ICON: Food allergy

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Food allergies can result in life-threatening reactions and diminish quality of life. In the last several decades, the prevalence of food allergies has increased in several regions throughout the world. Although more than 170 foods have been identified as being potentially allergenic, a minority of these foods cause the majority of reactions, and common food allergens vary between geographic regions. Treatment of food allergy involves strict avoidance of the trigger food. Medications manage symptoms of disease, but currently, there is no cure for food allergy. In light of the increasing burden of allergic diseases, the American Academy of Allergy, Asthma & Immunology; European Academy of Allergy and Clinical Immunology; World Allergy Organization; and American College of Allergy, Asthma & Immunology have come together to increase the communication of information about allergies and asthma at a global level. Within the framework of this collaboration, termed the International Collaboration in Asthma, Allergy and Immunology, a series of consensus documents called International Consensus ON (ICON) are being developed to serve as an important resource and support physicians in managing different allergic diseases. An author group was formed to describe the natural history, prevalence, diagnosis, and treatment of food allergies in the context of the global community. (J Allergy Clin Immunol 2012;129:906-20.)

Key words: *Food allergy, global, consensus, diagnosis, treatment*

The International Collaboration in Asthma and Allergy initiated an international coalition among the American Academy of Allergy, Asthma & Immunology; European Academy of Allergy and Clinical Immunology; World Allergy Organization; and American College of Allergy, Asthma and Immunology on food allergy. An author group was formed and then divided into individual committees. Within the committee, teams of authors

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This article is a product of an international coalition between the American Academy of Allergy, Asthma & Immunology; European Academy of Allergy and Clinical Immunology; World Allergy Organization; and American College of Allergy, Asthma & Immunology on food allergy.

Disclosure of potential conflict of interest: A. W. Burks is a minority stockholder in Allertein and Mast Cell, Inc; is on an advisory board or expert panel for Dannon Co Probiotics and Nutricia; has consulted for Exploramed Development, LLC, Intellijject, McNeil Nutritionals, Merck & Co, Novartis, Pfizer, Portola Pharmaceuticals, and Schering-Plough; has received research support from the National Institutes of Health (NIH), the Food Allergy and Anaphylaxis Network (FAAN), the Food Allergy Initiative (FAI), the National Peanut Board, SHS, and the Wallace Research Foundation; has provided legal consultation or expert witness testimony on the topic of food allergy; and is on the medical board of directors of FAAN. M. Tang has received study products from Nestlé Research Institute; has been an invited speaker on food allergy and anaphylaxis for Link Pharmaceuticals, Alphapharm, Nutricia, Wyeth, and Nestlé Nutrition Institute; and has served on advisory boards for Nestlé Nutrition Institute and Nutricia. S. Sicherer has consulted for, and received grants from FAI; has served as an advisor to FAAN; and has received grants from the National Institute of Allergy and Infectious Diseases (NIAID). P. A. Eigenmann is an ex-committee member of the European Academy of Allergy and Clinical Immunology. A. Fiocchi has received research support from Allegria Onlus. K. Beyer has received consulting fees and honoraria from Danone and Novartis; has received honoraria from Phadia, Infectopharm, Hipp, UCB, and Meda Pharma; and has received research support from the German Research Foundation, the European Union, Danone, and the Foundation for the Treatment of Peanut Allergy. R. Wood has consulted for the Asthma and Allergy Foundation of America, has received research support from the NIH, and is on the medical advisory board for FAAN. J. O. Hourihane has received research support from the Children's Research Foundation (Ireland), Danone, the Food Standards Agency (United Kingdom), and Stallergenes; in addition, his employer, University College Cork, holds a patent on challenge outcome predictor software. S. M. Jones has received research support from the NIH/NIAID, the National Peanut Board, and FAAN; in addition, she serves on an advisory board for FAAN. G. Lack has received sponsorship from Sodilac, Novartis, the Spanish Society of Allergy and Clinical Immunology, Danone Nutricia, and Nestlé; has received research support from the Immune Tolerance Network/NIH, National Peanut Board, Food Standards Agency, Medical Research Council, FAI, Action Medical Research, ALK Abelló, and Guy's & St Thomas' Charity; is a voluntary scientific advisor for the Anaphylaxis Campaign and National Peanut Board; and is scientific advisor for DBV Technologies. H. A. Sampson has consulted for Allertein Therapeutics, LLC; has served on advisory boards for ImmusanT and Novartis; has received research support from the NIH/NIAID and FAI; has served as a consultant or advisor to FAI, FAAN, and the University of Nebraska–FARRP; and is a part-owner of Herb Springs, LLC. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 30, 2012; accepted for publication February 2, 2012.

Available online February 23, 2012.

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0091-6749/$36.00

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doi:10.1016/j.jaci.2012.02.001

Abbreviations used
DBPCFC: Double-blind, placebo-controlled food challenge
NIAID: US National Institutes of Allergy and Infectious Diseases
PPV: Positive predictive value
sIgE: Food-specific IgE
SPT: Skin prick test

were created to generate content for specific sections of the article. Content was derived from literature searches, relevant published guidelines, and clinical experience. After a draft of the document was assembled, it was collectively reviewed and revised by the authors. Where evidence was lacking or conflicting, the information presented represents the consensus expert opinion of the group.

DEFINITION OF THE DISEASE AND EPIDEMIOLOGIC FEATURES

Food allergy

The term *food allergy* refers to an immune response directed toward food.[1] As defined in the 2010 US National Institutes of Allergy and Infectious Diseases (NIAID)–sponsored guidelines, food allergy is an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food."[2] This definition encompasses immune responses that are IgE mediated, non–IgE mediated, or a combination of both and is in agreement with other international guidelines.[3-5]

IgE-mediated reactions are characterized by an acute onset of symptoms generally within 2 hours after ingestion of or exposure to the trigger food. IgE-mediated reactions to foods typically involve the skin, gastrointestinal tract, and respiratory tract. Allergic sensitization occurs when food-specific IgE (sIgE) antibodies are produced by plasma cells that have differentiated from allergen-specific B lymphocytes. The sIgE antibodies bind to the surface of tissue mast cells and blood basophils, and on reexposure to the food, antigenic proteins in the food bind to and cross-link these cell surface–bound sIgE antibodies, which triggers the release of symptom-causing mediators, such as histamine and leukotrienes. Subjects can have allergic sensitization (production of sIgE) to food allergens without having clinical symptoms of an allergic reaction on exposure. Thus sensitization alone is not sufficient to define food allergy. An sIgE-mediated food allergy requires both the presence of sensitization and the development of specific signs and symptoms on exposure to that food.[2]

Non–IgE-mediated immunologic reactions (eg, cell mediated) include food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes. These conditions primarily affect infants or young children who present with abdominal complaints, such as vomiting, abdominal cramps, diarrhea, and occasionally blood in the stool and failure to thrive or poor weight gain. Examples of food allergy comorbidities with mixed IgE- and non–IgE-mediated causes include eosinophilic esophagitis and atopic dermatitis.

Table I shows specific food-induced allergic conditions on the basis of pathophysiology. The table does not include symptoms or disorders that are not specific clinical syndromes associated with food allergy; thus infantile colic, constipation, and gastrointestinal reflux disease are not listed. Isolated chronic rhinitis and asthma are not commonly attributed to food allergy; however, occupational exposure can trigger asthma (eg, Baker's asthma from wheat) or contact dermatitis. Celiac disease (and dermatitis herpetiformis associated with celiac disease) is a cell-mediated response against an enzyme, tissue transglutaminase, that can be triggered by an immune response to a food protein, gluten. Because celiac disease is an autoimmune disorder with distinct symptoms and prognosis different than those of atopic disorders, it will not be discussed further in this document. There are numerous adverse responses to foods that do not involve an immune response and therefore are not considered the result of food allergies.[2] These include metabolic disorders, such as lactose and alcohol intolerance, responses to pharmacologically active food components (eg, caffeine), or illness in response to toxins from microbial contamination.[6] Certain psychological or neurological responses, such as food aversion or rhinorrhea caused by spicy foods, can also mimic food allergy but are not considered allergic disorders.

Food allergens

Food allergens, which are usually proteins but sometimes haptens, are recognized by allergen-specific immune cells and elicit specific immunologic reactions.[2] Most food allergens can cause reactions when ingested either in the raw form or after being cooked or even digested, but some allergens, such as those in fruits and vegetables, cause allergic reactions primarily if eaten raw. Food allergens can also cause reactions if the allergenic proteins are inhaled, although this should be differentiated from simply inhaling the fragrance of a food, which does not cause allergic reactions. Cross-reactivity can occur when a food allergen has structural or sequence similarity with a different food allergen or aeroallergen. The likelihood of having clinical allergic reactions to cross-reactive allergens is highly variable and depends on the type of food. For example, clinical cross-reactivity among legumes is generally uncommon (eg, most persons with peanut allergy tolerate beans and peas), whereas clinical cross-reactivity among different types of crustacean shellfish is common.

Although any food can trigger an allergic response and more than 170 foods have been reported to cause IgE-mediated reactions, a minority of foods cause the majority of allergic reactions, with most being attributed to the "major food allergens" peanut, tree nuts, egg, milk, fish, crustacean shellfish, wheat, and soy.[2] Celery, mustard, sesame, lupine, and molluscan shellfish have been identified as significant allergens in European countries, and in Japan buckwheat is also a common allergen.[7]

Protein-containing food additives and coloring agents, such as annatto, carmine, and gelatin, can induce allergic reactions. Chemical additives, such as artificial flavors (eg, tartrazine) and preservatives (eg, glutamates and sulfites), might cause adverse reactions, but an immune mechanism has not been identified, and such reactions are classified as intolerances.

Symptoms and severity

The likelihood of an allergic reaction is related to the level of sIgE. Symptoms of food allergy (Table II)[2] can occur within minutes to hours of ingesting the trigger food and can vary in severity from mild to life-threatening. Severity of allergic reactions varies based on the amount of food ingested, coingestion of other foods, and preparation of the food (cooked, raw, or processed).[2] Severity also can be influenced by the patient's age, as well as rapidity of absorption, which can be influenced by whether the food was eaten on an empty stomach or close to a time of exercise. The

TABLE I. Specific food-induced allergic conditions

Pathology	Disorder	Key features	Most common causal foods
IgE mediated (acute onset)	Acute urticaria/angioedema	Food commonly causes acute (20%) but rarely chronic urticaria.	Primarily "major allergens" (see text)
	Contact urticaria	Direct skin contact results in lesions. Rarely this is due to direct histamine release (nonimmunologic).	Multiple
	Anaphylaxis	Rapidly progressive, multiple organ system reaction can include cardiovascular collapse.	Any but more commonly peanut, tree nuts, shellfish, fish, milk, and egg
	Food-associated, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion is followed temporally by exercise.	Wheat, shellfish, and celery most often described
	Oral allergy syndrome (pollen-associated food allergy syndrome)	Pruritus and mild edema are confined to oral cavity and uncommonly progress beyond the mouth (~7%) and rarely to anaphylaxis (1% to 2%). Might increase after pollen season.	Raw fruit/vegetables; cooked forms tolerated; examples of relationships: birch (apple, peach, pear, carrot), ragweed (melons)
	Immediate gastrointestinal hypersensitivity	Immediate vomiting, pain	Major allergens
Combined IgE and cell mediated (delayed onset/chronic)	Atopic dermatitis	Associated with food allergy in ~35% of children with moderate-to-severe rash	Major allergens, particularly egg, milk
	Eosinophilic esophagitis	Symptoms might include feeding disorders, reflux symptoms, vomiting, dysphagia, and food impaction.	Multiple
	Eosinophilic gastroenteritis	Vary on site(s)/degree of eosinophilic inflammation; might include ascites, weight loss, edema, obstruction	Multiple
Cell mediated (delayed onset/chronic)	Food protein–induced enterocolitis syndrome	Primarily affects infants; chronic exposure: emesis, diarrhea, poor growth, lethargy; re-exposure after restriction: emesis, diarrhea, hypotension (15%) 2 hours after ingestion	Cow's milk, soy, rice, oat, meat
	Food protein–induced allergic proctocolitis	Mucus-laden, bloody stools in infants	Milk (through breast-feeding)
	Allergic contact dermatitis	Often occupational because of chemical moieties, oleoresins. Systemic contact dermatitis is a rare variant because of ingestion	Spices, fruits, vegetables
	Heiner syndrome	Pulmonary infiltrates, failure to thrive, iron deficiency anemia	Cow's milk

presence of other comorbid conditions, such as asthma or atopic dermatitis, also can influence severity. The severity of a reaction cannot be accurately predicted by the severity of past reactions or by the sIgE levels or size of a skin prick test (SPT) wheal. Although reactions after a severe reaction are also likely to be severe,[8] mild reactions can also be followed by more severe reactions.[9]

Food-induced anaphylaxis is a serious allergic reaction that is rapid in onset and can cause death.[10] IgE-mediated food-induced anaphylaxis involves systemic mediator release from sensitized mast cells and basophils. In patients with food-dependent, exercise-induced anaphylaxis, whether a reaction occurs depends on the amount of time between food consumption and exercise, usually within 2 hours.

Fatalities are primarily from allergic reactions to peanuts and tree nuts, are associated with delayed treatment with epinephrine (adrenaline), and occur more often in teenagers and young adults with asthma and a previously diagnosed food allergy.[11-13] Other factors related to having fatal or near-fatal reactions include association of food allergy with asthma, absence of skin symptoms, patient denial of symptoms, concomitant intake of alcohol, or reliance on oral antihistamines to manage symptoms.[2,11,13]

Natural history and development of tolerance

The timing of food allergy development and resolution is variable and appears to be influenced by several factors. Food allergy in adults can represent a persistent allergy from childhood or *de novo* sensitization. There are few data regarding food allergy beginning in adulthood, but empiric evidence suggests food allergy that starts in adulthood often persists. In contrast, food allergies that start in childhood are often outgrown. The proportions of children who will outgrow allergy to a given food vary between analyses, but allergy to milk, egg, soy, or wheat is more likely to be outgrown than allergy to tree nuts or peanut.[14,15] Resolution of a food allergy can occur as late as the teenage years. Allergy to fish or crustacean shellfish, which most commonly develops in adulthood, usually persists.[16,17]

TABLE II. Symptoms of food-induced allergic reactions

Target organ	Immediate symptoms	Delayed symptoms
Cutaneous	Erythema	Erythema
	Pruritus	Flushing
	Urticaria	Pruritus
	Morbilliform eruption	Morbilliform eruption
	Angioedema	Angioedema
		Eczematous rash
Ocular	Pruritus	Pruritus
	Conjunctival erythema	Conjunctival erythema
	Tearing	Tearing
	Periorbital edema	Periorbital edema
Upper respiratory	Nasal congestion	
	Pruritus	
	Rhinorrhea	
	Sneezing	
	Laryngeal edema	
	Hoarseness	
	Dry staccato cough	
Lower respiratory	Cough	Cough, dyspnea, and wheezing
	Chest tightness	
	Dyspnea	
	Wheezing	
	Intercostal retractions	
	Accessory muscle use	
Gastrointestinal (oral)	Angioedema of lips, tongue, or palate	
	Oral pruritus	
	Tongue swelling	
Gastrointestinal (lower)	Nausea	Nausea
	Colicky abdominal pain	Abdominal pain
	Reflux	Reflux
	Vomiting	Vomiting
	Diarrhea	Diarrhea
		Hematochezia
		Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis)	
	Hypotension	
	Dizziness	
	Fainting	
	Loss of consciousness	
Miscellaneous	Uterine contractions	
	Sense of "impending doom"	

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In studies that examine the development of tolerance, case definitions of "food allergy" and "tolerance" are variable and strongly influence outcomes.[18] Some studies only report rates of sensitization, whereas other studies focus on clinical reactivity to specific foods. The definition of clinical reactivity is also not consistent between studies in that some rely solely on parental reports of food reactions, whereas others use food challenges or other more objective measures of true food allergy. These details are important in that a history of an adverse food reaction or even evidence of sensitization does not necessarily mean that a patient will exhibit a clinical reaction on exposure to that food.

For the purposes of this review, a search of the PubMed database with the key words "food allergy" and "natural history" from 2003 to 2011 was conducted. Also reviewed were articles cited in relevant articles. Two reviewers independently evaluated each article's pertinence. Reviewed articles are summarized in Table III.[19-27]

Levels of immune markers can predict clinical resolution of food allergy.[19,20,28] A high initial sIgE level is associated with a lower rate of resolution. In children reductions in sIgE levels often precede the onset of tolerance. Changes in immediate SPT responses are less well defined; reductions in the size of an SPT-induced wheal might be a marker for the onset of tolerance to a food, yet in some cases SPT responses remain positive long after tolerance has developed. Peters et al[29] extensively reviewed the predictive value of SPTs for challenge-proved food allergy. The predictability of an SPT wheal size cutoff for determining tolerance or allergy appears to be limited to each study population because of differences in sample populations, testing technique, and quality of the allergen test materials. The specific proteins within a food extract recognized by the sIgE of an individual patient can also predict the timing or likelihood of tolerance development or the risk of anaphylaxis.[30] This type of testing is termed component testing. The measurement of ratios of IgE and IgG for specific determinants of an individual food protein, termed epitopes, can also predict the clinical course of food allergy.[31,32]

PREVALENCE

Determining the prevalence of food allergy is challenging. The double-blind, placebo-controlled food challenge (DBPCFC) is the most reliable indicator of allergy to a food, but using DBPCFCs in prevalence studies is difficult because the format is time-consuming and not all foods are easily masked. Prevalence rates determined on the basis of patient self-reporting are in general higher than those determined on the basis of medical history and clinical testing. A 2010 systematic review underscores the difficulty in obtaining precise values of prevalence. Under contract from the NIAID, the RAND Corporation performed a systematic review of articles on the epidemiologic aspects of food allergy and concluded that food allergy affects more than 1% to 2% but less than 10% of the population.[1]

Rona et al[16] reported the results of a meta-analysis on the prevalence of food allergy to cow's milk, hen's egg, peanut, fish, and shellfish. On the basis of patient self-reporting of allergy to any food, overall prevalence rates were 12% in children and 13% in adults (based on 23 studies). When prevalence rates were calculated on the basis of either clinical testing and medical history or DBPCFC results, they were 3% for all ages (6 studies). Prevalence rates varied widely between studies within the meta-analysis. For example, rates of self-reported allergy varied from 3% to 35%.

Zuidmeer et al[33] reviewed the prevalence of food allergies to plants, including fruits, vegetables, legumes, tree nuts, wheat, cereals, soy, and seeds. Analyses were based on self-perception, test results, and oral food challenge results. Among the 6 studies including oral food challenges, the prevalence ranged from 0.1% to 4.3% each for fruits and tree nuts, 0.1% to 1.4% for vegetables, and less than 1% each for wheat, soy, and sesame. Among the studies that included patient-reported symptoms or skin test results, prevalence rates varied from 0% to 4.2% for fruits, 2.7% for vegetables/legumes, 4.5% for tree nuts, 1.2% for wheat, and 0.6% for soy.

TABLE III. Incidence of acquired food tolerance over time

Reference, year, country	Study design	Follow-up period	Study population	Sensitizing allergen	Outcome	Main results
Pyziak et al,[19] 2011, Poland	Prospective	Minimum 5 y	83 children with food allergy (including food and food-inhalant allergy) diagnosed during first 3 y of life	Milk, egg, soy, pork, beef	Incidence of acquired food tolerance: overall, according to type of allergy (food/food-inhalant allergy), type of allergen, disease beginning time	Overall incidence, 87.9%; incidence in food group, 95.5%; incidence in food-inhalant group, 78.9% ($P < .05$); no statistically significant difference in incidence according to allergen type. Tolerance is acquired more quickly in children affected by milk allergy (more than half acquiring tolerance after the third year of life) compared with other allergens acquiring tolerance after the fourth or fifth (beef) year of life. Children affected since the first year of life had significantly lower ability to obtain tolerance than children affected since the third year of life ($P < .05$).
Savage et al,[22] 2010, United States	Retrospective	Median 5 y	133 children (male, 72%) with history of allergic reaction to soy; median age at initial visit: 1 y	Soy	Incidence of acquired food tolerance over time (Kaplan-Meier analysis)	Kaplan-Meier analysis predicted resolution of soy allergy in 25% by age 4 y, 45% by age 6 y, and 69% by age 10 y. By age 6 y, 59% of children with a peak soy IgE level of <5 kU/L, 53% of children with a peak sIgE level of 5-9.9 kU/L, 45% of children with a peak sIgE level of 10-49.9 kU/L, and 18% of children with a peak sIgE level of >50 kU/L had outgrown soy allergy ($P < .01$ for trend).
Keet et al,[23] 2009, United States	Retrospective	31 mo	103 children ≤18 y with clinical history of allergic reaction to wheat and positive wheat IgE test	Wheat	Development of oral tolerance to wheat	Median age of tolerance was 79 mo (IQR, 42-190 mo). Twenty-nine percent achieved tolerance by age 4 y (95% CI, 19% to 43%), 45% by age 6 y (95% CI, 34% to 59%), 56% by age 8 y (95% CI, 43% to 69%), 62% by age 10 y (95% CI, 48% to 75%), 65% by age 12 y (95% CI, 51% to 78%), and 70% by age 14 y (95% CI, 55% to 84%).

(Continued)

TABLE III. *(Continued)*

Reference, year, country	Study design	Follow-up period	Study population	Sensitizing allergen	Outcome	Main results
Savage et al,[24] 2007, United States	Retrospective	Median 4.9 y	881 children (male, 68%) with history of allergic reaction to eggs; median age at initial visit: 14 mo	Egg	Incidence of acquired food tolerance over time (Kaplan-Meier analysis)	Kaplan-Meier analysis predicted resolution in 4% of patients with egg allergy by age 4 y, 12% by age 6 y, 37% by age 10 y, and 68% by age 16 y. Patients with persistent egg allergy had higher egg IgE levels at all ages to age 18 y. A patient's highest recorded egg IgE level, presence of other atopic diseases, and presence of other food allergies were significantly related to egg allergy persistence.
Levy et al,[25] 2007, Israel	Prospective	Transient CMA: mean duration of follow-up, 2.71 ± 2.24 y; persistent CMA: mean duration of follow-up, 5.13 ± 3.88 y	43 children with transient CMA (age range, 0.48-11 y) and 62 patients with persistent CMA (age range, 3-16.5 y).	Cow's milk	Incidence of acquired food tolerance; incidence of additional allergic diseases; symptoms and signs in both groups	Of the 43 patients with transient CMA, 20 children achieved tolerance to milk up to age 3 y, 13 up to age of 5 y, 7 up to age 9 y, and 3 up to age of 11 y. None of the patients in the persistent CMA group achieved tolerance. Patients with persistent CMA had a higher rate of asthma than patients with transient CMA (61.2% vs 18.6%, $P < .001$). Fifty patients with persistent CMA had 137 subsequent allergic reactions after diagnosis, 25% of the reactions were due to oral milk challenge at the clinic and 75% were due to accidental exposure, of which 13% required an emergency department visit and 8% required hospitalization.
Skripak et al,[21] 2007, United States	Retrospective	Median 5 y	807 children (male, 65%) with IgE-mediated CMA	Cow's milk	Incidence of acquired food tolerance over time	Rates of resolution were 19% by age 4 y, 42% by age 8 y, 64% by age 12 y, and 79% by 16 y. Patients with persistent allergy had higher cow's milk IgE levels at all ages to age 16 y. The highest cow's milk IgE level for each patient, defined as peak cow's milk IgE level, was found to be highly predictive of outcome ($P < .001$). Coexisting asthma ($P < .001$) and allergic rhinitis ($P < .001$) were also significant predictors of outcome.

(Continued)

TABLE III. *(Continued)*

Reference, year, country	Study design	Follow-up period	Study population	Sensitizing allergen	Outcome	Main results
Cohen et al,[26] 2007, Israel	Prospective	Average 6.7 y	45 patients (male, 53%) who experienced allergic reaction after ingestion of sesame-containing food	Sesame	Incidence of acquired food tolerance over time	Tolerance developed in only 20% of the patients. High sIgE levels (>0.15 IU) were demonstrated only in 75% of those in whom it was examined. Sixteen patients performed oral sesame food challenge, results of which were found to be positive in 88%.
Cantani and Micera,[27] 2004, Italy	Prospective	8 y	115 children (male, 57%) with food allergy; median age at initial visit, 14 mo	Cow's milk, egg, wheat	Incidence of acquired food tolerance over time	Only 66 children (57%) acquired food tolerance. The median age for tolerance to cow's milk was 7 y + 11 mo, that to egg was 6 y + 6 mo, and that to wheat was 7 y + 2 mo. However, a great number of both tolerant and intolerant children had multiple sensitizations, and there was onset of asthma in 54% of cases. Early onset, widespread or atypical (reverse pattern) skin lesions, family history positive for atopy, persisting food allergy, high levels of total and specific IgE antibodies, association with CMA and asthma were significantly predictive of a long-term morbidity of children with atopic dermatitis and CMA.
Shek et al,[20] 2004, United States	Retrospective	Maximum 10 y	66 patients with egg allergy and 33 patients with milk allergy	Cow's milk, egg	Incidence of acquired food tolerance over time	Twenty-eight of the 66 patients with egg allergy and 16 of the 33 patients with milk allergy lost their allergy over time. For egg, the decrease in sIgE levels ($P = .0014$) was significantly related to the probability of having clinical tolerance, with the duration between challenges having an influence ($P = .06$). For milk, there also was a significant relationship between the decrease in sIgE levels ($P = .0175$) and the probability of having tolerance to milk but no significant contribution with regard to time.

CMA, Cow's milk allergy; *IQR*, interquartile range.

In 2011, a large population-based study of challenge-proved food allergy in 12-month-old infants in Australia reported prevalence rates of 3% for peanut allergy, 8.9% for egg allergy, and 0.8% for sesame allergy.[34]

In the United States from 2005 to 2006, 8203 participants in the National Health and Nutrition Examination Survey had serum sIgE levels measured to peanut, cow's milk, egg white, and shrimp. Liu et al[35] estimated clinical food allergy by using sIgE levels and age-based criteria. On the basis of only these 4 foods, the overall prevalence of food allergy was estimated at 2.5%. The prevalence rates of clinical food allergy varied by food type and age group and, overall, were 0.4% for milk, 0.2% for egg, 1.3% for peanut, and 1.0% for shrimp. In children aged 1 to 5 years, clinical allergies to milk, egg, and peanut were estimated at 1.8% each.

A self-report questionnaire was used to evaluate the rates of peanut and tree nut allergies in natives of Singapore and the Philippines and expatriates in both countries among children 4 to 6 and 14 to 16 years old.[36] Rates of peanut and tree nut allergy among local inhabitants were near 0.5% for peanut and 0.3% for tree nut. However, rates among expatriates in Singapore were near 1.2% for each food, which were similar to rates reported in the United States and Canada.

A 2011-published analysis explored the variation in IgE antibodies to individual peanut proteins between subjects in Spain, Sweden, and the United States.[37] IgE antibodies to peanut extract and the peanut allergens rAra h 1, 2, 3, 8, and 9, as well as to cross-reactive birch (rBet v 1) and grass (rPhl p 1, 5, 7, and 12) pollen allergens, had varying levels of frequency. Whether and how these differences affect the prevalence or timing of onset of food allergy is not clear. However, the results do illustrate that allergy to a specific food can have different clinical and immunologic patterns in different areas of the world.

Changes in prevalence over time

The prevalence of food allergy appears to have increased in the past several decades. Self-reported survey data in the United States suggests there was an 18% increase in food or digestive allergies from 1997 to 2007.[38] A clinic in China reported an increased rate of food allergy, as confirmed by food challenge, from 3.5% in 1999 to 7.7% in 2009 ($P = .017$).[39]

A random-calling telephone survey across the United States in 1997, 2002, and 2008 suggested the rates of allergy in children increased significantly for tree nuts (0.2%, 0.5%, and 1.1%) and peanut (0.4%, 0.8%, and 1.4%).[40] Other studies of peanut allergy suggest modest increases in children, with perhaps a leveling off in the last decade.[41-43]

Prevalence rates of admissions for food-induced anaphylaxis in Australia increased 350% between 1994 and 2005. Rates of increase were greater for children less than 4 years of age and for peanut and tree nut anaphylaxis, with more modest increases noted for older age groups and other allergies, such as cow's milk or egg allergy.[13] Similar data have been reported in the United Kingdom.[44]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Because data from multiple studies suggest more than half of presumed food allergies are not allergies,[2] careful diagnosis is important to prevent unnecessary food avoidance.

Food allergy symptoms usually develop consistently after ingestion of a trigger food. However, smaller subthreshold quantities of a food allergen or extensively baked, heat-denatured, or fermented foods (eg, milk, egg, and soybean) are often ingested without inducing symptoms, and this must be taken into account when obtaining a history. In young children food allergy might present as food refusal because of symptoms the child cannot articulate, such as oropharyngeal tingling and burning, a metallic taste, difficulty swallowing, abdominal pain, or nausea.

Both a detailed medical history and a physical examination are needed to diagnose IgE-mediated, non–IgE-mediated, or mixed IgE- and non–IgE-mediated food allergy. The medical history should capture the possible causal food or foods, form or forms in which ingested (raw, semicooked, cooked, or baked), quantity ingested, time course of reactions, nature of reactions, and ancillary factors, such as exercise or ingestion of aspirin or alcohol.[45]

It is uncommon for children to have an IgE-mediated food allergy to a food eaten on multiple previous occasions, and the ability to tolerate a food in standard servings is the best historical evidence to exclude food allergy. IgE-mediated reactions to foods are usually stereotypical, and therefore atypical reactions (eg, a previously tolerated food causing a reaction or a delayed-onset reaction) suggest an alternative diagnosis. Several common allergenic foods (milk, egg, and wheat) commonly cause IgE-mediated and non–IgE-mediated or mixed IgE-mediated and non–IgE-mediated reactions, but others (peanut, sesame, and shellfish) nearly always cause only IgE-mediated reactions.

The symptoms of IgE-mediated, non–IgE-mediated, and mixed IgE- and non–IgE-mediated food allergy are presented in Tables I and II. IgE-mediated reactions typically present with symptoms affecting the skin (urticaria, angioedema, erythema, and pruritus), gastrointestinal tract (vomiting and abdominal pain), airways (persistent cough, hoarse voice, wheeze, stridor, respiratory distress, and nasal congestion), and, less commonly, circulatory system (pale and floppy infant or young child, hypotension, or collapse). IgE-mediated symptoms develop within minutes to 1 to 2 hours of ingesting the food. In contrast, non–IgE-mediated and mixed IgE- and non–IgE-mediated food allergy syndromes present with predominantly abdominal symptoms (vomiting, diarrhea, pain, and bloody stools) that develop several hours after ingestion of the food. Subjects should be evaluated for possible food allergy if they present with any of the above symptoms that consistently develop after ingestion of a food.[2]

Although the medical history often provides evidence for the type of food-induced allergic reaction and the potential causative food or foods involved, neither medical history nor physical examination alone is diagnostic of food allergy.[2] For IgE-mediated food allergies, additional testing for the presence of sIgE is required to confirm a diagnosis. There are no validated laboratory tests that can assist with diagnosing non–IgE-mediated or mixed IgE- and non–IgE-mediated food allergies. Allergen-specific IgE levels can be increased in some cases of mixed IgE- and non–IgE-mediated food allergy; however, the absence of sIgE does not exclude the diagnosis. In patients with non–IgE-mediated food allergies, sIgE levels are not increased. Diagnosis of non–IgE-mediated and mixed IgE- and non–IgE-mediated food allergies relies on elimination and reintroduction challenge of the food in question, with observations of a reduction

in symptoms on elimination and recurrence of symptoms with reintroduction. In some cases of gastrointestinal food allergy, endoscopy with biopsy will be needed to determine the response to dietary changes. Elimination should be directed to 1 or a few suspected foods from the diet. Broad elimination diets are not recommended,[2] although in some instances of severe gastrointestinal allergy, especially with failure to thrive, a trial of an elemental diet might be needed. A physician and dietician should supervise the elimination and reintroduction challenge program to monitor for response and recurrence of symptoms, and in some cases (eg, food protein–induced enterocolitis syndrome) the physician should perform reintroduction under careful observation. If possible, a registered dietitian with experience in managing food allergy should be consulted to oversee the elimination diet. A 6-week trial of elimination will usually be sufficient to determine response and decide on the necessity for longer-term food restrictions.

Diagnosis of IgE-mediated food allergy

Demonstration of sIgE aids the diagnosis of IgE-mediated food allergy. Allergen-specific IgE can be detected by SPTs or immunoassays of serum sIgE levels. These tests identify foods that might provoke IgE-mediated reactions, but neither can be considered diagnostic of food allergy and must be combined with the history.[2,46] Serum sIgE levels can be measured by using immunoassays (ImmunoCAP, Immunlite), which provide reliable and reproducible measurements, although results can take hours to days. SPTs are quick and simple to perform. The SPT wheal size is correlated with the likelihood of clinical allergy,[47,48] and 95% positive predictive thresholds (wheal size above which there is a >95% chance of clinical allergy) have been described for the common allergens.[49-51] However, wheal sizes can vary as a result of age, diurnal variation, site on the body where the SPT is performed, skin reactivity, and the SPT device and reagents used; therefore 95% positive predictive values (PPVs) established in a specific clinical setting might not be applicable to different populations and settings. Studies are needed to continue to define the diagnostic accuracy of 95% PPV wheal sizes for different foods, ages, diseases, and populations. Ninety-five percent PPVs for peanut, cow's milk, and egg SPT vary with age (lower in children <2 years of age).[50]

Although PPVs are influenced by the underlying prevalence of disease in the population being tested, 95% specificity thresholds are not influenced by the prevalence of food allergy and can be considered more generally useful. Ninety-five percent specificity thresholds for serum sIgE levels have been described for the majority of major allergens (egg, milk, peanut, fish, soy, and wheat).[49] In addition to the use of 95% PPVs and 95% specificity thresholds, some studies suggest that combining the results from SPTs and serum sIgE tests might assist with the diagnosis of clinical allergy.[46] Although serum concentrations of sIgE levels and SPT wheal sizes generally correlate with the likelihood of a clinical reaction, they do not correlate with or predict the severity of allergic reaction to a food.[49,52-56]

The development of recombinant or purified allergen sIgE tests against the individual major allergenic components in a food (eg, Ara h 2 in peanut) might improve the diagnosis of clinical allergy. Detection of sIgE to individual allergens holds promise for distinguishing sensitization from clinical allergy to a food. Traditionally, most tests for sIgE have used extracts derived from the whole food. Such whole-food sIgE test results can be positive if a subject has generated IgE antibodies against a component of that food that does not cause an allergic reaction (often as a result of cross-reactive antibodies to irrelevant allergens within the food). Emerging test systems, such as basophil histamine release assays, are used in research studies to evaluate IgE-mediated food allergy but have not been validated for use in clinical practice.

The DBPCFC is the most specific test for diagnosing food allergy and reliably distinguishes sensitization from clinical allergy. Ideally, the challenge is performed as a double-blind procedure; however, because of the time- and labor-intensive nature of this approach, single-blind or open food challenges are often performed in the clinical setting and might be considered diagnostic under certain circumstances, such as in young children or when objective (rather than subjective) symptoms of reaction are evident. A food challenge is indicated if sIgE test results do not correspond to the history or if a screening test result for sIgE is positive but less than the 95% PPV or 95% specificity threshold and the patient has not introduced the food into the diet. Follow-up oral food challenges are also necessary to review food allergy status and assess for resolution of food allergies. If SPT or serum sIgE test results are positive, food challenges must be done in a medical facility with onsite medical supervision and appropriate medications and resources available for emergency management of allergic reactions because there is a risk of an immediate allergic reaction and anaphylaxis. If the SPT or serum sIgE test result is negative in a patient who has not yet started consuming a food, the food can usually be introduced safely at home. Patients who have recently had a life-threatening reaction to a known food should not undergo a challenge with that food. If a patient is believed to have postprandial exercise-induced reactions, food challenge should be followed by exercise.[57] A number of sources have outlined procedures involved for oral food challenges.[2,46,58-61]

Mixed IgE-and non–IgE-mediated or non–IgE-mediated food allergy

Diagnosing mixed IgE- and non–IgE-mediated or non–IgE-mediated food allergies is more challenging than diagnosing IgE-mediated food allergy. The approach begins with the clinical history. A clear cause and effect between food ingestion and symptoms might not be clear because the symptoms of these types of food allergy are typically chronic versus immediate. If the clinical history is not definitive, diagnosis can usually be made by using food elimination followed by reintroduction challenge. Food challenges can also be performed to assess when the disease has been outgrown.[3] Home introduction challenges can be undertaken if the sIgE test result is negative and food protein–induced enterocolitis syndrome is not suspected.

Tests, such as contact dermatitis patch tests and atopy patch tests, have not been validated, and their usefulness is uncertain. However, the approach to diagnosis can vary depending on the specific condition. For eosinophilic esophagitis, SPTs, sIgE tests, and atopy patch tests might be helpful in identifying foods associated with the condition, but these tests alone might not be sufficient to confirm a diagnosis, and endoscopy might be required. For food protein–induced enterocolitis syndrome, medical history and oral food challenge are usually required to make a diagnosis. However, when infants or children have experienced hypotensive episodes or multiple reactions to the same food, a

diagnosis of food protein–induced enterocolitis can be made on the basis of a convincing history and absence of symptoms after eliminating the trigger food. The diagnosis of allergic proctocolitis should be made on the basis of medical history, resolution of symptoms after eliminating the causative food, and/or recurrence of symptoms after oral food challenge.

Intradermal tests, total serum IgE measurements, and atopy patch tests were not recommended for use in diagnosing food allergy in the NIAID-sponsored guidelines and in the Diagnosis and Rationale for Action Against Cow's Milk Allergy guidelines sponsored by the World Allergy Organization.[2,46] There are a multitude of tests that are not based on scientific rationale and do not reliably or reproducibly detect the presence of food allergy when subjected to formal analysis. Examples include vega testing, cytotoxic testing, iridology, kinesiology, food-specific IgG testing, pulse testing, and hair analysis.

Testing in high-risk children

Children with a parent or sibling with allergic disease are at increased risk of allergic disease. Available evidence does not support routine testing in such children at increased risk of food allergies before introducing into their diet highly allergenic foods, such as milk, egg, or peanut.[2] Infant feeding guidelines from the Australasian Society of Clinical Immunology and Allergy (ASCIA Infant Feeding Advice, www.allergy.org.au) recommend introducing all weaning foods (including the common food allergens) around 4 to 6 months of age, irrespective of the presence of family history of allergic disease or coexisting eczema. Nevertheless, evaluation by using SPTs or sIgE tests might be considered on an individual basis if the common food allergens have not yet been introduced into the diet. Testing can also be considered in infants with eczema that started in the first months of life. If screening sIgE test results are positive and greater than the 95% PPV or 95% specificity thresholds, clinical allergy is likely; however, if sIgE test results are positive but less than the 95% specificity or PPV thresholds for diagnosing clinical allergy, a challenge would be indicated to clarify the presence of allergy.

CONDITIONS ASSOCIATED WITH THE DISEASE

On the basis of survey data in the United States, children with food allergy have a 4-fold increased likelihood of having asthma, a 2.4-fold increased likelihood of atopic dermatitis, and a 3.6-fold increased likelihood of respiratory allergies compared with children without food allergy.[38] Other studies have similarly reported an increased co-occurrence of atopic dermatitis, allergic rhinitis, or asthma in patients with food allergy to peanut, tree nuts, or milk.[21,62,63] Specific rates of co-occurrence should be interpreted with caution because studies evaluating co-occurrence can be subject to selection bias.

Despite the frequent association of food allergy with asthma and eczema, food is rarely a trigger for exacerbation of symptoms in asthmatic patients (<2% of patients with asthma) and an uncommon trigger in patients with eczema that commences after 1 year of age. Nevertheless, food allergy can be an important cofactor in severe eczema that develops in early infancy.[64] A nonrandomized comparative study in a small number of infants suggests that an elimination diet improves atopic dermatitis associated with food allergy,[65] but the results have not been verified in larger analyses. Elimination diets might also be of use in some cases of childhood eczema, especially in those who have evidence of food triggers or persistent disease in spite of aggressive topical therapy.[66]

Although foods are rarely important triggers of asthma exacerbation, coexisting asthma is a strong risk factor for more severe food-induced allergic reactions (anaphylaxis), as well as for a fatal outcome from food-induced anaphylaxis.[11,12,67] Asthma is also a risk factor for longer persistence of food allergy.[28] It is therefore important to assess for the presence of asthma in patients with food allergy and to ensure adequate control. Data suggest that ongoing airway inflammation (as measured by exhaled nitric oxide levels) can persist in children with peanut allergy, even after asthma is thought to have resolved.[68,69] Such persistent airway inflammation might be important in the evolution of respiratory symptoms after food allergen exposure, even in children with asthma in apparent remission. Other medical conditions that are thought to increase the risks of food-induced anaphylaxis include heart conditions and use of β-blockers and angiotensin-converting enzyme inhibitors, which reduce the effectiveness of epinephrine.

TREATMENT OPTIONS AND PREVENTION

The primary therapy for food allergy is strict avoidance of the causal food or foods. This is true for IgE-mediated, non–IgE-mediated, and mixed IgE- and non–IgE-mediated food allergy syndromes. Although allergen avoidance is unproved in randomized controlled trials, it is the safest strategy for managing food allergy. Patients should be educated on how to read ingredient labels to avoid their allergens. In the United States, European Union, Australia, Japan, and Singapore, food-labeling laws require food manufacturers to declare in plain language on the food packaging whether one of the common allergens (egg, milk, wheat, soy, fish, crustacean shellfish, peanut, and tree nuts) or a product derived from them is used as an ingredient. Similar laws are not in place in many other countries, and in these settings care is required to identify hidden forms of allergens, such as ovalbumin or ovomucoid as ingredients of egg or casein from milk.

No randomized clinical studies have addressed whether food allergen avoidance diminishes nutritional status. However, studies that evaluated growth measurements against diet records have suggested that food allergy puts children at risk for inadequate nutrition.[70-72] Especially in the case of pediatric food allergy, it is advisable to involve a dietician in formulating a nutritionally adequate, allergen-free diet.

As a general rule, only those foods to which the patient is allergic should be avoided. In the past it was commonly recommended that a patient allergic to peanut should also avoid all nuts, irrespective of whether they were allergic to the other nuts. This was partly based on the now considered incorrect assumption that avoidance could prevent the development of allergy. It is currently hypothesized that acquisition of tolerance to foods is an active immune-mediated process that requires exposure to a food, perhaps during a "window of opportunity" early in life, which is currently poorly defined.[73] Hence a child with peanut allergy who is not allergic to cashew or other tree nuts would not be required to avoid individual tree nuts, although care must be taken to avoid cross-contamination. Nevertheless, there are some circumstances in which it is easier for a family to simply avoid all nuts for practical reasons, such as when language or literacy barriers make it difficult to ensure avoidance

TABLE IV. Pharmacologic management of anaphylaxis

In an outpatient setting
- First-line treatment
  - Epinephrine, IM; autoinjector or 1:1000 solution
    - Weight, 10-25 kg: 0.15-mg epinephrine autoinjector, IM (anterior-lateral thigh)
    - Weight >25 kg: 0.3-mg epinephrine autoinjector, IM (anterior-lateral thigh)
    - Epinephrine (1:1000 solution [IM]), 0.01 mg/kg per dose; maximum dose, 0.5 mg per dose (anterior-lateral thigh)
  - Epinephrine doses might need to be repeated every 5-15 min
- Adjunctive treatment
  - Place the patient in recumbent position if tolerated, with the lower extremities elevated
  - Bronchodilator (β_2-agonist): albuterol
    - MDI (child: 4-8 puffs; adult: 8 puffs) or
    - Nebulized solution (child: 1.5 mL; adult: 3 mL) every 20 min or continuously as needed
  - H_1 antihistamine: less-sedating second-generation antihistamines recommended

In a hospital-based setting
- First-line treatment
  - Epinephrine IM as above; consider continuous epinephrine infusion for persistent hypotension (ideally with continuous noninvasive monitoring of blood pressure and heart rate); alternatives are endotracheal or intraosseous epinephrine
- Adjunctive treatment
  - Place the patient in recumbent position, if tolerated, with the lower extremities elevated
  - Bronchodilator (β_2-agonist): albuterol
    - MDI (child: 4-8 puffs; adult: 8 puffs) or
    - Nebulized solution (child: 1.5 mL; adult: 3 mL) every 20 min or continuously as needed
  - H_1 antihistamine: less-sedating second-generation antihistamines are suggested
  - Corticosteroids
    - Prednisone at 1 mg/kg with a maximum dose of 60-80 mg orally or
    - Methylprednisolone at 1 mg/kg with a maximum dose of 60 to 80 mg IV
  - Supplemental oxygen therapy
  - IV fluids in large volumes if patients present with orthostasis, hypotension, or incomplete response to IM epinephrine
  - Vasopressors (other than epinephrine) for refractory hypotension, titrate to effect
  - Glucagon for refractory hypotension, titrate to effect
    - Child: 20-30 μg/kg
    - Adult: 1-5 mg
    - Dose can be repeated or followed by infusion of 5-15 μg/min
  - Atropine for bradycardia, titrate to effect

To instruct to patients at discharge
- First-line treatment
  - Epinephrine autoinjector prescription (2 doses) and instructions
  - Education on avoidance of allergen and emergency action plan
  - Follow-up with primary care physician
  - Consider referral to an allergist if first presentation or of unknown cause
- Adjunctive treatment
  - H_1 antihistamine: diphenhydramine every 6 h for 2-3 d; alternate dosing with a nonsedating second-generation antihistamine
  - H_2 antihistamine: ranitidine twice daily for 2-3 d
  - Corticosteroid: prednisone daily for 2-3 d

With the exception of epinephrine as first-line treatment, these treatments often occur concomitantly and are not meant to be sequential. Modified from Boyce et al.[2]
IM, Intramuscular; *IV*, intravenous; *MDI*, metered-dose inhaler.

of the specific food or when there are young toddlers in the home, and it is difficult to ensure the problem food is kept safely away from the allergic child. For some allergies, certain cross-reactive foods should also be avoided.

Avoidance of food allergens is difficult to maintain. It has been reported that half of children with IgE-mediated food allergy experience accidental ingestion of their allergen within 5 years, and 75% experience accidental ingestion within 10 years.[74] More recent data suggest that half of children with peanut allergy have accidental ingestion within 2 years.[8] Therefore a crucial aspect of managing IgE-mediated food allergy involves education of patients and families on the early recognition and emergency treatment of allergic reactions. Patients should be provided an emergency action plan that outlines the signs and symptoms of mild-to-moderate and severe reactions and treatment actions, including how to administer an epinephrine autoinjector if one is prescribed. Having an emergency action plan might promote empowerment and improve health outcomes.[75]

Education on situations of increased risk for accidental ingestion, such as eating out at restaurants or a friend's home and children's birthday parties, is also important. It has been reported that 40% to 100% of deaths from food-induced anaphylaxis involve ingestion of foods catered or prepared away from the home.[11,13,67] Information on how to minimize the risks of cross-contact of foods with an allergen during meal preparation and serving can help to prevent accidental ingestion and reactions.

The decision to prescribe an epinephrine autoinjector will depend on the presence of risk factors for anaphylaxis or death from anaphylaxis, such as having poorly controlled asthma, being an adolescent or young adult, having allergy to peanut or tree nuts

or history of anaphylaxis to another allergenic food, and being more than 20 minutes from a hospital or other appropriate medical facility.[76] In United States–based guidelines it has been recommended that patients with food allergy with the following be prescribed an epinephrine autoinjector: a history of a prior systemic allergic reaction; food allergy and asthma; or known food allergy to peanut, tree nuts, fish, or crustacean shellfish.[2] The same guidelines suggest consideration should be given to prescribing an epinephrine autoinjector to all patients with food allergy who have IgE-mediated reactions. Guidelines in the United Kingdom and Australia indicate that an epinephrine autoinjector is usually not recommended for patients with positive sIgE or SPT results who have not had a clinical allergic reaction.[76] If prescribed an epinephrine autoinjector, patients must be educated on how to use the device because their use is not intuitive[77] and must be provided with an emergency action plan that outlines when and how to use the device. If an epinephrine autoinjector is not prescribed, it is important to review the criteria that would prompt the need for an epinephrine autoinjector on a regular basis, ideally annually.

Prescribing an epinephrine autoinjector does not remove the risk of anaphylaxis or death from anaphylaxis. It has been reported that early and repeated administration of epinephrine does not prevent death in 12% to 14% of anaphylaxis-related fatalities.[11,67]

The long-term ongoing management of food allergy must include an at least annual physician's review to assess for accidental ingestion, reactions, or both; nutritional adequacy of the diet; and approaches for allergen avoidance, including reading ingredient labels and being familiar with situations of increased risk for accidental ingestion. The physician must also assess for asthma and ensure adequate control of any coexisting asthma, reeducate on the early recognition and emergency treatment of acute allergic reactions, update the emergency action plan, and reassess the need for an epinephrine autoinjector. The education and assessment provided as part of the annual review are particularly important as children prepare for secondary school because adolescence is a time of increased risk for death from anaphylaxis.

Because the course of food allergy can change over time and new food allergies can develop, long-term management of patients also involves monitoring for evidence of tolerance or for development of new food allergies. Monitoring involves collecting interim histories regarding reactions to foods and, if indicated, performing SPTs or blood tests for sIgE. The optimal interval for follow-up testing is not known. Allergy to some foods, such as milk and egg, can be outgrown relatively quickly, whereas allergy to other foods, such as peanut and tree nuts, is usually not outgrown. Testing every 12 to 18 months is often the practice in the first 5 years of life for monitoring whether allergy to milk, egg, soy, or wheat has resolved, with this interval extended to every 2 to 3 years thereafter. A similar course can be followed for monitoring of peanut allergy because some data suggest that although there is a low likelihood of outgrowing this food allergy, resolution of allergy most commonly occurs by 5 years of age.[78] For allergies to tree nuts, fish, and crustacean shellfish, testing can be performed less frequently (every 2-4 years).[2] If a patient has had a recent food-induced allergic reaction, then there is little reason to retest for several years.

Medications for preventing or treating food allergy

There are currently no recommended medications for preventing IgE-mediated, non–IgE-mediated, or mixed IgE- and non–IgE-mediated food-induced allergic reactions. Recommended treatment of acute IgE-mediated allergic reactions is outlined in Table IV.[2] Epinephrine is the mainstay for the treatment of acute, severe systemic allergic reactions (anaphylaxis). Antihistamines are used to manage symptoms of nonsevere allergic reactions.[2] Anti-inflammatory therapies can be beneficial for eosinophilic esophagitis or gastroenteritis.[79] When antihistamines alone are administered to treat acute allergic reactions, patients should be monitored for more significant symptoms. If symptoms become more severe, epinephrine should be administered immediately. For patients with a history of severe allergic reactions, epinephrine can be administered at the onset of mild symptoms.

As soon as a patient is recognized as having anaphylaxis, they should be placed in a recumbent position with lower extremities elevated (if tolerated); they should not stand up and move because this has been reported to result in sudden death in cases of severe anaphylaxis.[80] If a patient has ongoing or progressive symptoms, epinephrine dosing might need to be repeated after 5 to 15 minutes.

Patients who receive epinephrine for food-induced anaphylaxis should be transported by ambulance to an emergency facility for observation because biphasic reactions can occur in up to 20% of cases.[81] Systemic corticosteroids are often recommended to prevent biphasic or protracted anaphylactic reactions, but evidence supporting their use is lacking.[82] For most patients with anaphylaxis, a reasonable length of observation is 4 to 6 hours; for patients with severe or refractory symptoms, prolonged observation or hospital admission might be needed.[83,84]

The risk of anaphylaxis and the burden of allergen avoidance can create anxiety and diminish quality of life in patients with food allergy and their caregivers.[85,86] Education related to managing food allergy might improve patient and caregiver quality of life and successful allergen avoidance.

Diet during pregnancy or lactation

It is unclear whether restricting maternal diet during pregnancy or lactation affects the development or clinical course of food allergy. Several organizations have published guidelines aimed at dietary recommendations in the "high-risk infant," which is typically defined as the infant without evidence of clinical allergy but with a sibling or parent with atopic disease.[2,5,87,88] The American Academy of Pediatrics and the NIAID-sponsored guidelines, as well as the Australasian Society of Clinical Immunology and Allergy Guidelines, do not recommend restrictions on consuming potential food allergens during pregnancy or lactation.[2,88,89] These recommendations are similar to those suggested in the latest revised European statement.[90] The NIAID guidelines further recommend that all infants be exclusively breast-fed, without maternal diet restriction of allergens, until 4 to 6 months of age, unless breast-feeding is contraindicated for medical reasons. Introduction of solid foods should not be delayed beyond 4 to 6 months of age. Potentially allergenic foods can be introduced at this time.

Studies are ongoing to help further address the issues of dietary avoidance during pregnancy and lactation and the role of early versus delayed allergen exposure in the development of clinical disease. A study by Sicherer et al[91] showed an increased risk of peanut sensitization in a cohort of infants with milk and egg allergy born to mothers who had increased ingestion of peanut during pregnancy but not during breast-feeding. Other groups have shown associations between peanut sensitization and maternal peanut ingestion during pregnancy and breast-feeding,[92] whereas others

have seen no association with antenatal exposure.[93] Retrospective studies by Lack and colleagues suggest that for certain populations, early dietary introduction of allergenic foods (eg, peanut) might prevent the development of clinical allergy.[94-96] The HealthNuts study in Australian infants showed that early introduction of egg between 4 and 6 months of age was associated with a reduced risk for egg allergy compared with later introduction.[97]

In formula-fed infants, using soy formula rather than cow's milk formula does not appear to be an effective means of preventing the development of food allergy in at-risk infants, which were defined as those with a biological parent or sibling with allergic rhinitis, asthma, atopic dermatitis, or food allergy,[98] nor does there appear to be any harm in using soy formula in regard to the development of food allergy. There might be some benefit to using hydrolyzed infant formulas, as opposed to cow's milk formula, in at-risk infants who are not exclusively breastfed.[83,99-101] The established guidelines and current evidence base suggest that partially or extensively hydrolyzed formulas can be used as alternatives to cow's milk or soy in the high-risk infant. In infants and children with known milk allergy, only extensively hydrolyzed milk protein formulas or amino acid–based formulas should be used. The preventive effects of hydrolyzed infant formula vary between studies, and none has shown a reduction in allergy to foods other than cow's milk. The expense and limited availability of extensively hydrolyzed formulas might limit their practicality for many patients.

UNMET NEEDS

Diagnostic assays and evaluations

Oral food challenges are accurate and sensitive, but they put patients at risk for allergic reactions. They also require extensive resources to conduct and monitor. SPTs and measurement of sIgE antibodies are safer than food challenge but have poor specificity and do not always correlate with clinical reactivity. Standardization of food challenge procedures and interpretation should be promoted. New approaches to improve the diagnosis of clinical allergy without the need for a food challenge are needed.

Treatment

Strict avoidance of allergens is not curative and leaves patients at risk for accidental exposure. As such, several new therapeutic approaches are being tested in clinical trials,[102] but none is ready for clinical care. Systemic subcutaneous immunotherapy has been investigated in the past but resulted in significant adverse effects.[103] Alternative forms of therapy have been sought to provide systemic treatment with reduced risk and side effects. For a variety of food allergens, oral immunotherapy is effective in reducing clinical reactivity in some patients, but its ability to induce tolerance remains uncertain. In addition, the approach places patients at risk for severe reactions and is therefore not appropriate for widespread use. Diets containing extensively heated (baked) milk and egg might represent an alternative approach to food oral immunotherapy; however, further studies of this approach are necessary. Sublingual immunotherapy has shown early promising results to decrease sensitization with low side effect profiles during treatment. Treatments with modified antigens, epicutaneously administered allergen immunotherapy, or Chinese herbal therapy are being explored for future use. Additionally, treatment with anti-IgE mAbs or prebiotics/probiotics either alone or in combination with other forms of immunotherapy might increase the threshold doses needed to stimulate an allergic reaction and provide enhanced safety profiles for patients. Recently, a pilot study has been reported in which 11 children with cow's milk allergy underwent a successful and safe desensitization with oral immunotherapy in combination with anti-IgE therapy.[104] Further work to evaluate the long-term effectiveness and safety of these new therapies is ongoing and needed before they are used in the mainstream care of children or adults with food allergy.

Areas of additional research or study

Areas or issues in need of further research include rates of remission for specific food allergies; timing of follow-up testing for specific allergenic foods; the incidence, prevalence, and epidemiology of food allergy in areas around the globe; genetic and epigenetic factors that influence clinical food allergy in different populations and locales; factors that might cause higher morbidity and mortality from food allergy (aside from asthma); biomarkers of disease and response to therapy; efficacy and safety related to the use of emerging therapies for food allergy; and the most effective methods for educating patients, families, health care professionals, and others to protect patients at risk for anaphylaxis.

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