease inhibitors. Many proteins generated by the plant defense system have been found to be major allergens, including a collection of 14 types of pathogenesis-related proteins, protease inhibitors, and proteases. Pathogenesis-related proteins are generated by plants in response to various pathogens (eg, viruses, molds, and parasites) and environmental stresses and consequently can be present in variable quantities within the same fruit or vegetable species. Profilins, which play a major role in the regulation of polymerization of actin filaments and comprise a large portion of the class 2 allergens, are highly conserved throughout the plant kingdom and frequently show cross-reactivity between pollen and food.³² Patients often become sensitized to the inhaled pollen and, because of the cross-reactivity with profilins in the fruit or vegetable, experience oral and pharyngeal symptoms when ingesting the raw fruit or vegetable (ie, the pollen-food allergy or oral allergy syndrome). The majority of these class 2 allergens are presumably comprised of conformational epitopes and therefore highly heat labile, susceptible to enzymatic degradation, and difficult to isolate, often making standardized extracts for diagnostic purposes unsatisfactory. However, in the past 5 years, cDNAs for many of these proteins have been isolated and recombinant proteins have been generated, suggesting that better diagnostic materials should be available in the near future. The variety of animal-related allergens appears to be more limited in number and cross-reactivity. A steadily increasing number of food allergens have been identified, cloned, sequenced, and expressed as recombinant proteins, as listed in on the International Union of Immunological Societies Allergen Nomenclature Subcommittee's Web site (<http://www.allergen.org/>).

CLINICAL DISORDERS

Food hypersensitivities develop in genetically predisposed individuals,³⁴ presumably 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 come in contact with and bind circulating food allergens and activate the cells to release potent mediators and cytokines. As depicted in

TABLE II. Food hypersensitivity disorders

IgE mediated	
Gastrointestinal	Oral allergy syndrome, gastrointestinal anaphylaxis
Cutaneous	Urticaria, angioedema, morbilliform rashes and flushing
Respiratory	Acute rhinoconjunctivitis, bronchospasm (wheezing)
Generalized	Anaphylactic shock
Mixed IgE and cell mediated	
Gastrointestinal	Allergic eosinophilic esophagitis, allergic eosinophilic gastroenteritis
Cutaneous	Atopic dermatitis
Respiratory	Asthma
Cell mediated	
Gastrointestinal	Food protein–induced enterocolitis, food protein–induced proctocolitis, food protein–induced enteropathy syndromes, celiac disease
Cutaneous	Contact dermatitis, dermatitis herpetiformis
Respiratory	Food-induced pulmonary hemosiderosis (Heiner syndrome)

Table II, a number of IgE-, cellular-, and mixed IgE- and cell-mediated food hypersensitivity disorders have been described. There is little evidence to implicate antigen-antibody complex–mediated hypersensitivity in food-related disorders.

Gastrointestinal food hypersensitivity reactions

As depicted in Table III, a number of gastrointestinal food hypersensitivities have been described. As indicated above, the pollen-food allergy syndrome (oral allergy syndrome) is elicited by a variety of plant proteins that cross-react with airborne allergens, especially birch, ragweed, and mugwort pollens.³² Patients with ragweed allergy might react to fresh melons and bananas, patients with grass pollen allergy might have symptoms when ingesting raw tomatoes, and patients with birch pollen allergy might have symptoms after the ingestion of raw potatoes, carrots, celery, apples, pears, hazelnuts, and kiwi. Because the allergens responsible for these reactions are easily broken down by heat or gastric enzymes, most patients only experience allergic symptoms in the oral and pharyngeal mucosa. Gastrointestinal anaphylaxis typically presents as acute nausea, colicky abdominal pain, and vomiting and generally occurs with allergic manifestations in other target organs.¹

Allergic eosinophilic esophagitis (AEE) and allergic eosinophilic gastroenteritis (AEG) might be due to IgE-mediated food allergy, non-IgE-mediated food allergy, or both and are characterized by infiltration of the esophagus, stomach, and/or intestinal walls with eosinophils, basal zone hyperplasia, papillary elongation, absence of vasculitis, and peripheral eosinophilia in up to 50% of patients.^{35,36} AEE is seen most frequently during infancy

through adolescence and typically presents with symptoms of gastroesophageal reflux (ie, nausea, dysphagia, vomiting, and epigastric pain).^{35,37-41} AEE is being diagnosed more frequently in the adult population because gastroenterologists are more routinely performing biopsies on adults with normal-appearing esophageal mucosa.⁴² The prevalence of atopic disorders and food allergy is quite high in patients with AEE, but the food allergy is often not IgE mediated (ie, negative skin test result). Some patients appear to have an association between pulmonary and esophageal inflammation, with some patients reporting seasonal esophageal symptoms.⁴³ In a murine model repeated delivery of allergen or IL-13 to the lung induced esophageal eosinophilic inflammation, much like AEE.⁴⁴ AEE appears to be increasing in frequency over the past 5 years, which some believe might be due to the increased early use of antacids and prokinetic agents in young infants with symptoms of reflux. It should be noted that antacids are required for sensitization in murine models of anaphylaxis^{45,46} and that a recent study demonstrated the need for antacids to induce fish allergy in another murine model.⁴⁷ The long-term prognosis of AEE has not been clearly delineated, but there is concern that patients who are not appropriately treated might go on to have Barrett's esophagitis.⁴³

AEG can occur at any age, including in young infants, in whom it might present as pyloric stenosis with outlet obstruction and postprandial, projectile emesis.⁴⁸ Weight loss or failure to thrive is a hallmark of this disorder. Depending on the extent and location of the inflammatory involvement, patients might present with abdominal pain, vomiting, diarrhea, blood loss in the stools, iron-deficiency anemia, and protein-losing enteropathy.^{49,50} Like AEE, AEG can involve IgE-mediated mechanisms, non-IgE-mediated mechanisms, or both to food allergens. Studies suggest an abnormal T_H2 response because increased numbers of T_H2 cells have been found in the peripheral blood and infiltrating the intestinal mucosa.^{51,52}

Food protein–induced proctocolitis is another of the eosinophilic gastrointestinal disorders but only appears to involve a non-IgE-mediated mechanism. It generally presents in the first few months of life because of food proteins passed in maternal breast milk (about 50% of infants⁵³) or to milk- or soy-based formulas.^{53,54} Infants typically appear healthy and grow well but are identified because of gross or microscopic blood in the stool. Lesions are confined to the distal large bowel and consist of mucosal edema, with infiltration of eosinophils in the epithelium and lamina propria.⁴³

Food protein–induced enterocolitis syndrome is a cell-mediated hypersensitivity disorder most commonly seen in infants before 3 months of age but might be delayed in breast-fed babies.⁵⁵ Symptoms are most commonly provoked by cow's milk or soy protein–based formulas but might be caused by other foods in older infants (eg, various cereal grains).^{55,56} Breast-fed babies virtually never have symptoms while breast-feeding but might be sensitized through food proteins passed in the breast milk

TABLE III. Gastrointestinal food hypersensitivities

Disorder	Mechanism	Symptoms	Diagnosis
Pollen-food allergy syndrome (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 SPT 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 (ie, skin, respiratory tract) often involved	Clinical history and positive SPT responses or RAST results; ± 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, SPTs, endoscopy and biopsy, elimination diet and challenge
Allergic eosinophilic gastroenteritis	IgE mediated and/or cell mediated	Recurrent abdominal pain, irritability, early satiety, intermittent vomiting, FTT, and/or weight loss	Clinical history, SPTs, endoscopy and biopsy, elimination diet and challenge
Food protein–induced proctocolitis	Cell mediated	Gross or occult blood in stool; typically thriving; usually presents in first few months of life	SPT responses negative; elimination of food protein → clearing of most bleeding in 72 h; ± endoscopy and biopsy; challenge induces bleeding within 72 h
Food protein–induced enterocolitis	Cell mediated	Protracted vomiting and diarrhea (± bloody) not infrequently with dehydration; abdominal distention, FTT; vomiting typically delayed 1-3 h after feeding	SPT responses negative; elimination of food protein → clearing of symptoms in 24-72 h, challenge → recurrent vomiting within 1-2 h, ~15% have hypotension
Food protein–induced enteropathy, celiac disease (gluten-sensitive enteropathy)	Cell mediated	Diarrhea or steatorrhea, abdominal distention and flatulence, weight loss or FTT, ± nausea and vomiting, oral ulcers	Endoscopy and biopsy IgA; elimination diet with resolution of symptoms and food challenge; celiac: IgA anti-gliadin and anti-transglutaminase antibodies

Used with permission from *J Allergy Clin Immunol*. 2003;111(suppl):S540-7. SPT, Skin prick test; FTT, failure to thrive.

and experience a reaction on the first few feedings of the whole food.⁵⁶ Patients typically present with prolonged projectile vomiting that begins about 1 to 3 hours after allergen ingestion. About 15% of these infants have hypotension, presumably caused by volume depletion, increased TNF- α secretion, or both.^{57,58} In adults shellfish (eg, shrimp, crab, and lobster) hypersensitivity might provoke a similar syndrome, with delayed onset of severe nausea, abdominal cramps, and protracted vomiting.

Dietary protein–induced enteropathy (excluding celiac disease) generally presents in the first several months of life with diarrhea (mild-to-moderate steatorrhea in about 80%) and poor weight gain.⁵⁹ Biopsy reveals a patchy villous atrophy, a prominent mononuclear round cell infiltrate, and few eosinophils.⁵⁹ Celiac disease is a more extensive enteropathy leading to malabsorption and is associated with sensitivity to gliadin found in wheat, rye, and barley. Celiac disease is associated with HLA-DQ2, which is present in more than 90% of patients with celiac disease.⁶⁰

Infantile colic is due to food hypersensitivity in a minority of infants presenting with this disorder. Infantile colic is an ill-defined syndrome of paroxysmal fussiness characterized by inconsolable agonized crying that generally develops in the first 2 to 4 weeks of life and persists through the third to fourth month of life.⁶¹

Cutaneous food hypersensitivity reactions

As depicted in Table IV, IgE, cellular, and mixed IgE and cellular reactions to foods can induce a variety of cutaneous hypersensitivity disorders. Acute urticaria and angioedema are among the most common symptoms of food-induced allergic reactions, although the exact prevalence of these reactions is unknown. Acute contact urticaria caused by food (eg, meats, vegetables, and fruits) also is common. Food allergy is infrequently the cause of chronic urticaria and angioedema (symptoms lasting >6 weeks).^{62,63}

TABLE IV. Cutaneous food hypersensitivities

Disorder	Mechanism	Symptoms	Diagnosis
Acute urticaria and angioedema	IgE mediated	Pruritus, hives, and/or swelling	Clinical history; SPTs or RAST; ± challenge
Chronic urticaria and angioedema	IgE mediated	Pruritus, hives, and/or swelling of >6 wk duration	Clinical history; SPTs or RAST; elimination diet; challenge
Atopic dermatitis	IgE and cell mediated	Marked pruritus; eczematous rash in classic distribution	Clinical history; SPTs; CAP-System FEIA (ie, 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 anti-gliadin and anti-transglutaminase antibodies; ± endoscopy

Used with permission from *J Allergy Clin Immunol*. 2003;111(suppl):S540-7.
SPT, Skin prick test.

TABLE V. Respiratory food hypersensitivities

Disorder	Mechanism	Symptoms	Diagnosis
Allergic rhinoconjunctivitis	IgE mediated	Periocular pruritus, tearing, and conjunctival erythema, nasal congestion, rhinorrhea, sneezing	Clinical history, SPTs, elimination diet, food challenge
Asthma	IgE and cell mediated	Cough, dyspnea, wheezing	Clinical history, SPTs, elimination diet, food challenge
Heiner's syndrome	?	Recurrent pneumonia, pulmonary infiltrates, hemosiderosis, iron-deficiency anemia, FTT	Clinical history, peripheral eosinophilia, milk precipitins (if caused by milk), ± lung biopsy, elimination diet

Used with permission from *J Allergy Clin Immunol*. 2003;111(suppl):S540-7.
SPT, Skin prick test; FTT, failure to thrive.

Atopic dermatitis (atopic eczema dermatitis syndrome) is a form of eczema that generally begins in early infancy and is characterized by typical distribution, extreme pruritus, and a chronically relapsing course.⁶⁴ Allergen-specific IgE antibody-bound Langerhan's cells play a unique role as nontraditional receptors.⁶⁵ Ingestion of specific foods in patients with food allergy has been shown to provoke a markedly pruritic, erythematous, morbilliform rash. In addition, a murine model of food-induced atopic dermatitis has been reported.⁶⁶ Urticarial lesions in younger children are rarely seen when there are extensive eczematous lesions, but gastrointestinal and respiratory symptoms frequently develop. In one study about 45% of adult patients with atopic dermatitis and birch pollen allergy were found to have worsening of their eczema within 48 hours of ingesting Bet v 1-containing foods (eg, raw apples, carrots, and celery), even in the absence of noticeable immediate oral symptoms.⁶⁷

Food-induced contact dermatitis is often seen among food handlers, especially among those who handle raw fish, shellfish, meats, and eggs.⁶⁸ 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.⁶⁹

Respiratory food hypersensitivity reactions

Food allergy can induce a number of disorders in the respiratory tract, as depicted in Table V. Acute respiratory symptoms caused by food allergy generally represent isolated IgE-mediated reactions, whereas chronic respiratory symptoms represent a mix of IgE- and cell-mediated reactions. Isolated rhinoconjunctivitis is rarely the result of a food-induced allergic reaction, although it frequently occurs in association with other food allergy symptoms. Asthma is an uncommon manifestation of food allergy, although acute bronchospasm is usually seen with other food-induced symptoms.⁷⁰ However, airway hyperreactivity and worsening of asthma also can be induced in the absence of marked bronchospasm after the ingestion of

small amounts of food allergens in sensitized subjects.⁷¹ Interestingly, food allergy recently was found to be a major risk factor for severe life-threatening asthma. Roberts et al⁷² reported that about one half of asthmatic children requiring intubation for severe asthma had food allergy compared with about 10% of asthmatic patients seen at the same hospital. Vapors or steam containing proteins emitted from cooking food (eg, fish)^{73,74} can induce asthmatic reactions and even anaphylaxis. It has been estimated that about 1% of asthma in adults might involve reactions to inhalational exposures to food, especially in the workplace.⁷⁵ Similarly, particulate matter, such as peanut dust in airplanes, can induce allergic reactions,⁷⁶ whereas the smell of peanut butter, primarily organic solvents, is not likely to induce allergic symptoms.⁷⁷ 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 responses or reactions to a food. Heiner's syndrome is a rare form of food-induced pulmonary hemosiderosis typically caused by cow's milk.⁷⁸

Generalized anaphylaxis caused by food allergies accounts for at least one third to one half of anaphylaxis cases seen in hospital emergency departments.^{79,80} In addition to variable expression of cutaneous, respiratory, and gastrointestinal symptoms, patients might have cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias.⁸¹ Curiously, serum β -tryptase levels are rarely increased in food-induced anaphylaxis.^{82,83} In a survey of 32 fatal food-induced anaphylaxis cases,⁷⁹ a number of common factors were evident: most were adolescents or young adults, virtually all had a previous history of reacting to the implicated food (usually not life-threatening), virtually all of the victims had asthma, only 10% had epinephrine available for use at the time of their reaction, about 10% of subjects 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. Food-associated exercise-induced anaphylaxis is a form of anaphylaxis that occurs only when the patient exercises within 2 to 4 hours of ingesting a food. In the absence of exercise, the patient can ingest the food without any apparent reaction.⁸⁴ It might account for up to one half of the cases of exercised-induced anaphylaxis and is most common in female patients 15 to 35 years of age.⁸⁵ Omega-5 gliadin found in wheat has been shown to be a major cause of food-dependent, exercise-induced anaphylaxis.⁸⁶⁻⁸⁸ Diagnosis is based on patient history and the demonstration of food-specific IgE antibodies.

DIAGNOSIS AND MANAGEMENT

Diagnosing adverse food reactions

The approach to diagnosing adverse food reactions has changed little over the past 5 years,² as recently

reviewed,^{89,90} although new laboratory approaches are proving useful for the diagnosis of IgE-mediated food allergy. The medical history continues to be a mainstay in the diagnostic process, attempting to establish whether a food-induced allergic reaction occurred, which food was involved, and what allergic mechanism was likely involved. Diet diaries can be a useful supplement to a medical history, especially in chronic disorders. Elimination diets are implemented both for diagnostic and therapeutic purposes. In some cases, such as AEE and AEG, several weeks of an elemental diet with amino acid formulas are necessary to stabilize patients before conducting food challenges.

From a diagnostic standpoint, it is helpful to categorize food hypersensitivity disorders by 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 might involve both IgE- and non-IgE-mediated mechanisms and are variable in their time of onset. Various algorithms for diagnosing food allergy have been proposed.^{89,90}

Laboratory studies. For IgE-mediated disorders, skin prick tests provide a rapid method to screen patients for sensitivity to specific foods. Allergens eliciting a wheal at least 3 mm larger than that produced by the negative control are considered positive, indicating the possibility that the patient has symptomatic reactivity to the specific food, with strongly positive results (eg, median wheal diameter >8-10 mm) indicating a greater likelihood of clinical reactivity. In infants less than 2 years of age, skin prick tests to milk, egg, or peanuts with wheal diameters of 8 mm or larger are reportedly more than 95% predictive of reactivity.⁹¹ Negative skin test responses essentially confirm the absence of IgE-mediated allergic reactivity (negative predictive accuracy, >95%).² In general, negative skin prick test responses are extremely useful for excluding IgE-mediated food allergies, but positive skin test responses, for the most part, suggest the presence of clinical food allergy. However, in some clinical situations, a positive skin test response might be considered confirmatory when combined with a recent and clear-cut history of a food-induced allergic reaction to the food in question. 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, and therefore the fresh food must be used for skin testing.⁹²

A number of investigators have examined the use of the atopy patch test in addition to skin prick tests for the diagnosis of non-IgE-mediated food allergy, primarily in patients with atopic dermatitis and AEE.⁹³⁻⁹⁸ Although the atopy patch test shows promise in identifying foods that might be eliciting non-IgE-mediated reactions, at this time there are no standardized reagents or methods of application or interpretation. Nonspecific irritation is a common finding in standard patch testing and therefore requires skill in interpretation.⁹⁹

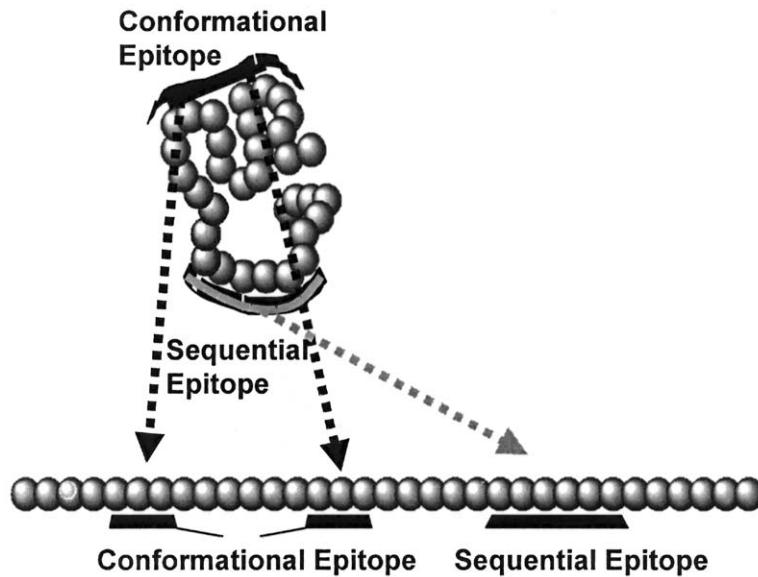


FIG 1. Conformational epitopes are destroyed when the native shape of a protein is altered—eg, by cooking or hydrolysis—whereas sequential epitopes are not affected.

TABLE VI. Predictive value of food allergen-specific IgE levels

95% Predictive Level

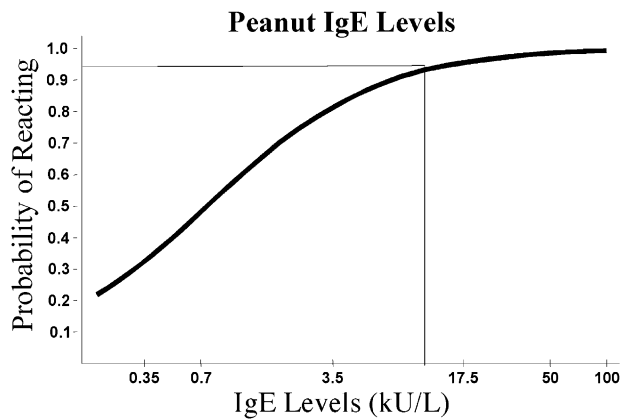
Allergen	[kU _A /L]	PPV
Egg	7	98
- Infants \leq 2 yrs ⁺	2	95
Milk	15	95
- Infants \leq 2 yrs ⁺⁺	5	95
Peanut	14	100
Fish	20	100
Tree nuts ⁺⁺⁺	~15	~95
Soybean	30	73
Wheat	26	74

⁺ Boyano MT, et al. *Clin Exp Allergy* 2001; 31(9):1464-9.

⁺⁺ Garcia-Ara C, et al. *J Allergy Clin Immunol* 2001; 107(1):185-90.

⁺⁺⁺ Clark AT, Ewan P. *Clin Exp Allergy*. 2003; 33(8):1041-5

PPV = Positive predictive value



Increasing probability of clinical reactivity with increasing level of food-antigen specific IgE value; note: values <0.35 do not exclude allergic reactivity

RASTs and similar qualitative in vitro assays provide suggestive evidence of IgE-mediated food allergy, but these assays are giving way to quantitative measurements of food-specific IgE antibodies (eg, CAP System FEIA, Pharmacia-Upjohn Diagnostics), which have been shown

to be more predictive of symptomatic IgE-mediated food allergy.¹⁰⁰⁻¹⁰³ Table VI provides diagnostic levels of food-specific IgE for a variety of foods. When a patient has a food-specific IgE level exceeding any of these values, they are greater than 95% likely to experience an allergic

reaction if they ingest the specific food. As indicated in the accompanying figure in Table VI, there is a direct correlation between the food-specific IgE level and the probability that an individual will react to a food if ingested. Consequently, when the medical history is taken into account, a clinician might conclude that an allergen-specific IgE level that is 60% predictive of reactivity is sufficient to make the diagnosis of clinical food allergy. It should also be noted from the figure that a patient with an allergen-specific IgE level of less than 0.35 kU/L might still experience an allergic reaction. Consequently, if there is any suspicion of possible allergic reactivity, a negative skin prick test response, physician-supervised food challenge, or both are necessary to confirm the absence of clinical food allergy.

Recent advances in technology have enabled investigators to map allergenic epitopes of many major food allergens and determine specifically where individual patient's IgE antibodies bind to these proteins.¹⁰⁴⁻¹¹⁰ In mapping major food allergens (ie, egg and milk), it became apparent that both conformational and sequential epitopes might be responsible for allergic reactions. However, individuals who possess IgE antibodies to sequential epitopes react to the food in any form (eg, extensively cooked or partially hydrolyzed), whereas those with IgE antibodies primarily to conformational epitopes appear to tolerate small amounts of the food after extensive heating or partial hydrolysis because the tertiary structure of the protein is altered and the conformational epitopes are destroyed,^{111,112} as depicted in Fig 1. In addition, it was shown that patients with egg and milk allergy with IgE antibodies directed at sequential epitopes tend to have persistent allergy, whereas those with IgE antibodies primarily to conformational epitopes tend to have clinical tolerance.^{113,114} Further analysis revealed that determining epitope-specific binding might correlate with clinical reactivity better than quantitative IgE values to the whole protein.¹¹⁵ As reported in the April 2004 issue of the Journal by Shreffler et al,¹¹⁶ evaluating the number of allergenic epitopes bound by patient IgE antibodies might be useful for predicting the clinical severity of food-induced allergic reactions. By using overlapping peptide microarray technology, the authors report that patients with IgE antibodies binding to many epitopes (ie, broad epitope diversity) tend to have more severe allergic reactions compared with those who have IgE antibodies binding to relatively few epitopes. New miniaturized technology under development (protein and peptide microarrays) might someday enable physicians to screen patients to a number of foods with just a few drops of blood and tell whether they will react to a specific food, identify potential cross-reactivities on the basis of homologous epitopes, and predict how severe their reaction might be and whether they are likely to outgrow their allergy (ie, development of clinical tolerance).

When evaluating patients with gastrointestinal hypersensitivities, a number of standard laboratory studies might be useful. About one half of patients with AEE and

AEG have peripheral eosinophilia, and patients with severe AEG might have anemia, blood in the stool, and decreased serum protein, albumin, and IgG levels (with preservation of IgA and IgM).^{35,43,117} Endoscopy and biopsy are the most definitive approaches for diagnosing many of the gastrointestinal hypersensitivities. Greater than 10 to 20 eosinophils per 40X high-power field in the esophagus is diagnostic of AEE, especially if the pH probe is normal and there is a lack of response to antireflux medication.¹¹⁷ Eosinophils are normally present in the gastric and intestinal mucosa, and therefore eosinophil numbers must be greater to make the diagnosis of AEG. In patients with suspected celiac disease, the presence of IgA anti-tissue transglutaminase (anti-endomysium) and anti-gliadin antibodies are greater than 90% predictive of celiac disease,^{118,119} although endoscopy and biopsy are definitive.¹²⁰ (When performing serology for diagnosis, patients must be ingesting gluten-containing foods, and IgA deficiency must be excluded because it is more frequent in patients with celiac disease.³⁵)

Oral food challenges. The double-blind, placebo-controlled food challenge (DBPCFC) remains the gold standard for the diagnosis of food allergies.² A number of reviews have outlined this procedure,¹²¹⁻¹²³ and efforts to standardize challenge materials are underway.¹²⁴ The clinical history results, skin test (RAST) results, or both indicate which foods should be evaluated by DBPCFCs. Open or single-blind food challenges are often used to screen foods unlikely to provoke food-induced allergic reactions. To increase the likelihood of a nonequivocal food challenge result, suspect foods should be eliminated for 7 to 14 days before challenge and longer in some non-IgE-mediated gastrointestinal disorders (eg, AEE and AEG). Many young children with AEE and AEG have multiple food allergies, and consequently, it is necessary to start them on an elemental formula (ie, Neocate or EleCare) for 4 to 6 weeks before initiating the challenges.¹²⁵ Medications that could interfere with the evaluation of food-induced symptoms (eg, antihistamines and β -adrenergic bronchodilators) must be discontinued. If the result of the blinded challenge is negative, it must be confirmed by means of an open feeding under observation to rule out the rare false-negative challenge result.

In some non-IgE-mediated food allergies (eg, dietary protein-induced enterocolitis), allergen challenges might require up to 0.3 to 0.6 g of food protein per kilogram of body weight given in 1 or 2 doses, and patients should be observed for up to 4 hours.⁵⁵ Hypotension might occur in about 15% of these challenges, and therefore intravenous hydration therapy should be available. In other non-IgE-mediated disorders (eg, AEE and AEG), the patient might require several feedings over a 1- to 3-day period to elicit symptoms. The length of the observation period is dependent on the type of reaction suspected. Patients with histories of life-threatening anaphylaxis should be challenged only when the history and laboratory testing cannot conclusively determine the causative food or the patient is believed to have developed clinical tolerance. Multiple

IgE-mediated food allergies are uncommon and, if suspected, must be confirmed by means of DBPCFC. In AEE and AEG multiple food allergies are common, and open or single-blind food challenges are often used to screen potential allergens, especially because it might take repeated feedings over a few days to elicit symptoms.

Therapy of food-induced allergic disorders

Once the diagnosis of food hypersensitivity is established, the only proved therapy remains elimination of the offending allergen, although as outlined below, a number of promising therapeutic modalities are on the horizon. Patients, their caregivers, or both must be educated about food allergen avoidance (ie, reading food labels, avoiding high-risk situations [eg, buffets], early recognition of allergic symptoms, and early management of anaphylactic reactions).² Excellent educational materials are available through organizations such as the Food Allergy and Anaphylaxis Network (Fairfax, Va; 1-800-929-4040 or <http://www.foodallergy.org>) to assist patients in avoiding known allergens and coping with their food allergies. Patients with food allergy with asthma or a history of a previous severe reaction or reaction to peanuts, nuts, seeds, or seafood should be given self-injectable epinephrine in addition to a written emergency plan for treatment of an accidental ingestion.¹²⁶⁻¹²⁹ Unfortunately, most individuals experiencing fatal food-induced allergic reactions did not have injectable epinephrine available at the time of their reaction,⁷⁹ and even more disturbing, most patients with food allergy treated in emergency departments in the United States are not given prescriptions for epinephrine (eg, EpiPen) or referred to an allergist for evaluation.¹³⁰ Clinical tolerance develops to most food allergens over time, except for peanuts, nuts, and seafood.^{2,8} Children with low levels of peanut-specific IgE should be reevaluated to determine whether they have outgrown their allergy. Clinical tolerance develops in about 20% of young children with peanut allergy, but children who experience an allergic reaction beyond the age of 5 years are unlikely to develop clinical tolerance. Children with a history of reactivity to peanut, no recent allergic reactions, and a peanut-specific IgE level of less than 5 kU/L should be reevaluated for clinical tolerance.⁸ However, it has become apparent that unlike the development of clinical tolerance to most foods, a small minority of patients with peanut allergy might redevelop clinical reactivity, even after having a negative peanut challenge result.^{131,132} Symptomatic reactivity to food allergens is generally very specific, and patients with IgE-mediated food allergies rarely react to more than one member of a botanical family or animal species.¹³³

In the non-IgE-mediated food hypersensitivities, allergen avoidance is the mainstay of therapy. In AEE and AEG responsible food allergens might need to be eliminated from the diet for up to 8 weeks to bring about resolution of symptoms and up to 12 weeks to bring about

normalization of intestinal histology.^{37,125} It appears that clinical tolerance eventually develops in most children (except for patients with celiac disease), although the long-term outcomes of most of these disorders have not been well studied. Periodic reintroduction of food allergens under physician supervision is warranted to determine whether clinical tolerance has developed (ie, every 1-2 years for food-induced enterocolitis, proctocolitis, and enteropathy and AEE and AEG).

Antihistamines might partially relieve symptoms of oral allergy syndrome¹³⁴ and IgE-mediated skin symptoms but do not block systemic reactions. A recent study investigating the ability of activated charcoal to bind peanut protein suggested that activated charcoal might be useful in the treatment of accidental food allergen ingestion.¹³⁵ As discussed by Simons¹³⁶ in this issue of the Journal, that study was done *in vitro*, and studies on the absorption of other foods and prospective studies in human subjects are warranted before broadly recommending this approach. Systemic corticosteroids are generally effective in treating chronic IgE-mediated disorders (eg, atopic dermatitis or asthma) or non-IgE-mediated gastrointestinal disorders (eg, AEE or AEG¹³⁷ and dietary-induced enteropathy). A course of corticosteroids can be used to reverse severe inflammatory symptoms, but the side effects of protracted use are unacceptable. Recently, a number of investigators have reported some success in treating patients with AEE with swallowed fluticasone from metered-dose inhalers,¹³⁸ although esophageal candidiasis can occur in about 15% of patients.¹³⁹

A number of novel forms of immunotherapy are being explored for the treatment of IgE-mediated food allergy.¹⁴⁰ In a double-blind placebo-controlled study of monthly injections of anti-IgE antibodies (TNX-901; 450 mg/mo), patients with peanut allergy required significantly greater amounts of peanut protein to elicit allergic symptoms compared with control subjects (mean level of peanut protein to elicit symptoms before/after therapy: 177.6 mg/2805 mg [approximately one half to 8 peanut kernels], $P = .001$, compared with 300 mg/900 mg, $P =$ not significant).¹⁴¹ About 25% of the treated group (450-mg dose) tolerated 8 g of peanut (approximately 22 peanut kernels), and another 25% failed to tolerate any increase in their peanut threshold. Interestingly, this did not appear to correlate with individual levels of peanut-specific IgE. Another anti-IgE preparation, omalizumab (Xolair), is approved for use in patients with severe asthma but has not yet been evaluated for its efficacy in treating patients with peanut allergy. Theoretically, anti-IgE antibody therapy should be protective against multiple food allergens, although it would have to be administered indefinitely to maintain its protective effect. Another nonspecific therapy that has shown promise in the murine model of anaphylaxis is a concoction of traditional Chinese herbs.¹⁴² This preparation completely protected the mice during subsequent peanut challenges and reduced peanut-specific IgE levels and T_H2 responsiveness.

Some studies have suggested that standard immunotherapy for treating birch or ragweed pollen-induced rhinitis might eliminate symptoms of the pollen-food allergy syndrome, although further studies are needed to confirm this.^{143,144} However the risk/benefit ratio of traditional immunotherapy for the treatment of peanut allergy was considered unacceptable.¹⁴⁵ Consequently, a number of alternative immunotherapeutic strategies are under investigation. In one approach the immunodominant epitopes of the 3 major peanut proteins, Ara h 1 to Ara h 3, were altered by means of a single amino acid substitution, which dramatically reduced IgE binding to individual epitopes.¹⁴⁶ By using a mouse model of peanut anaphylaxis,⁴⁶ heat-killed *Escherichia coli* containing mutated recombinant Ara h 1 to Ara h 3 was injected or administered rectally to sensitized mice.¹⁴⁷ Mice receiving the heat-killed *E coli* containing modified Ara h 1 to Ara h 3 had a marked decrease in their peanut-specific IgE levels and T_H2 responsiveness compared with sham-treated mice and did not have anaphylactic symptoms after oral challenge with peanut. Other immunomodulatory approaches under investigation include the use immunostimulatory sequences (ie, CpG motifs) that have been found to be effective in reversing IgE-mediated sensitization in patients with ragweed allergy.^{148,149} By using a similar approach, immunostimulatory sequence-conjugated Ara h 2 has shown some promise in a murine model of peanut anaphylaxis. Another potential immunotherapeutic approach would be the use of a chimeric protein (eg, Ara h 2-Fc γ) that could form complexes with allergen-specific IgE bound to mast cells and basophils. Saxon and coworkers^{150,151} have shown that the simultaneous complexing of Fc ϵ RI and Fc γ RII receptors can effectively inhibit mast cell and basophil function.

A number of anecdotal reports have suggested that cromolyn sodium¹⁵² or leukotriene inhibitors^{153,154} might be effective for treating AEE or AEG, but these approaches have not been documented in controlled trials. Recently, a number of patients with hypereosinophilia syndrome, including a patient with AEG, were treated with anti-IL-5 antibodies.¹⁵⁵ Peripheral eosinophilia cleared readily, and the patient with AEG was reported to have experienced good clinical improvement.

Prevention of food hypersensitivity

Allergists have long debated the efficacy of various measures in preventing the development of food allergy.¹⁵⁶ Meta-analyses of existing studies suggest a beneficial role for breast-feeding high-risk infants for the first 3 to 6 months of life in the prevention of atopic disease.^{157,158} At this time, there are no conclusive studies indicating that the manipulation of the mother's diet during pregnancy or while breast-feeding or the restriction of allergenic foods from the infant's diet will prevent the development of food allergy. A large ongoing study in Germany comparing the use of various hypoallergenic infant formulas with cow's milk formulas as a supplement

to breast-feeding or as a weaning formula in high-risk infants suggests that extensively hydrolyzed casein formula or partially hydrolyzed whey formula might be useful in the prevention of some atopic disease and food allergy,¹⁵⁹ as suggested by a recent multivariate analysis.¹⁶⁰ Currently, 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 solids be delayed until 6 months of age, and that major allergens, such as peanuts, nuts, and seafood, be introduced after 3 years of age.

The past 5 years has shown a tremendous growth of knowledge and interest in the area of food allergy. Perhaps one of the most notable changes is our appreciation for the size of the problem, with epidemiologic studies indicating that food hypersensitivities affect up to 6% of children less than 3 years of age and approximately 4% of the general population. Studies in the past have fairly well characterized the food hypersensitivity disorders, but more recent studies have contributed to our understanding of the basic immunopathologic mechanisms, although much remains to be done in this area. Current studies of allergen characterization and immunologic mechanisms should provide a better understanding of the immunopathology of these disorders and new, more specific forms of diagnosis and therapy.

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