

# Food allergy: a practice parameter

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## PREFACE

Food allergy, as defined for the purposes of this document, is a condition caused by an IgE-mediated reaction to a food substance. Adverse reactions to foods may also occur due to non-IgE-mediated immunologic and nonimmunologic mechanisms. Representing an important subset of all adverse food reactions, food allergy is often misunderstood. However, because of im-

portant new scientific information, its evaluation and management have changed substantially in recent years.

The prevalence of potentially life-threatening food allergy to peanuts and tree nuts is increasing. This has resulted in an increased awareness among the general public, leading to policy changes in schools, eating establishments, and the airline industry. At the same time, diagnostic evaluation in patients suspected of having food allergy has become both

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The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing *Food Allergy: A Practice Parameter*. **This is a complete and comprehensive document at the current time. These clinical guidelines are designed to assist clinicians by providing a framework for the evaluation and treatment of patients and are not intended to replace a clinician's judgment or establish a protocol for all patients. The medical environment is a changing environment and not all recommendations will be appropriate for all patients.** Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters.

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Any request for information about or an interpretation of these practice parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion. This parameter was edited by Dr Nicklas in his private capacity and not in his capacity as a medical officer with the Food and Drug Administration. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

more sophisticated and more challenging. The objective of Food Allergy: A Practice Parameter is to improve the care of patients by providing the practicing physician with an evidence-based approach to the diagnosis and management of IgE-mediated (allergic) food reactions. The Task Force recognizes the importance of non-IgE-mediated immunologic and nonimmunologic food reactions and the role of the allergist-immunologist in their identification and management. These conditions are discussed in the context of differential diagnosis.

This guideline was developed by the Joint Task Force on Practice Parameters, which has published 20 practice parameters for the field of allergy-immunology (see list of publications in the “Acknowledgments” section). The 3 national allergy and immunology societies—the American College of Allergy, Asthma and Immunology (ACAAI), the American Academy of Allergy, Asthma, and Immunology (AAAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI)—have given the Joint Task Force the responsibility for both creating new parameters and updating existing parameters. Although several previous parameters have addressed the diagnosis and management of anaphylaxis, this document is the first parameter that focuses on such reactions with respect to foods. It was written and reviewed by specialists in the field of allergy and immunology and was supported by the 3 allergy and immunology organizations noted above.

The working draft of this Food Allergy Practice Parameter was prepared by the Joint Task Force on Practice Parameters with the help of Scott Sicherer, MD. Preparation of this draft included a review of the medical literature using a variety of search engines such as PubMed. Published clinical studies were rated by category of evidence and used to establish the strength of a clinical recommendation (Table 1). The working draft of the Parameter was then reviewed by a number of experts on food allergy selected by the supporting organizations. This document represents an evidence-based, broadly accepted consensus opinion.

The Food Allergy Practice Parameter contains an annotated algorithm that presents the major decision points for the appropriate evaluation and management of patients suspected of having food allergy. This is followed by summary statements, which represent the key points in the evaluation and management of food allergies. These summary statements can also be found before each section in this document, followed by text that supports the summary statement(s), which are, in turn, followed by graded references that support the statements in the text.

The sections on diagnosis and management represent the core of this practice parameter. The diagnosis section discusses guidelines for establishing the diagnosis of food allergy and emphasizes the importance of obtaining a detailed history that is compatible with this diagnosis. There is also a detailed discussion of the appropriate use of skin prick or puncture tests, serologic tests for specific IgE, and oral food challenges. The section on management discusses strategies

Table 1. Classification of Evidence and Recommendations\*

Category of evidence	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least 1 randomized controlled trial
IIa	Evidence from at least 1 controlled study without randomization
IIb	Evidence from at least 1 other type of quasi-experimental study
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-controlled studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
LB	Evidence from laboratory-based studies†
Strength of recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II or III evidence
E	Directly based on category LB evidence†
F	Based on consensus of the Joint Task Force on Practice Parameters†

\* Adapted from Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ*. 1999;318:593–596.

† Added by current authors.

for avoidance and guidelines for anticipating and implementing the medical treatment of food allergy reactions.

In addition to the sections on diagnosis and management, this parameter includes sections on immunology of food allergy, differential diagnosis, prevalence and epidemiology, natural history, risk factors, food allergens (including cross-reactivity), food additives, food-dependent exercise-induced anaphylaxis (EIA), genetically modified foods, and management in specific circumstances (eg, schools).

There are a number of objectives of this parameter on Food Allergy, including (1) development of an improved understanding of food allergy among health care professionals, medical students, interns, residents, and fellows, as well as managed care executives and administrators; (2) establishment of guidelines and support for the practicing physician; and (3) improvement in the quality of care for patients with food allergy.

## GLOSSARY

1. An *allergic epitope* denotes a specific peptide domain within a protein associated with allergenic potential.

2. *Autotolerance* refers to the state of balance of the innate and adaptive immune systems in the gastrointestinal tract, whereby systemic immune responses to ingestants and commensal bacteria are prevented.

3. *Class 1 Chitinases* are plant defense proteins. The allergenic activity of plant Class 1 chitinases seems to be lost by heating.

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4. A *conformational epitope* consists of allergenic domains located at various noncontiguous amino acid regions of folded proteins.

5. *In vitro assays to detect serum food specific IgE antibody.* Modern in vitro detection systems generally do not use radioimmunoassay procedures (radioallergosorbent test [RAST]) but detect serum IgE by exposing serum to allergen bound to a solid matrix and using a secondary labeled (eg, fluorescent or enzyme-tagged) anti-IgE antibody to detect the bound IgE antibody. There are a variety of manufacturers, substrates, and manners of reporting results, including the Pharmacia Unicap System, Diagnostic Products Corp, AlaSTAT, and Hycor Hy-Tech. These assays use a total serum IgE heterologous reference curve based on a World Health Organization IgE standard and quantitative results are reported in kIU/L.

6. *Likelihood ratio* is the likelihood that a given test result would be expected in a patient with the disorder compared with the likelihood that the same result would be expected in a patient without the disorder.

7. *Lipid transfer protein (LTP)* is a family of 9-kDa polypeptides, widely found in the vegetable kingdom and implicated in cuticle formation and defense against pathogens. They are thermostable and resistant to pepsin digestion, which makes them potent food allergens.

8. *Mucosal adaptive immunity* refers to the unique and bidirectional abilities to confer protection against enteric pathogens while providing tolerance to ingested foods and commensal bacteria.

9. *Oral food challenge.* A procedure during which potentially allergenic foods are gradually introduced through ingestion, generally under physician supervision, often in a “blinded” and possibly placebo-controlled design to prevent bias in interpretation, to observe for potential clinical reactions.

10. *Panallergen* is a term that describes a homologous protein with conserved IgE-binding epitopes across species that cross-react with foods, plants, and pollen.

11. *Percutaneous skin test (PST)*, such as prick or puncture tests, is a modality to identify food-specific IgE antibody by observing a wheal-flare response after percutaneous introduction of the allergen (commercial, or in some cases fresh, extract) into the skin by prick or puncture using a device such as a lancet or other sharp instrument.

12. *Phenylcoumarin benzylic ether reductase and isoflavonoid reductase* are enzymes in the biosynthesis of plant lignans and isoflavonoids important in human health protection (eg, for both the treatment and prevention of onset of various cancers) and in plant biology (eg, in defense functions and in tree heartwood development).

13. *Predictive value* is the proportion of persons with a positive test result who have the disorder (positive predictive value) or the proportion of those with a negative test result without the disorder (negative predictive value).

14. *Profilins* are ubiquitous intracellular proteins highly cross-reactive among plant species and are one of several

identified proteins responsible for cross-sensitivity among plant pollen and food. Profilins are highly conserved proteins in all eukaryotic organisms and are present in pollen and a wide variety of vegetable foods.

15. *Sensitivity and Specificity.* *Sensitivity* refers to the proportion of patients with a disorder who test positive, and *specificity* is the proportion of individuals without a disorder who have a negative test result.

16. *Toll-like receptors* are human innate immune receptors. The designation of “toll” was adapted from homologous innate immunity receptors originally discovered in *Drosophila* species. Currently, there are 10 human toll-like receptors.

17. *Transgenic foods* are foods that are genetically manipulated to contain insertions of foreign genetic DNAs selected for their ability to improve crop productivity or add nutritional value to the native food.

18. *Tropomyosin* is a muscle protein that inhibits contraction of a muscle by blocking the interaction of actin and myosin.

## EXECUTIVE SUMMARY

Adverse reactions to foods have been reported in up to 25% of the population at some point in their lives, with the highest prevalence observed during infancy and early childhood. Such reactions are generally divided on a basis of the underlying pathophysiologic changes that produced the reaction, eg, food allergy, food intolerance, pharmacologic reactions, food poisoning, and toxic reactions (see the “Differential Diagnosis of Adverse Reactions to Foods” section). Although adverse reactions to foods are common, food allergy, defined for the purposes of this document as an IgE-mediated response to a food, represents only a small percentage of all adverse reactions to foods. Individuals with atopy appear more likely to develop food allergies compared with the general population. Infants with moderate to severe atopic dermatitis appear to have the highest occurrence (see section “Prevalence and Epidemiology” section). In addition, children who develop an IgE-mediated reaction to one food are at greater risk of developing IgE-mediated reactions to other foods and/or inhalants.

Many studies indicate that the true prevalence of food allergy is much lower than the number of suspected food allergies. Therefore, health care professionals should not perpetuate false assumptions about food allergy. If a patient is incorrectly diagnosed as having a reaction to a food, unnecessary dietary restrictions may adversely affect quality of life, nutritional status, and, in children, growth. Severely restricted diets may lead to the development of eating disorders, especially if they are used for prolonged periods, or may make the patient susceptible to false claims of scientifically unproven and often costly techniques that offer no actual benefit. In addition, unintentional exposure to foods falsely thought to cause adverse reactions can provoke unnecessary panic and use of medications that have potentially potent adverse effects.

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IgE-mediated reactions to food allergens may occur as a consequence of (1) sensitization through the gastrointestinal tract; (2) sensitization through the respiratory tract to airborne proteins that are either identical (eg, occupational exposure) or homologous to those in particular foods (see “Classification of Major Food Allergens and Clinical Implications” section); or (3) sensitization through epidermis having impaired barrier function. Characteristics of the proteins themselves and the particular type and degree of immune response that they elicit determine the clinical manifestations of the condition that results from patient exposure. Mucosal adaptive immunity in the gastrointestinal tract is influenced by the nature and the dose of antigen, the immaturity of the host, genetic susceptibility, the rate of absorption of a dietary protein, and the conditions of antigen processing (see “Mucosal Immune Responses Induced by Foods” section). Molecular and immunologic techniques can provide data on which allergens or epitopes of an allergen in a particular food may be responsible for specific clinical outcomes (see “Cross-reactivity of Food Allergens” section). IgE antibodies may be directed to a variety of potential allergenic proteins in foods (eg, casein and whey proteins in cow’s milk, egg white proteins in hen’s eggs, parvalbumin in finned fish, and tropomyosin in shellfish).

Immune responses to a particular allergen can vary, depending on the method of exposure and the condition of the food. For example, there are a variety of immune responses to wheat that include (1) acute IgE-mediated reactions, (2) local inhalational reactions (baker’s asthma), (3) systemic reactions that occur when wheat is ingested following exercise, and (4) cell-mediated reactions in atopic dermatitis and celiac disease. Patients who are allergic to egg proteins may be able to tolerate these allergens when eggs are processed as an ingredient in prepared foods. Cooking a food may increase or decrease the patient’s ability to tolerate a food.

Recent studies with molecular biological techniques have characterized a variety of cross-reacting allergens among foods, including tropomyosins, bovine IgG, lipid transfer protein, profilin, and chitinases. Although IgE cross-reactivity to multiple foods is common, clinical correlation is often limited (see “Cross-reactivity of Food Allergens” section).

Although sensitivity to most food allergens, such as milk, wheat, and egg, tend to remit in late childhood, persistence of other food allergies, eg, peanut, tree nut (walnut, cashew, Brazil nut, pistachio), and seafood, are most likely to continue throughout the patient’s life (see “Natural History of Food Allergy” section). The natural history of specific foods varies substantially. For example, children who have become sensitized to cow’s milk, hen’s egg, wheat, and soybean through the gastrointestinal tract will usually lose this sensitivity as they get older. Peanut allergy, on the other hand, is usually not lost as the patient gets older, with only approximately 20% of children with peanut allergy losing this sensitivity. Peanut allergy affects approximately 0.6% of the general population and is the most common cause of fatal

food-induced anaphylaxis, with those at greatest risk being adolescents with asthma.

On the other hand, allergy to fruits and vegetables, which are the most common food allergies reported by adults, may develop later in life as a consequence of shared homologous proteins with airborne allergens (eg, pollens). Why food allergy persists in some patients and not in others is unclear, although recent studies suggest that this is more likely to occur with foods that contain linear allergenic epitopes.

Risk factors associated with the development of food allergy include a personal or family history of atopy or food allergy in particular, possible maternal consumption of major food allergens during either pregnancy or breastfeeding, atopic dermatitis, and transdermal food exposure. An infant at increased risk is a candidate for intervention, which may include breastfeeding and avoidance of highly sensitizing and/or solid foods at a young age, to reduce this risk.

Reactions that occur in individuals after the ingestion, inhalation, or contact with foods or food additives can vary from mild, gradually developing symptoms limited to the gastrointestinal tract to severe, rapidly progressing, life-threatening anaphylactic reactions that may be triggered by even small amounts of food allergen. Immunologic reactions to foods or food additives are characterized by a strong temporal relationship between the onset of the reaction and exposure to a specific food or food additive and may include cutaneous manifestations, gastrointestinal symptoms, respiratory symptoms, hypotension, and laryngeal edema, occurring separately or together.

Anaphylaxis after exposure to foods can include a combination of symptoms that reflect reactions in the respiratory, dermatologic, cardiovascular, and other organ systems. In children, anaphylaxis occurs most frequently after ingestion of peanuts, other legumes, tree nuts, fish, shellfish, milk, and eggs. Most IgE-mediated reactions to foods in adults are caused by peanuts, tree nuts, fish, and shellfish. In highly sensitive patients, inhalation of food allergens may produce anaphylaxis. Anaphylaxis may also occur when foods are ingested before or after exercise (see “Food-Dependent Exercise-Induced Anaphylaxis” section).

Immunologic reactions to foods encompass more than just IgE-mediated reactions. Nevertheless, this monograph will focus primarily on IgE-mediated reactions that have been defined for the purposes of this document as food allergy. An IgE-mediated reaction to foods may be difficult to distinguish from other types of reactions to foods, such as food intolerance, especially if symptoms are primarily or exclusively gastrointestinal (see “Differential Diagnosis of Adverse Reactions to Foods” section). IgE-mediated reactions can also occur in the upper and lower respiratory tract, usually as part of an anaphylactic reaction that may involve the skin and/or gastrointestinal tract. In IgE-mediated reactions (1) the time from ingestion of the food to symptom onset is usually rapid (eg, within minutes), (2) small amounts of food may elicit severe reactions, and (3) reactions will usually continue to occur with reexposure. IgE-associated food reactions such as

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those triggering atopic dermatitis are more difficult to discern by history alone and may occur hours after food ingestion.

It is important to recognize that there are a number of other immunologic and nonimmunologic reactions that can produce symptoms after exposure to foods or food additives (see "Differential Diagnosis of Adverse Reactions to Foods" section). These reactions include conditions that are considered to be examples of food intolerance and conditions that are considered to be neither food allergy nor food intolerance, such as scombroid poisoning. Specific clinical and laboratory tests are available for many of these conditions.

The evaluation of food allergy begins with a detailed history, including a list of suspect foods, the quantity of food eliciting a reaction, the reproducibility of the reaction in relationship to food ingestion, the time between exposure and reaction, the clinical manifestations produced, whether there has been resolution of symptoms with elimination of the suspect food, and the overall duration of symptoms and after each exposure. This can be augmented by a written recording of dietary intake.

A clinically relevant physical examination, with particular focus on suspected targeted organ systems (eg, cutaneous, respiratory, and gastrointestinal) should be performed. The presence of atopic disorders such as asthma, atopic dermatitis, and allergic rhinitis implies an increased risk of food allergy. The physical examination may also reveal alternative diagnoses that make food allergy less likely.

Initial evaluation may be enhanced by certain testing procedures (see "Diagnosis of Food Allergy" section). Skin prick or puncture tests are often useful in screening patients with suspected food allergy. Commercial food extracts from foods with stable proteins (eg, peanut, milk, egg, tree nuts, fish, shellfish) are reliable to detect specific IgE antibodies in most patients, whereas extracts from foods that contain labile proteins (eg, many fruits and vegetables) are less reliable. Under these conditions, pricking the food and then the patient may be useful. It is important to recognize that skin or in vitro test results may remain positive even though the patient's skin is no longer clinically sensitive. Intracutaneous (intradermal) skin tests are not recommended because they are potentially dangerous. In addition, they are overly sensitive and are associated with an unacceptable rate of false-positive reactions. A positive skin test result may indicate food allergy (positive predictive value  $\leq 50\%$ ), but a negative skin test result virtually rules out an IgE-mediated mechanism (negative predictive value  $\geq 95\%$ ). If done, skin testing should be performed selectively for suspected foods, because allergy to multiple foods is not common. From an epidemiologic standpoint, generally larger wheal-flare reactions on prick or puncture tests and higher concentrations of food-specific IgE measured by in vitro tests correlate with a greater likelihood of a reaction.

In vitro tests may also provide useful information to evaluate possible IgE-mediated reactions. Situations in which these tests may be particularly valuable include but are not limited to (1) patients with a history of a life-threatening

reaction to the suspected food; (2) patients who have medical conditions (eg, extensive atopic dermatitis or dermatographism that could interfere with interpretation of skin test results); (3) patients with a nonreactive histamine control (eg, due to medications that suppress skin test response); or (4) women known to be pregnant (see Practice Parameters for Allergy Diagnostic Testing). If the patient has a history of an anaphylactic reaction and test results for specific IgE antibodies are positive, no further evaluation is usually required. A number of other diagnostic tests (eg, atopy patch tests) are currently under investigation for IgE-mediated reactions to foods. Provocation-neutralization is considered disproved as a diagnostic method in allergy, whereas hair analysis, food specific IgG or immune complex assays, and newer versions of the previously disproved cytotoxic tests are considered unproven or experimental.

The rational selection, application, and interpretation of tests for food-specific IgE antibodies requires the following: (1) consideration of the epidemiology and underlying immunopathophysiology of the disorder under investigation; (2) the importance of making a definitive diagnosis; (3) estimation of prior probability that a disorder or reaction is attributable to a particular food; and (4) an understanding of the utility of the diagnostic tests being used.

Challenge with a suspected food may help to determine if the test results were either falsely negative or falsely positive. Initial challenge can be performed in an open or single-blinded fashion. When such challenges are performed, the physician must recognize the potential for bias that is introduced if both the patient and the physician are not blinded. Double-blind, placebo-controlled food challenge is most likely to provide the physician with a valid evaluation of the patient's capacity to react to a given food and has the highest positive predictive value. In most patients, a diagnosis of an IgE-mediated reaction to a particular food or food additive can be best made by obtaining a detailed history in conjunction with a positive test result for specific IgE antibodies to the food and a positive challenge result with the food, especially if the challenge is performed in a double-blind, placebo-controlled manner. Patients who have a history of reactions to foods that could be IgE-mediated benefit from consultation with an allergist-immunologist.

The management of food allergy relies primarily on avoidance of exposure to suspected or proven foods (see "General Management of Food Allergy" section). This can best be done if the specific foods responsible for the patient's symptoms are identified by history and appropriate tests. If this is not possible, patients with chronic symptoms may benefit from an elimination diet, remembering that patients have an increased risk of unintentional food allergen exposure in a number of special circumstances, such as schools and restaurants (see "Management in Special Settings and Circumstances" section). Because of the potential for inadvertent exposure to foods, education of the patient and/or the patient's advocate is essential. This includes reading labels and recognition that unfamiliar terms may indicate the presence

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of a clinically relevant food. Vague or inaccurate labeling and cross-contamination of packaged foods or foods eaten in restaurants are potential hazards. Avoidance of the implicated food may encourage future tolerance, especially with cow's milk, egg, and soy. Patient outcomes may be improved when avoidance measures are maintained over time. This has been shown to be associated with loss of symptomatic reactivity in both children and adults to specific food allergens.

Currently, there is no known oral or parenteral agent that has been shown consistently to prevent IgE-mediated reactions to foods. Reliance on such treatment can lead to tragic consequences. Immunotherapy to food proteins is currently experimental.

Injectable epinephrine is the treatment of choice for an anaphylactic reaction, regardless of the cause (see Anaphylaxis and Stinging Insect Hypersensitivity Practice Parameters). For this reason, patients who have experienced IgE-mediated reactions to a food or their caregivers should be educated and provided with injectable epinephrine to carry with them. Because anaphylactic reactions may be prolonged or biphasic, it is reasonable to instruct the patient to carry more than one epinephrine injector, to seek immediate medical care after a reaction, and to be monitored for an appropriate period (see "General Management of Food Allergy" section).

## SUMMARY STATEMENTS

### *Mucosal Immune Responses Induced By Foods*

*Summary Statement 1.* Mucosal adaptive immunity has dual functions of protection against enteric pathogens and maintenance of autotolerance against dietary proteins and commensal bacteria. (E)

*Summary Statement 2.* Factors that regulate gastrointestinal immune balance include the nature and dose of the antigen, immaturity of the host, genetic susceptibility, the rate of absorption of a dietary protein, and the conditions of antigen processing. (E)

*Summary Statement 3.* Food allergens are generally glycoproteins with molecular weights ranging from 10 kDa to 70 kDa. (E)

*Summary Statement 4.* The more common food allergens in infants and young children are cow's milk, hen's egg, peanut, tree nuts, soybeans, and wheat, whereas the adult counterparts are peanuts, tree nuts, fish, crustaceans, mollusks, fruits, and vegetables. (B)

*Summary Statement 5.* Major allergenic epitopes have been identified and genes for some of the major allergens have been cloned and sequenced. (E)

*Summary Statement 6.* Innate allergenicity of foods may be determined by a combination of factors such as solubility, resistance to pH, heat, and proteolysis by digestive enzymes. (E)

*Summary Statement 7.* Structural amino acid sequences, either sequential or conformational, account for cross-reactivity between foods. Sequential epitopes may be particularly

important for persistence of allergenicity beyond childhood (eg, casein hypersensitivity). (B)

*Summary Statement 8.* The specific factor(s) that confer allergenicity rather than tolerogenicity are unknown. (E)

*Summary Statement 9.* Characteristic IgE- and mast cell-mediated mechanisms occur in food-induced anaphylaxis, the oral allergy syndrome, and atopic dermatitis. (B)

*Summary Statement 10.* IgE-mediated reactions to foods may occur in neonates on first postnasal exposure, presumably due to in utero sensitization. Since sensitization to dietary allergens in breast milk may occur in the late postnatal period, breastfeeding mothers should avoid highly allergenic foods if familial allergic susceptibility is present. (B)

*Summary Statement 11.* Both serum and secretory specific IgA to dietary proteins may be produced in healthy subjects and allergic patients. (B)

*Summary Statement 12.* The significance of IgM, IgG, and IgG subclass antibodies (eg, the role of IgG4) in food allergy is less well understood and highly controversial. (B)

*Summary Statement 13.* The role of cellular in vitro correlates as diagnostic or prognostic indicators of food allergy is not established. (B)

*Summary Statement 14.* The role of specific cytokine profiles in serum or peripheral mononuclear cells of food allergic patients has not been established in the mechanism of food allergy. (B)

*Summary Statement 15.* Certain bacterial products, viruses, parasites, and T-cell-independent antigens stimulate systemic immune responses rather than tolerance to the oral protein when coadministered with oral proteins. (B)

*Summary Statement 16.* Sensitization to foods is much more likely to occur in the early neonatal period. (B)

*Summary Statement 17.* Intestinal malabsorption and/or stasis may predispose patients to food allergy. (B)

*Summary Statement 18.* Genetic susceptibility, as defined by single nucleotide polymorphisms or specific haplotypes, has been implicated in several common food allergy phenotypes. (B)

### *The Clinical Spectrum of Food Allergy*

*Summary Statement 19.* Allergic food reactions to foods (IgE-mediated reactions) are characterized by a temporal relationship between the reaction and prior exposure to food. Such reactions can be generalized or localized to a specific organ system and can be sudden, unexpected, severe, and life-threatening. (D)

*Summary Statement 20.* Food allergens are a frequent cause of severe anaphylaxis, particularly in patients with concomitant asthma and allergy to peanut, nut, or seafood. Such reactions may be biphasic or protracted. Food allergy should be considered in the differential diagnosis of patients who have idiopathic anaphylaxis. (C)

*Summary Statement 21.* The pollen-food allergy syndrome (oral allergy syndrome) is characterized by the acute onset of oropharyngeal pruritus, sometimes including lip angioedema, usually beginning within a few minutes after oral mucosal

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contact with particular raw fruits and vegetables during eating. (B)

*Summary Statement 22.* IgE-mediated gastrointestinal reactions can present with only gastrointestinal symptoms or with other nongastrointestinal manifestations. (D)

*Summary Statement 23.* Allergic eosinophilic gastroenteritis (eosinophilic gastroenteropathy) is characterized by postprandial gastrointestinal symptoms associated with weight loss in adults and failure to thrive in infants. (C)

*Summary Statement 24.* Upper and lower respiratory tract manifestations of IgE-mediated reactions to foods, such as rhinoconjunctivitis, laryngeal edema, and asthma, can occur with or without other IgE-mediated symptoms. Isolated respiratory manifestations from exposure to foods is rare and has been reported most frequently in an occupational setting. (C)

*Summary Statement 25.* Many inhaled food proteins in occupational settings may affect workers regularly exposed to such foods as flour (bakers' asthma), egg white, and crustaceans. (A)

*Summary Statement 26.* IgE-mediated cutaneous reactions, such as acute urticaria or angioedema and acute contact urticaria, are among the most common manifestations of food allergy. Food allergy is commonly suspected though rarely incriminated in chronic urticaria and angioedema but is implicated in at least one third of children with atopic dermatitis. (B)

#### *Prevalence and Epidemiology*

*Summary Statement 27.* The prevalence of food allergy as reported in double-blind studies is not as great as that perceived by the public. It varies between 2% and 5% in most studies, with definite ethnic differences. (B)

*Summary Statement 28.* The prevalence of food allergy is higher in certain subgroups such as individuals with atopic dermatitis, certain pollen sensitivities, or latex sensitivity. (B)

#### *Natural History of Food Allergy*

*Summary Statement 29.* Although sensitivity to most food allergens such as milk, wheat, and eggs tends to remit in late childhood, persistence of certain food allergies such as peanut, tree nut, and seafood most commonly continues throughout one's lifetime. (B)

*Summary Statement 30.* The natural history of specific foods varies considerably. (C)

#### *Risk Factors and Prevention of Food Allergy*

*Summary Statement 31.* The rate of observed food allergy in children born to families with parental asthma was approximately 4-fold higher than expected when compared with an unselected population. (B)

*Summary Statement 32.* Food allergy prevention strategies include breastfeeding, maternal dietary restrictions during breastfeeding, delayed introduction of solid foods, delayed introduction of particular allergenic foods, and the use of supplemental infant formulae that are hypoallergenic or of reduced allergenicity. However, the effectiveness of these

strategies for safeguarding against the development of food allergies has not been established. (B)

#### *Cross-Reactivity of Food Allergens*

*Summary Statement 33.* Recent studies with molecular biological techniques have characterized a variety of cross-reacting allergens among foods. (C)

*Summary Statement 34.* In vitro cross-reactivity to multiple shared food allergens is common, but clinical correlation of the cross-reactivity is variable. (C)

*Summary Statement 35.* Cow's milk allergy is a common disease of infancy and childhood. Goat's milk cross-reacts with cow's milk. Ninety percent of cow's milk allergic patients will react to goat and/or sheep's milk. (A)

*Summary Statement 36.* Hen's egg allergens cross-react with certain avian egg allergens, but the clinical implications of such cross-reactivity are unclear. (B)

*Summary Statement 37.* In vitro cross-reactivity between soybean and other legume foods is extensive, but oral food challenges demonstrate that clinical cross-reactivity to other legumes in soy bean sensitive children is uncommon and generally transitory. (B)

*Summary Statement 38.* Patients with peanut allergy generally tolerate other beans (95%), even soy. Evaluation of legume allergy in a patient with peanut allergy should be individualized but avoidance of all legumes is generally unwarranted. (B)

*Summary Statement 39.* There is significant cross-reaction between different species of fish. Although there is limited investigation of the clinical relevance of such cross-reactivity, patients who are clinically allergic to any species of fish should be cautious about eating fish of another species until the clinical relevance of such cross-reactions to that species can be demonstrated by an accepted food challenge. (B)

*Summary Statement 40.* Crustaceans, such as shrimp, crab, crawfish, and lobster, are a frequent cause of adverse food reactions, including life-threatening anaphylaxis. There is considerable risk of cross-reactivity between crustaceans. Less well defined is cross-reactivity between mollusks and crustaceans. (C)

*Summary Statement 41.* Crustaceans do not cross-react with vertebrate fish. (B)

*Summary Statement 42.* Seafood allergy is not associated with increased risk of anaphylactoid reaction from radiocontrast media. (F)

*Summary Statement 43.* Patients with wheat allergy alone show extensive in vitro cross-reactivity to other grains that is not reflected clinically. Therefore, elimination of all grains from the diet (ie, wheat, rye, barley, oats, rice, corn) of a patient with grain allergy is clinically unwarranted and may be nutritionally detrimental. (B)

*Summary Statement 44.* Evaluation of cross-reactivity among tree nuts (walnut, hazelnut, Brazil nut, pecan) is characterized by shared allergens among tree nuts and between tree nuts and other plant-derived foods and pollen. Clinical reactions to tree nuts can be severe and potentially

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fatal and can occur from the first exposure to a tree nut in patients allergic to other tree nuts. In most cases, elimination of all tree nuts from the diet is appropriate. (C)

*Summary Statement 45.* Since the proteins of cacao nut undergo extensive modification into relatively nonallergenic complexes during the processing of commercial chocolate, clinical sensitivity to chocolate is vanishingly rare. (D)

*Summary Statement 46.* Although IgE-mediated reactions to fruits and vegetables are commonly reported, clinically relevant cross-reactivity resulting in severe reactions is uncommon. (C)

*Summary Statement 47.* The latex-fruit syndrome is the result of cross-reactivity between natural rubber latex proteins and fruit proteins. Class 1 chitinases (Hev b 6, hevein-like proteins), profilins (Hev b 8),  $\beta$ -1, 3-gluconases (Hev b 2), and other cross-reactive polypeptides have been implicated. The most commonly reported cross-reactive foods include banana, avocado, kiwi, and chestnut, but many other fruits and some nuts have been identified in cross-reactivity studies. (D)

*Summary Statement 48.* Seed storage proteins appear to be the main allergens in the edible seeds; in particular, 2S albumin family proteins (part of the cereal prolamin superfamily) have been demonstrated as allergens in sesame, mustard, sunflower, and cottonseed. Cross-reactivity has not been well-studied. (E)

#### *Adverse Reactions to Food Additives*

*Summary Statement 49.* The number of additives used by the food industry is extensive. Only a small number of additives have been implicated in IgE-mediated or other (immunologic or nonimmunologic) adverse reactions. Adverse reactions to food additives, therefore, are rare. (C)

*Summary Statement 50.* Food additives may cause anaphylaxis, urticaria or angioedema, or asthma. These reactions can be severe or even life-threatening; fatalities have been described. (C)

*Summary Statement 51.* Tartrazine (FD&C yellow No. 5) sensitivity is extremely rare. There is no convincing evidence to support the contention that tartrazine “cross-reacts” with cyclooxygenase-inhibiting drugs. (B)

*Summary Statement 52.* Monosodium glutamate (MSG) sensitivity is a rare cause of urticaria or angioedema. (C) It is also a rare cause of bronchospasm in patients with asthma. (B)

*Summary Statement 53.* Sulfites produce bronchospasm in 5% of the asthmatic population, in most cases due to generation of sulfur dioxide in the oropharynx. (A) Sulfite-induced anaphylaxis has also been described. (B)

*Summary Statement 54.* “Natural” food additives, including annatto, carmine, and saffron, as well as erythritol (ERT; 1,2,3,4-butanetetrol), a sweetener, may be rare causes of anaphylaxis. (C)

*Summary Statement 55.* Adverse reactions (anaphylaxis, urticaria or angioedema, or bronchospasm) from food additives should be suspected when symptoms after food or

beverage consumption occur some but not all the time, suggesting that the reaction occurs only when an additive is present. (C)

*Summary Statement 56.* Management entails avoiding foods or beverages that contain the implicated additive and using self-injectable epinephrine for life-threatening reactions, especially for individuals who are sulfite sensitive. (B)

#### *Genetically Modified Foods*

*Summary Statement 57.* Many of the major food groups have undergone modification by gene manipulation or replacement, and several of these food products are currently on grocery store shelves. (C)

*Summary Statement 58.* The possibility exists that transgenic plant proteins in novel genetically modified foods could cause severe food allergy, including anaphylactic shock, if allergenic determinants (amino acid sequences) in the transgenic proteins share a high degree of homology to those of known food allergens. (E)

*Summary Statement 59.* As illustrated by recent introduction of corn engineered to contain a pesticide,  $\delta$  endotoxin (derived from *Bacillus thuringiensis*), into the human food chain, food allergy to such engineered foods could occur in workers previously exposed and sensitized to this endotoxin or in other highly susceptible atopic patients. (A)

*Summary Statement 60.* The potential allergenicity of newly developed genetically modified foods should be investigated on a case-by-case basis by individual commercial developers and appropriate regulatory agencies. (D)

#### *Diagnosis of Food Allergy*

*Summary Statement 61.* The primary tools available to diagnose adverse reactions to foods include history (including diet records), physical examination, skin prick or puncture tests, serum tests for food specific IgE antibodies, trial elimination diets, and oral food challenges. (B)

*Summary Statement 62.* A detailed dietary history, at times augmented with written diet records, is necessary to determine the likelihood that food is causing the disorder, identify the potential triggers, and determine the potential immunopathophysiology. (D)

*Summary Statement 63.* A physical examination may reveal the presence of atopic disorders, such as asthma, atopic dermatitis, and allergic rhinitis, that indicate an increased risk for food allergy or reveal alternative diagnoses that may reduce the likelihood of food allergy. (C)

*Summary Statement 64.* Tests for food specific IgE antibody include PSTs (prick or puncture) and serum assays. These tests are highly sensitive (generally >90%) but only modestly specific (approximately 50%) and therefore are well suited for use when suspicion of a particular food or foods is high but are poor for the purpose of screening (eg, using panels of tests without consideration of likely causes). (B)

*Summary Statement 65.* Intracutaneous (intra-dermal) skin tests for foods are potentially dangerous, overly sensitive



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(increasing the rate of a false-positive test result), and not recommended. (D)

*Summary Statement 66.* Results of PSTs and serum tests for food specific IgE antibody may be influenced by patient characteristics (eg, age), the quality and characteristics of reagents (eg, variations in commercial extracts, cross-reacting proteins among food extracts), and techniques (eg, assay types, skin test devices, location of test placement, mode of measurement). (B)

*Summary Statement 67.* Increasingly higher concentrations of food specific IgE antibodies (reflected by increasingly larger PST response size and/or higher concentrations of food-specific serum IgE antibody) correlate with an increasing risk for a clinical reaction. (C)

*Summary Statement 68.* A trial elimination diet may be helpful to determine if a disorder with frequent or chronic symptoms is responsive to dietary manipulation. (D)

*Summary Statement 69.* Graded oral food challenge is a useful means to diagnose an adverse reaction to food. (B)

*Summary Statement 70.* A number of additional diagnostic tests are under investigation, including atopy patch tests, basophil activation assays, and tests for IgE binding to specific epitopes. (E)

*Summary Statement 71.* Some tests, including provocation neutralization, cytotoxic tests, IgG antibodies directed to foods, and hair analysis, are either disproved or unproven; therefore, they are not recommended for the diagnosis of food allergy. (C)

*Summary Statement 72.* Ancillary tests may be needed to confirm the diagnosis of food intolerance or immune reactions to foods, such as breath hydrogen tests for lactose intolerance or gastrointestinal biopsy to determine eosinophilic inflammation or atrophic villi. (D)

*Summary Statement 73.* The rational selection, application, and interpretation of tests for food-specific IgE antibodies require consideration of the epidemiology and underlying immunopathophysiology of the disorder under investigation, the importance of making a definitive diagnosis, estimation of prior probability that a disorder or reaction is attributable to particular foods, and an understanding of the test utility. (D)

#### *Food-Dependent Exercise-Induced Anaphylaxis (EIA)*

*Summary Statement 74.* Individuals with food-dependent EIA develop neither anaphylaxis with ingestion of food without subsequent exercise nor anaphylaxis after exercise without temporally related ingestion of food. (A)

*Summary Statement 75.* Two subsets of patients with food-dependent EIA have been described<sup>1</sup>: one subset may develop anaphylaxis when exercising in temporal proximity to ingestion of *any type of food*<sup>2</sup>; another subset may experience anaphylaxis with exercise in conjunction with ingestion of a *specific food*. (A)

*Summary Statement 76.* Management of food-dependent EIA entails avoiding exercising in proximity to food con-

sumption, carrying self-injectable epinephrine, exercising with a “buddy,” and wearing medic-alert jewelry. (C)

#### *Differential Diagnosis of Adverse Reactions to Foods*

*Summary Statement 77.* Non-IgE-mediated immunologic reactions to foods have been implicated in such entities as (1) food-induced enterocolitis and colitis, (2) malabsorption syndromes (eg, celiac disease), (3) cow’s milk-induced syndromes, and (4) dermatitis herpetiformis. (C)

*Summary Statement 78.* Food-induced enterocolitis and colitis are most commonly seen in infants several hours after ingestion of food proteins, most notably those in cow’s milk or soy formulas. Infants with food-induced enterocolitis develop severe protracted vomiting and diarrhea compared with infants with food-induced colitis who usually appear healthy. Both groups of patients present with blood and eosinophils in the stool, although colitis more often presents with gross blood. (C)

*Summary Statement 79.* Immune-mediated malabsorption syndromes that result in diarrhea and weight loss (or lack of weight gain) may occur secondary to intolerance to a variety of food proteins, including those in cow’s milk, soy, wheat, other cereal grains, and eggs. (C)

*Summary Statement 80.* Celiac disease is a severe form of malabsorption characterized by total villous atrophy and extensive cellular infiltrates due to an immunologic reaction to gliadin, a component of gluten found in wheat, oat, rye, and barley. The diagnosis of the disease is crucial, since the removal of gluten from the diet can lead to reversal of histopathologic changes and recovery of gastrointestinal function. (C)

*Summary Statement 81.* In a subset of infants, colic and gastroesophageal reflux disease have been attributed to adverse reactions to cow’s milk. However, an immunologic basis for these conditions has not been clearly established. (A)

*Summary Statement 82.* Dermatitis herpetiformis is characterized by a chronic, intensely pruritic, papulovesicular rash symmetrically distributed over the extensor surfaces of the extremities and the buttocks associated with gluten ingestion and often with gluten-sensitive enteropathy. Direct immunofluorescence or specific immunologic assays may be helpful in making the diagnosis. (B)

*Summary Statement 83.* Cow’s milk-induced pulmonary hemosiderosis (Heiner syndrome) is an extremely rare condition in infants and toddlers that also may be related to egg or pork hypersensitivity and for which the immunopathology is poorly understood. It is characterized clinically by recurrent episodes of pneumonia associated with pulmonary infiltrates, hemosiderosis, gastrointestinal blood loss, iron-deficiency anemia, and failure to thrive. The presence of precipitating antibodies to the responsible antigen is necessary but not sufficient to make the diagnosis. (C)

*Summary Statement 84.* Toxic food reactions, bacterial contamination of food, and pharmacologic food reactions may mimic IgE-mediated reactions and should be considered

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early in the differential diagnosis because of the serious nature of such reactions. (C)

*Summary Statement 85.* Pharmacologic adverse food reactions occur after ingestion of foods with pharmacologically active substances, such as vasoactive amines, in particular histamine (scombroid poisoning), and produce a wide range of clinical manifestations, especially gastrointestinal and central nervous system in nature. Patients may present with flushing, sweating, nausea, vomiting, diarrhea, headache, palpitations, dizziness, swelling of the face and tongue, respiratory distress, and shock. (C)

*Summary Statement 86.* Enzymatic food reactions are caused by the ingestion of normal dietary amounts of foods in individuals susceptible to such reactions because of medications, disease states, malnutrition, or inborn errors of metabolism (eg, lactose intolerance). (C)

*Summary Statement 87.* Reactions not related to specific food ingestion but due to the act of eating that can be misdiagnosed as reactions to foods include gustatory or vasomotor rhinitis, carcinoid syndrome, idiopathic anaphylaxis, systemic mastocytosis, inflammatory bowel disease, and irritable bowel syndrome. (C)

*Summary Statement 88.* Conditions incorrectly identified as being related to food ingestion include multiple sclerosis, attention-deficit disorder, autism and other behavioral conditions, chronic fatigue syndrome, and the “yeast connection.” (C)

#### *General Management of Food Allergy*

*Summary Statement 89.* The key to the management of patients with food allergy is avoidance of foods known to have or suspected of having caused a reaction. (F)

*Summary Statement 90.* Since elimination diets may lead to malnutrition or other serious adverse effects (eg, personality change), every effort should be made to ensure that the dietary needs of the patient are met and that the patient and/or caregiver(s) are fully educated in dietary management. Once the diagnosis of food allergy is confirmed, the patient should be advised to avoid eating the food. (D)

*Summary Statement 91.* In some cases, severe allergic reactions may be seen in patients who only inhale or come in contact with food allergens, thereby making avoidance even more difficult. (D)

*Summary Statement 92.* The successful avoidance of food allergens relies on (1) identification in each patient of the specific food that caused the reaction; (2) recognition of cross-reacting allergens in other foods; (3) education of the patient and/or caregiver about avoidance measures, with particular emphasis on hidden food allergens or additives; and (4) willingness of the educated patient and/or caregiver to read labels carefully, inquire at restaurants, and take other measures to prevent inadvertent exposure to known or suspected allergens. (D)

*Summary Statement 93.* In selected cases, reevaluation of patients with food allergy may be important to determine if food allergy has been lost over time. (F)

*Summary Statement 94.* If there is a history of suspected or proven IgE-mediated systemic reactions to foods, injectable epinephrine should be given to patients and/or caregivers to carry with them and they should be instructed in its use. (F)

*Summary Statement 95.* Prophylactic medications have not been shown to be effective in consistently preventing severe, life-threatening reactions to foods and may mask a less severe IgE-mediated reaction to a food, knowledge of which could prevent a more severe reaction to that food in the future. (D)

#### *Management in Special Settings and Circumstances*

*Summary Statement 96.* Fatal and near-fatal food anaphylactic reactions tend to occur away from home after an unintentional ingestion of a food allergen by individuals with a known allergy to the same food. (C)

*Summary Statement 97.* Delay in the administration of injectable epinephrine is a common feature of fatal food allergic reactions. (C)

*Summary Statement 98.* Peanut and tree nuts account for most fatal and near-fatal food allergic reactions in the United States. (C)

*Summary Statement 99.* Allergic reactions that result from direct skin contact with food allergens are generally less severe than reactions due to allergen ingestion. Reactions that result from inhalation of food allergens are generally less frequent and less severe than reactions caused by either direct skin contact or ingestion. Exceptions to these generalizations are more likely in occupational environments and other settings in which food allergen sensitization occurred via either inhalation or skin contact. (B)

*Summary Statement 100.* Schools and childcare centers should have policies for facilitating food allergen avoidance, including staff education regarding label reading and cross-contamination, prohibition of food or utensil sharing, and increased staff supervision during student meals. (D)

*Summary Statement 101.* Schools and childcare centers should have policies ensuring prompt treatment of food anaphylaxis, including a requirement for physician-prescribed treatment protocols for food allergic students, staff education regarding recognition and treatment of anaphylaxis, and the ready availability of injectable epinephrine. (D)

*Summary Statement 102.* It is important to inform workers in a restaurant or other food establishment about a history of a systemic food allergic reaction, although this does not ensure that the meal will be free of the offending food. (C)

*Summary Statement 103.* Allograft transplant recipients may acquire specific food allergic sensitivities from organ donors. (B)

*Summary Statement 104.* Patients with latex allergy have an increased risk of experiencing IgE-mediated food-induced symptoms, including anaphylaxis, particularly when ingesting banana, avocado, kiwi, or chestnut. (C)

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### Future Directions

*Summary Statement 105.* Future strategies for diagnosis, treatment, and prevention of food allergy will involve the use of new molecular and immunologic techniques. (B)

*Summary Statement 106.* Although there is no evidence at this time to justify the use of humanized anti-IgE monoclonal antibody for preventing severe food allergy responses, future research will determine the clinical feasibility of such an approach and the use of short-chain Fc $\epsilon$ RI peptides antagonistic to the Fc $\epsilon$ RI  $\alpha$ -chain. (B)

*Summary Statement 107.* New approaches in evidence-based medicine aim to more precisely define the potential clinical outcomes reflected in test results through mathematical calculations of data derived through clinical studies, such as the application of likelihood ratios.

## CLASSIFICATION OF MAJOR FOOD ALLERGENS AND CLINICAL IMPLICATIONS

As indicated elsewhere in this document, IgE antibody responses toward food allergens may occur as a consequence of sensitization through the gastrointestinal route of exposure or by initial sensitization through the respiratory route to airborne allergens with proteins that are homologous to the ones in particular foods (pollen food-related syndrome, occupationally related or oral allergy syndrome). Characteristics of the proteins themselves and the particular type and degree of immune responses that they elicit affect the clinical manifestations of the resulting disease. The clinical outcome is that particular foods such as cow's milk, hen's egg, wheat, and soybean are allergens that affect primarily infants and young children who become sensitized through the gastrointestinal route of exposure but eventually may develop tolerance to these foods.<sup>1</sup> Allergy to peanut, nuts from trees, finned fish, and shellfish emerge primarily from gastrointestinal exposure, but such allergies are more persistent.<sup>1,2</sup> Allergic responses to fruits and vegetables are typically mild and primarily develop later in life as a consequence of their sharing homologous proteins with airborne allergens (eg, pollens).<sup>3</sup> Molecular and immunologic techniques are providing data to determine which allergens, or epitopes of an allergen, in a particular food may be responsible for specific clinical outcomes. However, there has been no clear-cut means to predict the allergenic potential of a particular protein.<sup>4</sup> A list of allergenic foods has been compiled<sup>5</sup> but is ever-growing, as is characterization of the causal allergens on a molecular level. It is fair to conclude that virtually any food may induce an allergic reaction in some individuals, yet some are more likely to do so. In the following section, epidemiologic and clinical features of several important allergens are summarized to provide relevant food-specific information for clinicians undertaking evaluation and management of these food allergies.

### *Cow's Milk*

Several prospective epidemiologic studies indicate that cow's milk allergy affects approximately 2.5% of infants,<sup>6-9</sup> al-

though tolerance is often achieved (approximately 85%) by the age of 3 to 5 years.<sup>1,7</sup> A variety of clinical manifestations are observed with both IgE antibody- and cell-mediated origins. Alternative mammalian milks, such as goat or sheep, are poor substitutes because more than 90% of cow's milk allergic children will react to these as well.<sup>10</sup> IgE antibodies may be directed to a variety of potential allergenic proteins in cow's milk, in particular casein and whey proteins.<sup>11</sup> IgE antibody-mediated cow's milk allergy in infants indicates an increased risk of the development of other food allergies (up to 50%) and inhalant allergies (up to 80%).<sup>12</sup> Reactions are generally not life-threatening, but death from cow's milk anaphylaxis has occurred.<sup>13</sup> It has been observed clinically that cow's milk allergic children may tolerate small amounts of cow's milk protein, for example, in baked goods; the ramifications of this observation for children who continue to consume such products on induction of potential tolerance are unknown. Infants with IgE antibody-mediated cow's milk allergy usually tolerate extensively hydrolyzed formulas based on cow's milk protein (approximately 98%)<sup>14</sup> or soy (approximately 85%),<sup>15</sup> although the American Academy of Pediatrics has not considered soy a good choice for substitution in the first year of life in an attempt to prevent food allergy for those with a predilection toward food allergy.<sup>16</sup> Between 13% and 20% of children with IgE antibody-mediated cow's milk allergy in referred populations also react to beef.<sup>17</sup>

### *Hen's Egg*

Allergy to hen's egg affects approximately 2.5% of infants and young children, and tolerance is usually achieved by the age of 5 years.<sup>1,18,19</sup> The major allergenic proteins are found in the egg white. Sensitization to hen's egg in infancy indicates an increased risk of sensitization to respiratory allergens later in life.<sup>20</sup> Allergic responses are usually not life-threatening, but death from egg-induced anaphylaxis has been reported.<sup>13</sup> Egg sensitized children sometimes tolerate egg in baked products or may experience contact urticaria from egg and yet ingest it without symptoms; these phenomena appear to occur when IgE antibodies are directed to some of the more labile (eg, conformational) epitopes of hen's egg allergenic proteins.<sup>21,22</sup> Sensitization by the inhalant route occurs in a significant number of egg processing workers.<sup>23,24</sup>

### *Peanut*

Allergy to peanut affects approximately 0.6% of the general population in the United States and is potentially severe.<sup>25</sup> In case series of fatal food-induced anaphylaxis, peanut allergic reactions are generally the most common culprit, with the highest-risk groups being adolescents with asthma.<sup>13,26</sup> Although long-term studies are lacking, a peanut allergy established in childhood appears to be long-lived,<sup>27</sup> although approximately 20% of children with a peanut allergy established under the age of 2 years will eventually tolerate peanut.<sup>28,29</sup> Recurrence of resolved peanut allergy has been observed.<sup>30</sup> Highly refined peanut oil is usually tolerated by

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persons with peanut allergy, but processing variations exist and sources may not be easily traced, so avoidance of even refined peanut oils may be advisable for persons with this allergy.<sup>31–33</sup>

#### *Soybean*

This legume is responsible for a variety of clinical manifestations of allergy, both IgE mediated and cell mediated, primarily affecting infants and young children. Population prevalence has not been widely studied but appears to be 0.3% to 0.4% and typically transient.<sup>1</sup> Deaths from soy allergy are extremely rare and have been reported primarily from Sweden.<sup>34</sup> Processed soybean oil is typically considered safe for patients with soy allergy.<sup>35</sup>

#### *Tree Nuts*

Allergy to nuts from trees (eg, walnut, cashew, Brazil nut, pistachio) affect approximately 0.5% of the persons in the United States.<sup>25</sup> Tree nut allergic reactions can be severe and account for a relatively high proportion of fatal reactions in several case series.<sup>13,26</sup> The allergy is considered to be long-lived, although limited studies exist to document the long-term course. Variation of severity of clinical reactions may in part be related to the particular proteins to which immune responses are directed. For example, certain nuts contain proteins that are pollen cross-reactive and other stable proteins for which gastrointestinal routes of sensitization are more probable; the mode of sensitization and specific immune response therefore correlates with the causal protein(s) within the nut.<sup>36</sup> This differential type of allergy to tree nuts is pertinent in particular for hazel nut, which has proteins that are birch pollen related. Certain tree nuts also share homologous proteins that vary by specific nut type but may be clinically relevant.<sup>37,38</sup> A high rate of coexisting allergy to peanut (which is a legume) and at least some tree nuts (approximately 30% to 50%) is observed particularly among referral populations,<sup>39,40</sup> and although studies show homologous proteins between these foods by *in vitro* inhibition, the clinical relevance of such observations is not fully explored.<sup>37</sup> For safety concerns, some authorities suggest avoidance of all tree nuts for persons with peanut allergy or any single tree nut allergy. Individualization is possible when nuts known to be tolerated are eaten without risk of contact compared to nuts with proven clinical sensitivity.<sup>40,41</sup>

#### *Wheat*

The variety of adverse immune responses to wheat include forms of IgE-mediated acute reactions, inhalational reactions (baker's asthma), reactions that occur when wheat ingestion is followed by exercise (wheat-dependent EIA), and cell-mediated reactions such as those observed in atopic dermatitis and gastrointestinal allergic disorders, including celiac disease. For IgE-mediated reactions, children are typically affected and the allergy is usually outgrown,<sup>1</sup> except for exercise-associated reactions. In young children, allergy to multiple grains is generally uncommon (approximately 20%).<sup>42</sup> The type of immune response and triggering allergen

partially define the clinical manifestations of the allergy (e.g., baker's asthma caused by inhalation of water soluble proteins and  $\omega$ -5 gliadin specific IgE responsible for acute reactions in children and in wheat-dependent EIA<sup>43,44</sup>).

#### *Fish*

Allergic reactions to finned fish are potentially severe. Reactions to multiple types of fish in an individual with fish allergy are common, but not the rule.<sup>45,46</sup> Parvalbumin is the dominant allergen in finned fish. Fish allergy is considered long-lived, although resolution is reported.<sup>47</sup>

#### *Shellfish*

Allergic reactions to crustacean shellfish, such as shrimp, lobster, and crab, are potentially severe. Reactions to multiple types of shellfish in an individual with crustacean shellfish allergy is common, but not the rule.<sup>48</sup> The dominant allergen is invertebrate tropomyosin, a muscle protein also found in mollusks, other bivalves, and even insects and acarids (cockroach, dust mite).<sup>49,50</sup>

#### *Seeds*

Anecdotal descriptions of IgE-mediated reactions (some life-threatening) have been reported to various seeds, including cottonseed, anise, caraway, coriander, fennel, and dill.<sup>51,52</sup> In recent years, allergy to sesame, sunflower, poppy, and mustard is being reported with increasing frequency from those areas of the world where these particular seeds are ingredients of indigenous recipes.<sup>53–57</sup> Reactions to these foods appear to be potentially severe. Known plant storage proteins (eg, the 2s albumin families are being identified as causal allergenic proteins).<sup>53</sup>

#### *Fruits and Vegetables*

IgE antibody-mediated reactions to fruits and vegetables are the most common type of food allergy reported by adults in France.<sup>58</sup> Reactions are typically mild, confined to the oral cavity, and related to initial sensitization to pollens that share homologous proteins with the implicated fruits and vegetables; this is known as the pollen-food syndrome or oral allergy syndrome.<sup>3</sup> However, systemic reactions to fruits and vegetables may also occur. Severe reactions to fruits have been associated with the presence of IgE antibody to particular proteins, such as lipid transfer proteins or storage proteins, that may be more stable and/or to which sensitization may have occurred through the gastrointestinal route in contrast to the milder symptoms attributed to reactions to less stable allergens such as profilin.<sup>36,59</sup>

## **MUCOSAL IMMUNE RESPONSES INDUCED BY FOODS**

### *Introduction*

*Summary Statement 1.* Mucosal adaptive immunity has dual functions of protection against enteric pathogens and maintenance of autotolerance against dietary proteins and commensal bacterial. (E)

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As a prelude to understanding gastrointestinal immune responses to foods, it should be appreciated that ingestion of dietary antigens occurs in the context of countervailing functional requisites of host defense, namely, systemic immunity or oral tolerance. The mucosal adaptive immune system has evolved to protect against dire consequences of enteric pathogens while at the same time establishing a state of autotoxic tolerance to immune responses that might be engendered by dietary proteins and commensal bacteria. Microorganisms or nonviable particulates (M/NVPs) are preferentially transported into the Peyer patch through microfold M cells, which together with the underlying subepithelium form dome-like structures throughout the small intestine.<sup>60</sup> Similar to other secondary lymphoid organs, dendritic cells in the Peyer patch present M/NVP antigens chiefly to CD4<sup>+</sup> and CD8<sup>+</sup> T cells but also to CD4<sup>+</sup> T cells in the lamina propria and mixed populations of interepithelial T cells, many of which are of the  $\gamma\delta$  T-cell receptor phenotype, resulting in active immune responses.<sup>61</sup> By contrast, gastrointestinal encounters with relatively large doses of soluble protein almost always stimulate tolerance.<sup>62</sup> Paradoxically, human systemic reactions to food are chiefly due to specific IgE-mediated hypersensitivity, although both humoral IgE- and cell-mediated reactions after oral induction and challenge by proteins are easily suppressed in rodent animal models.<sup>62,63</sup> The reason for this disparity is unknown. It suggests, however, that reinduction of tolerance to dietary allergens is a possible therapeutic approach for the future treatment of food allergy, especially in view of the fact that respiratory mucosal tolerance has been accomplished by oral ingestion of respiratory allergens.<sup>64</sup>

*Summary Statement 2.* Factors that regulate gastrointestinal immune balance include the nature and dose of the antigen, immaturity of the host, genetic susceptibility, the rate of absorption of a dietary protein, and the conditions of antigen processing. (E)

Many of the regulatory factors that govern the fine balance between systemic immune responses and oral tolerance have been deduced from rodent models.<sup>62</sup> For example, the nature and dose of the antigen, immaturity of the host, the rate of absorption of a dietary protein, antigen processing by dendritic cells having low levels of costimulatory molecules, and the immunosuppressive milieu of the Peyer patch are all known to favor the induction of peripheral tolerance to dietary proteins rather than systemic immunity.<sup>62,65-67</sup> The consequences of the tolerant state include functionally inactive (anergic) antigen-specific T cells, regulatory suppressor CD4<sup>+</sup> CD25<sup>+</sup> T cells, or anergic regulatory cells (T<sub>H</sub>3 or Tr1 cells) producing cytokines (ie, transforming growth factor  $\beta$  [TGF- $\beta$ ], interleukin 10 [IL-10]) that inhibit both antigen-specific and subsequent nonspecific (bystander) immune responses throughout the peripheral and local immune systems.<sup>62</sup> Under certain circumstances, both systemic immunization and T-cell tolerance may be produced by the same dietary antigen.<sup>68</sup> For example, oral administration of keyhole limpet hemocyanin (KLH) to human volunteers before KLH parenteral immunization completely abolished

KLH delayed hypersensitivity with a concomitant brisk humoral response consisting of anti-KLH-specific antibodies of all isotopes and IgA-anti-KLH antibodies in saliva and intestinal secretions. Thus, the innate properties of dietary proteins appear to be important determinants in the pathogenesis of food allergy.

#### *Allergens*

*Summary Statement 3.* Food allergens are generally glycoproteins with molecular weights ranging from 10 kDa to 70 kDa. (E)

Food allergens generally consist of glycoproteins with molecular weights ranging from 10 kDa to 70 kDa.<sup>4</sup> By definition, these glycoproteins are allergens because they cross-link specific IgE antibody on mast cells or basophils.

*Summary Statement 4.* The more common food allergens in infants and young children are cow's milk, hen's egg, peanut, tree nuts, soybeans, and wheat, whereas the adult counterparts are peanuts, tree nuts, fish, crustaceans, mollusks, fruits, and vegetables. (B)

Relatively few foods account for most IgE-mediated allergic reactions in both children and adults. The more common food allergens in infants and young children are cow's milk, hen's egg, peanuts, tree nuts, soy beans, and wheat, whereas the adult counterparts are peanuts, tree nuts, fish, crustaceans, mollusks, fruits, and vegetables.<sup>69</sup>

Certain panallergens found in multiple foods are nonspecific and may confound clinical diagnostic testing. These include pathogenesis-related proteins, which often cause the oral allergy syndrome, protease inhibitors, and actin-binding profilins.<sup>4,70,71</sup>

*Summary Statement 5.* Major allergenic proteins have been identified and genes for some of the major allergens have been cloned and sequenced. (E)

Major allergenic proteins have been identified in peanuts, tree nuts, hen's eggs, cow's milk, wheat, soy, fish, and shellfish.<sup>72</sup> Genes for many of the major allergens, particularly peanuts, have been cloned and sequenced.<sup>73,74</sup>

*Summary Statement 6.* Innate allergenicity of foods may be determined by a combination of factors such as solubility, resistance to pH, heat, and proteolysis by digestive enzymes. (E)

Physical characteristics that may account for innate allergenicity of these foods include aqueous solubility aiding rapid absorption, resistance to low pH, heat, and resistance to proteolysis by digestive enzymes.<sup>72</sup> For these reasons, they resist degradation during food preparation and digestion within the gastrointestinal tract.

*Summary Statement 7.* Structural amino acid sequences, either sequential or conformational, account for cross-reactivity between foods. Sequential epitopes may be particularly important for persistence of allergenicity beyond childhood (eg, casein hypersensitivity). (B)

Amino acid structural characteristics of major allergens may account for 2 important clinical aspects of food allergy. Cross-reactions are more likely to occur if amino acid se-

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quence homology exceeds 70% or if 2 proteins share 8 or more sequential amino acids.<sup>75</sup> Persistence of clinical allergy to certain foods (eg,  $\alpha$ -s1 casein) beyond childhood may be dependent on sequential rather than conformational B-cell epitopes.<sup>76</sup> Recently, it has been suggested that conserved 3-dimensional structures and biologic activities, which include most plant food allergens, should be evaluated for allergenicity and cross-reactivity of specific foods.<sup>77</sup>

*Summary Statement 8.* The specific factor(s) that confer allergenicity rather than tolerogenicity are unknown. (E)

Apart from the physical characteristics cited above, the specific factor(s) that confer allergenicity rather than tolerogenicity on specific foods is unknown. It has been proposed that other unknown gastrointestinal proteins, cytokines, or bacterial flora act as adjuvants or tolerance “busters” in genetically susceptible hosts. Thus, tolerogenic effects of oral dietary antigen can be converted to either systemic T<sub>H</sub>1 or T<sub>H</sub>2 immune responses by coadministration of immune stimulating complexes or cholera toxin.<sup>78,79</sup>

#### *Systemic Immune Responses to Dietary Antigens*

*Summary Statement 9.* Characteristic IgE- and mast cell-mediated mechanisms occur in food-induced anaphylaxis, the oral allergy syndrome, and atopic dermatitis. (B)

Food hypersensitivity is characterized by both a reproducible adverse reaction that can be demonstrated by double-blind challenge tests and an abnormal immunologic immune response(s) to the food. Once tolerance is by-passed, one, several, or all isotypic immunoglobulin classes may be synthesized as a consequence of systemic priming by allergenic food proteins. In addition, food-induced immune functions of antigen-specific lymphocytes may be regulatory, effector, or both.<sup>62</sup>

Characteristic IgE- and mast cell-mediated mechanisms occur in food-induced anaphylaxis, the oral allergy syndrome, and atopic dermatitis.<sup>80,81</sup> Specific IgE antibodies are detected by direct skin prick tests or in vitro serologic tests. In general, the sensitivity of in vivo or in vitro tests is variable because certain proteins (eg, fresh fruits and vegetables) are relatively unstable.

Release of mediators (eg, histamine, peptidoleukotrienes) from IgE-sensitized basophils has also been used to confirm food-specific anaphylaxis.<sup>80,82</sup> Interestingly, the basophils of food allergic persons frequently demonstrate spontaneous release of histamine.<sup>80</sup> In addition, peripheral blood mononuclear cells (PBMCs) of food allergic patients also release IgE-dependent histamine-releasing factors.<sup>80</sup>

*Summary Statement 10.* IgE-mediated reactions to foods may occur in neonates on first postnasal exposure, presumably due to in utero sensitization. Since sensitization to dietary allergens in breast milk may occur in the late postnatal period, breastfeeding mothers may choose to avoid highly allergenic foods if familial allergic susceptibility is present. (B)

IgE sensitization to food may occur in neonates on first postnatal exposure to the food. Presumably, prior exposure

occurred in utero, but elicitation of the clinical response during the early neonatal period is consistent with the almost complete absence of oral tolerance known to be present during this time.<sup>83</sup> Sensitization to dietary allergens in breast milk during the late neonatal period may occur.<sup>84</sup> When the probability of inherited allergy is high, breastfeeding mothers may wish to avoid highly allergenic foods.<sup>85</sup> However, the extent of benefit, if any, remains to be determined, and this recommendation is not held by all investigators.<sup>86,87</sup> Persistent IgE sensitization to food for more than 1 year is a strong risk factor for subsequent allergies affecting the respiratory tract.<sup>88</sup> Intestinal parasitization by *Giardia lamblia* appears to enhance the development of food hypersensitivity.<sup>89</sup>

*Summary Statement 11.* Both serum and secretory specific IgA to dietary proteins may be produced in healthy subjects and allergic patients. (B)

Both serum and secretory specific IgA to dietary proteins may be produced in healthy subjects and allergic patients. In some instances, the levels of the local secretory IgA<sub>2</sub> subclass of IgA may be increased in the absence of measurable levels of serum IgA (IgA1).<sup>90</sup> Secretory IgA2 antibodies are thought to play a vital role in excluding absorption of potentially dangerous antigens or pathogens.<sup>61</sup> Oral ingestion of micro-particles that contain dietary proteins leads to enhanced synthesis of IgA2 secretory antibodies compared with soluble proteins alone.<sup>90</sup>

*Summary Statement 12.* The significance of IgM, IgG, and IgG subclass antibodies (eg, the role of IgG4) in food allergy is less well understood and highly controversial. (B)

The significance of IgM and IgG isotypic antibodies in food hypersensitivity is much less well understood and highly controversial. It has been documented that food specific IgM and IgG antibodies are produced after single or repeated feedings of relatively large doses of food proteins in both healthy and allergic persons.<sup>68,91,92</sup> In the case of KLH, a protein to which most humans have not been exposed, both IgM and IgG systemic responses occur concurrently with complete cellular immune tolerance. In a recent report concerning sesame seed sensitization, it was determined that specific IgG responses were more polymorphic with respect to the total number of peptide epitopes than is the case with specific IgE.<sup>92</sup> The roles of specific IgG and/or its subclasses (IgG1, IgG2, IgG3, IgG4) as diagnostic or prognostic indicators of clinical allergy have not been substantiated.<sup>93,94</sup> This may be due, in part, to the fact that current commercial assays for IgG and its subclasses may detect antibody directed against nonspecific proteins (eg, lectins, ubiquitous plant proteins) or cross-reactive carbohydrate determinants in foods, and these irrelevant antibodies may be present as often in healthy subjects as they are in patients complaining of adverse food reactions.<sup>95</sup>

Antigliadin and antiendomysial (transglutaminase) antibodies have been studied extensively in gluten-sensitive enteropathy. The presence of antiigliadin antibodies strongly

suggests that gluten-sensitive enteropathy is due, in part, to a dietary element. Both serum and secretory levels of IgA are increased, whereas IgG levels are only minimally elevated and the IgM level is often decreased.<sup>96</sup>

#### Cell-Mediated Immunity

**Summary Statement 13.** The role of cellular in vitro correlates as diagnostic or prognostic indicators of food allergy is not established. (B)

Indices of cell-mediated immunity, such as lymphocyte proliferation, have been implicated as possible correlates of food hypersensitivity. However, the proliferative responses in these studies were marginal, relatively few patients were studied, and PBMC counts may not reflect the functional status of T cells in the Peyer patch, lamina propria, or interepithelial tissues.<sup>97-100</sup> In animal models, T cells in these sites show relatively low levels of proliferation.<sup>80</sup> In gluten-sensitive enteropathy, although it has been postulated that effector mechanisms might be pathogenetic, PBMC proliferative responses are normal, whereas increased proliferation of T cells from mesenteric lymph nodes has been noted.<sup>96</sup>

#### Cytokines and Chemokines

**Summary Statement 14.** The role of specific cytokine profiles in serum or peripheral mononuclear cells of food allergic patients has not been established in the mechanism of food allergy. (B)

As yet no consensus exists about the in vivo role of cytokines and chemokines in food allergy. The available information is derived from in vitro cultures of PBMCs stimulated with food allergens and serum cytokine levels after human challenge experiments or animal experimental models. Neither T<sub>H</sub>1 nor T<sub>H</sub>2 cytokines appear to be predominant. Following challenge experiments by independent investigators, PBMCs from food allergic patients were found to secrete significant amounts of IL-2, interferon- $\gamma$ , IL-4, and tumor necrosis factor  $\alpha$ .<sup>97,101</sup> In animal models, increased levels of regulatory cytokines, such as TGF- $\beta$  and IL-10, were demonstrated after intragastric feeding.<sup>62</sup> In several eosinophilic gastrointestinal allergy models, IL-5 and exotoxin both appear to play critical roles.<sup>102,103</sup>

#### Local Factors

**Summary Statement 15.** Certain bacterial products, viruses, parasites, and T-cell-independent antigens stimulate systemic immune responses rather than tolerance to the oral protein when coadministered with oral proteins. (B)

Certain bacterial products (cholera toxin), viruses (ie, poliovirus, rotavirus), parasites (ie, *G lamblia*), and T-cell-independent antigens (ie, TNP-Ficoll) stimulate systemic immune responses rather than tolerance when coadministered orally with proteins.<sup>104</sup> Oral administration of proteins combined with nonviable particulates (eg, microencapsulation) also favors systemic priming rather than tolerance. Proinflammatory cytokines may affect nonlymphocyte populations of cells in the gut. Tumor necrosis factor  $\alpha$  stimulates neutrophil degranulation and synthesis of inflammatory IL-1,

IL-6, and granulocyte-macrophage colony-stimulating factor cytokines, which have been implicated in the pathogenesis of inflammatory bowel disease.<sup>105</sup> Stem cell factor and *G lamblia* proteins may potentiate mediator release from mast cells.<sup>89,105</sup> It has also been proposed that postprandial increases in gastrin may stimulate and potentiate release of mediators from intestinal mast cells.<sup>106</sup>

#### Host Factors

**Summary Statement 16.** Sensitization to foods is much more likely to occur in the early neonatal period. (B)

As discussed above, sensitization is much more likely to occur in the neonatal period and also tends to wane in elderly patients.<sup>62</sup>

**Summary Statement 17.** Intestinal malabsorption and/or stasis may predispose patients to food allergy. (B)

Intestinal malabsorption problems due to either intestinal stasis or increased motility are other variables that must be considered.<sup>80</sup>

**Summary Statement 18.** Genetic susceptibility, as defined by single nucleotide polymorphisms or specific haplotypes, has been implicated in several common food allergy phenotypes. (B)

Genetic susceptibility, as defined by single nucleotide polymorphisms or specific haplotypes, has been implicated in several prototypes of food hypersensitivity and will undoubtedly play a more prominent role as further exploration of the genome is accomplished.<sup>107,108</sup>

## THE CLINICAL SPECTRUM OF FOOD ALLERGY

A wide spectrum of adverse reactions may occur after ingestion of food. These are typically classified on the basis of the underlying pathogenesis (Table 2), which is relevant to the management of patients with adverse reactions to food. Adverse food reactions can be divided on the basis of immunologic and nonimmunologic mechanisms. The clinical presentation of the latter may mimic immunologic reactions. The

Table 2. Diversity of Conditions Associated With IgE-Mediated Reactions to Foods

I. Systemic IgE-mediated reactions (anaphylaxis)
A. Immediate-onset reactions
B. Late-onset reactions
II. IgE-mediated gastrointestinal reactions
A. Oral allergy syndrome
B. Immediate gastrointestinal allergy
III. IgE-mediated respiratory reactions
A. Asthma and rhinitis secondary to ingestion of food
B. Asthma and rhinitis secondary to inhalation of food (eg, occupational asthma)
IV. IgE-mediated cutaneous reactions
A. Immediate-onset reactions
1. Acute urticaria or angioedema
2. Contact urticaria
B. Late-onset reactions
1. Atopic dermatitis

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former may include IgE-mediated and non-IgE-mediated reactions. In addition, there are conditions, not related consistently to food ingestion, such as irritable bowel syndrome or inflammatory bowel disease, symptoms of which may mimic reactions to food. These conditions are important to recognize, because patients may have an incorrect opinion in regard to whether a clinical condition is due to food ingestion. In particular, patients with psychological disorders often attribute their reactions to foods. Physicians must be aware that this is a frequent occurrence in adult patients and food allergy may not be the major cause of their symptoms. Although this document will focus on food-induced IgE-mediated reactions, it is essential that the practicing physician be able to identify and separate food-induced IgE-mediated reactions from other types of reactions to food.

*Summary Statement 19.* Allergic food reactions to foods (IgE-mediated reactions) are characterized by a temporal relationship between the reaction and prior exposure to food. Such reactions can be generalized or localized to a specific organ system and can be sudden, unexpected, severe, and life-threatening. (D)

IgE-mediated reactions are typically characterized by a temporal relationship between exposure to a specific food and the onset of the reaction. For example, anaphylactic symptoms and signs that occur in a setting of recent food ingestion strongly point toward an IgE-mediated food allergic reaction. Late-onset reactions may occur as sequelae of IgE-mediated or IgE-associated reactions to food in patients with atopic dermatitis and/or gastrointestinal allergy.<sup>109–111</sup> Patients with IgE-mediated reactions to food may experience gastrointestinal, respiratory, and/or skin manifestations. These may be limited to specific organ systems or involve multiple organ systems. The spectrum of IgE-mediated reactions to foods ranges from very mild to severe and life-threatening.

*Summary Statement 20.* Food allergens are a frequent cause of severe anaphylaxis, particularly in patients with concomitant asthma and allergy to peanut, tree nut, or seafood. Such reactions may be biphasic or protracted. Food allergy should be considered in the differential diagnosis of patients who have idiopathic anaphylaxis. (C)

Food allergens are a frequent cause of severe anaphylaxis seen in an emergent setting.<sup>112–116</sup> In fact, food-induced anaphylaxis is the most common cause of anaphylaxis seen in hospital emergency departments.<sup>117,118</sup>

Anaphylactic reactions may occur as a result of a number of different foods. In children living in North America, anaphylaxis occurs most frequently after ingestion of peanuts, tree nuts, fish, crustaceans, milk, and eggs.<sup>119</sup> Patients who have concomitant asthma and allergy to peanut, nut, or seafood appear to be at highest risk of severe anaphylactic reactions.<sup>26</sup> Patients who develop anaphylaxis may experience biphasic or protracted reactions.<sup>26,120</sup> Evaluation of food allergy should be considered in patients who present with idiopathic anaphylaxis.<sup>118,121,122</sup> There are frequent reports of food reactions, ranging from mild to severe, that come from

“hidden” foods either due to cross-contamination or insufficient labeling.<sup>123–127</sup>

In highly sensitive patients, inhalation of food allergens in fumes or volatile products (eg, from cooking or occupational exposure) may produce IgE-mediated reactions, since cooking may enhance or reduce allergenicity of certain food proteins.<sup>128–134</sup> Tragically, most fatalities from anaphylaxis to foods have occurred in adolescents or young adults, most of whom knew that they were allergic to the food that precipitated the reaction.<sup>13,26</sup>

*Summary Statement 21.* The pollen-food allergy syndrome (oral allergy syndrome) is characterized by the acute onset of oropharyngeal pruritus, sometimes including lip angioedema, usually beginning within a few minutes after oral mucosal contact with particular raw fruits and vegetables during eating. (B)

The pollen-food related syndrome (oral allergy syndrome) is a form of contact allergy with mild oral symptoms triggered by particular raw fruits or vegetables. Symptoms and signs may include itching (pruritus) and edema of the lips, tongue, palate, and throat and usually start within a few minutes after contact with these foods.<sup>3,135,136</sup>

The syndrome is attributed to initial sensitization to pollens.<sup>137</sup> Ragweed-sensitive patients may experience such symptoms when they eat banana or melon, whereas birch pollen-sensitive patients may experience such symptoms when they eat raw carrot, celery, cherry, pear, walnut, potato, apple, hazelnut, or other less frequently reported foods.<sup>3,137–140</sup> Grass allergy is associated with symptoms caused by melon, tomato, and orange,<sup>3,141,142</sup> whereas mugwort allergy is associated with melon, apple, peach, and cherry.<sup>143–145</sup>

The raw fruits and vegetables share cross-reacting proteins with particular pollens, which are the source of initial sensitization. Some responsible cross-reacting allergens (profilins) appear to be heat labile, since these patients generally can ingest foods that would provoke symptoms in the fresh state when they are in a cooked or canned form without symptoms.<sup>146–150</sup> Heat processing of food may not only increase but also decrease the patient's ability to tolerate a food.<sup>150,151</sup> Reactions progress to systemic manifestations, including anaphylaxis, in approximately 1% to 2% of patients who initially have contact reactions. The syndrome should be distinguished from mild oral symptoms caused by stable proteins in the same fruits and vegetables or in other foods (eg, peanut) where subsequent systemic reactions may occur with higher frequency.

The following features of this syndrome should also be considered<sup>137,152–154</sup>: (1) symptoms may be more prominent following the associated pollen season (priming); (2) causal proteins are concentrated in the peel of some fruits; and (3) reactions to all related foods is unlikely but sensitivity to more than one type is common. In addition, reactions to the same foods of a more severe nature may be attributable to stable proteins in these foods. This sometimes correlates with positive skin test results to commercial extracts that contain these more stable allergens.<sup>152,155,156</sup>



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*Summary Statement 22.* IgE-mediated gastrointestinal reactions can present not only with gastrointestinal symptoms but also with other nongastrointestinal manifestations. (D)

IgE-mediated gastrointestinal reactions may occur without other IgE-mediated symptoms, may develop within minutes to several hours after ingestion of the food allergen, and are characterized by nausea, abdominal pain, vomiting, and diarrhea. Gastrointestinal symptoms can also be part of an IgE-mediated systemic reaction (eg, anaphylaxis).<sup>26</sup>

*Summary Statement 23.* Allergic eosinophilic gastroenteritis (eosinophilic gastroenteropathy) is characterized by postprandial gastrointestinal symptoms associated with weight loss in adults and failure to thrive in infants. (C)

IgE-mediated food allergy often cannot be demonstrated in patients who are diagnosed as having allergic eosinophilic gastroenteritis. Eosinophilic gastroenteritis is rare in adults, and food allergy is rarely incriminated as the cause of this condition. The presence of eosinophils alone is not conclusive evidence of food allergy. Eosinophilic esophagogastronteropathy (allergic eosinophilic esophagogastronteritis, allergic eosinophilic esophagitis, allergic eosinophilic enterocolitis, dietary protein enterocolitis, or proctitis)<sup>157</sup> may be due to an IgE-mediated reaction to food in a subset of patients and is characterized by postprandial nausea and vomiting, abdominal pain, diarrhea (occasionally steatorrhea), and weight loss in adults or failure to thrive in infants. Reactions may occur at any location of the gastrointestinal tract from the esophagus to the rectum and include eosinophilic esophagitis, eosinophilic gastritis, and eosinophilic enterocolitis.<sup>158–162</sup>

Histopathologic lesions, characterized by prominent numbers of eosinophils, are associated with this condition and have been demonstrated on biopsy specimens in areas of the gastrointestinal tract from the esophagus to the rectum. This disorder has been associated with IgE-mediated reactions in a small subset of patients. Characteristically, there is infiltration of the esophageal, gastric, or intestinal mucosal, muscular, and/or serosal layers of the stomach or intestine with eosinophils as demonstrated on gastrointestinal biopsy specimen and peripheral eosinophilia.<sup>163–166</sup>

Patients with eosinophilic gastroenteropathy who have food-induced symptoms generally have other atopic disorders and elevated serum IgE levels and may or may not have positive skin prick test results to a variety of foods and inhalants, peripheral blood eosinophilia, iron deficiency anemia, and hypoalbuminemia.<sup>166–168</sup> Rarely, patients may present with an acute abdomen due to acute bowel obstruction, bowel perforation, or duodenal mass or have symptoms that mimic acute appendicitis, a pancreatic neoplasm, or a duodenal ulcer.<sup>169–178</sup> Esophageal involvement<sup>158</sup> is not uncommon in children and may be associated with gastroesophageal reflux,<sup>179,180</sup> although some cases of gastroesophageal reflux in children may not be associated with eosinophilia.

*Summary Statement 24.* Upper and lower respiratory tract manifestations of IgE-mediated reactions to foods, such as rhinoconjunctivitis, laryngeal edema, and asthma can occur

with or without other IgE-mediated symptoms. Isolated respiratory manifestations from exposure to foods is rare and has been reported most frequently in an occupational setting. (C)

IgE-mediated reactions to foods can also occur in the upper and lower respiratory tract. Isolated airway manifestations are rare, but they not uncommonly accompany allergic reactions that involve the skin and gastrointestinal tract. These include manifestations of rhinoconjunctivitis, laryngeal edema, and asthma. Bronchospasm occurring as part of an anaphylactic reaction may make the reaction more difficult to treat. Many foods have been reported to cause respiratory symptoms on inhalation, usually in an occupational setting (eg, crab,<sup>181,182</sup> flour,<sup>183,184</sup> soybean,<sup>185</sup> fish,<sup>186</sup> dried fruits and teas,<sup>187</sup> casein,<sup>188</sup> roasted coffee, clam, egg white, and shrimp<sup>189</sup>). However, highly sensitized patients may experience respiratory symptoms in other settings (eg, aerosolization of seafood allergen in the process of cooking,<sup>129</sup> buckwheat flour in buckwheat chaff-stuffed pillows,<sup>190</sup> and green beans and chards<sup>191</sup>). Patients do not always experience a reaction on ingestion of the food allergen that produced a reaction on inhalation. On the other hand, patients who are originally sensitized by inhalation can develop a reaction on ingestion of the food.<sup>23,24</sup>

*Summary Statement 25.* Many inhaled food proteins in occupational settings may affect workers regularly exposed to such foods as flour (baker's asthma), egg white, and crustaceans. (A)

Baker's asthma is an example of a food-related occupational lung disease that affects workers regularly exposed by inhalation to flour (usually wheat)<sup>192–198</sup> or to mold-derived enzymes used as flour additives,<sup>199–201</sup> as well as occasionally insects found in flour.<sup>202</sup> Ingestion of wheat products usually causes no reaction in patients with baker's asthma.<sup>203</sup> Skin tests or in vitro measurements of IgE are positive to wheat flour extracts and/or mold-derived enzymes in these patients.<sup>195,199–201,203</sup> Bronchial provocation testing is helpful in determining the causative agent in such settings.<sup>195,199–204</sup>

*Summary Statement 26.* IgE-mediated cutaneous reactions, such as acute urticaria or angioedema and acute contact urticaria, are among the most common manifestations of food allergy. Food allergy is commonly suspected but rarely incriminated in chronic urticaria and angioedema but is implicated in at least one third of children with atopic dermatitis. (B)

IgE-mediated cutaneous reactions, such as acute urticaria and angioedema, are among the most common manifestations of food allergy. The exact prevalence of these reactions is unknown. Acute contact urticaria, which is usually IgE mediated, should be distinguished from both irritant and allergic contact dermatitis. This condition may result from contact with shellfish,<sup>129,205</sup> raw meats,<sup>206–211</sup> fish,<sup>212,213</sup> raw vegetables,<sup>214–222</sup> fruits,<sup>223–231</sup> rice,<sup>232–235</sup> egg,<sup>236–240</sup> mustard,<sup>241,242</sup> beer,<sup>243,244</sup> milk,<sup>238,245,246</sup> and many other foods. Food allergens can penetrate intact skin or areas where there is a defective

skin barrier.<sup>247</sup> Food allergy is commonly suspected but is rarely incriminated in chronic urticaria and angioedema.

Food allergy is implicated in at least one third of children with atopic dermatitis, most frequently to egg, milk, peanut, soy, and wheat.<sup>248–252</sup> Food allergy as a cause or trigger of atopic dermatitis in adults is rare.<sup>253</sup>

Figure 1 provides an algorithm for the diagnosis and management of patients with a history of adverse reactions to food.

### ALGORITHM AND ANNOTATIONS

1. Adverse reactions to food are common in the population. In contrast, food allergy represents a small percentage of all adverse reactions to food. The proper diagnosis and subsequent management of food allergy rely heavily on historical

features of the adverse reaction. The following historical information should be obtained: (1) identification of the suspect food or foods, (2) the amount of time between ingestion of the food and development of symptoms, (3) symptoms attributed to the food, (4) amount of food required for a reaction, (5) reproducibility of symptoms on prior or subsequent ingestion, (6) requirement for other cofactors (eg, exercise), and (7) length of time from last reaction. After a detailed history has been obtained, a determination of whether the adverse reaction to food is likely to be IgE mediated or IgE associated is essential.

2. There are several historical features that are suggestive of an IgE-mediated food reaction. Manifestations of an IgE-mediated reaction may include pruritus, urticaria or angioedema, gastrointestinal symptoms, rhinoconjunctivitis, bron-

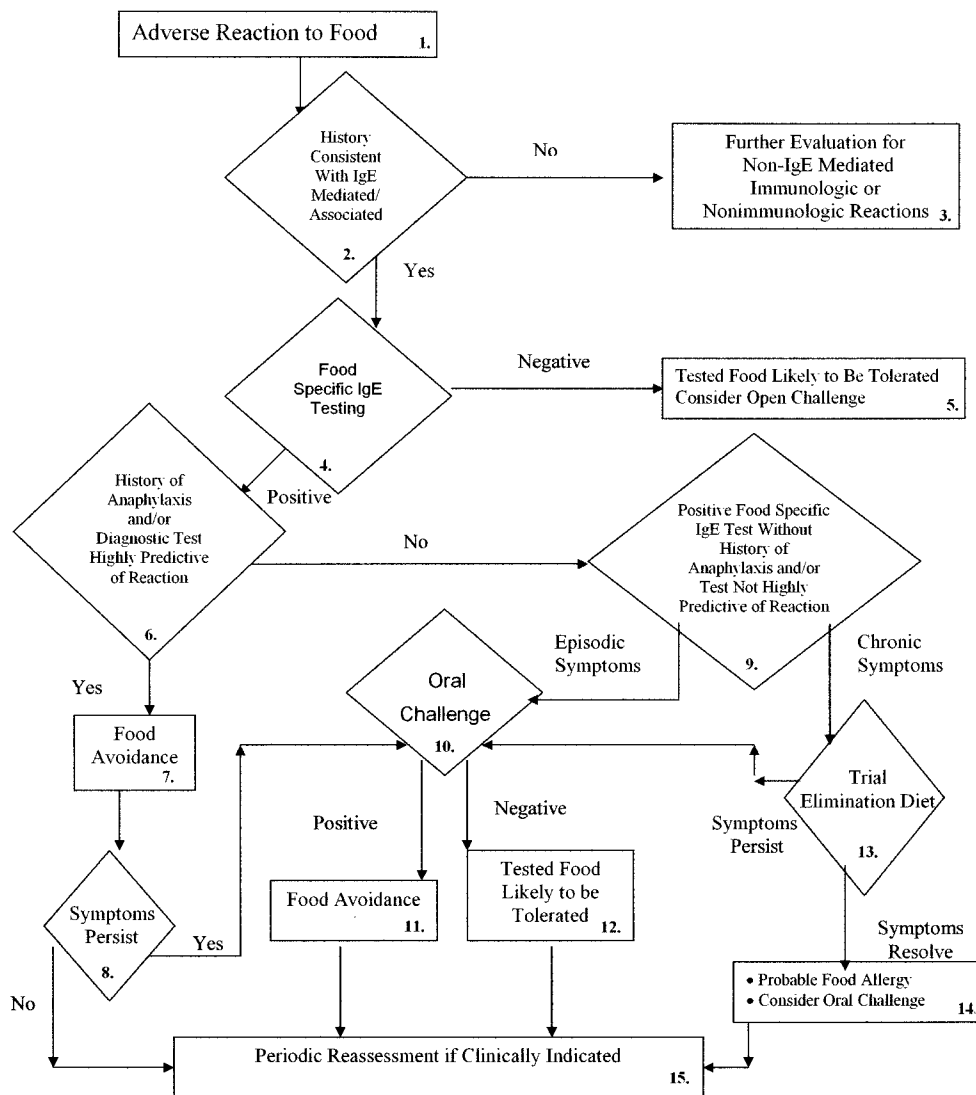


Figure 1. Algorithm for diagnosis and management of food allergy.

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chospasm, and anaphylaxis. Symptoms of oral allergy syndrome are usually restricted to the oropharynx and include pruritus, tingling, and angioedema of the lips, tongue, palate, and throat. Rhinoconjunctivitis or asthma as a sole manifestation of food allergy is rare; however, these symptoms occur commonly in association with other manifestations in food allergy. The time from ingestion to symptom onset in food allergy is typically rapid, usually within minutes, but may be delayed up to an hour and rarely up to a few hours. In addition, small quantities of food may elicit even severe reactions. Reexposure also provokes a reaction.

IgE-associated food reactions such as those triggering atopic dermatitis are more difficult to discern by history alone. The symptoms seen with IgE-associated reactions in atopic dermatitis are primarily pruritus and papulovesicular eruptions. These symptoms may develop minutes to hours after ingestion of the food.

3. Only a minority of adverse reactions to food are IgE mediated or IgE associated. Some adverse reactions to foods may be immune mediated but not involve IgE in their pathogenesis. Examples include gastrointestinal reactions (eg, food-induced enterocolitis, celiac disease, Crohn disease), cutaneous reactions (eg, dermatitis herpetiformis), and pulmonary reactions (Heiner syndrome). Nonimmunologic food reactions include diverse entities such as lactose intolerance, food poisoning, and scombroid poisoning. The evaluation for these non-IgE-mediated reactions may include diagnostic procedures such as food challenge, skin biopsy, stool cultures, and gastrointestinal biopsy. Specific evaluation for each of these non-IgE-mediated reactions is discussed in further detail in the "Differential Diagnosis of Adverse Reactions to Food" section.

4. If the history is consistent with an IgE-mediated or IgE-associated food reaction, specific IgE testing is the next step. Methods of testing for food-specific IgE include PSTs (prick or puncture) and serum tests for specific IgE. Both methods offer high sensitivity and are therefore useful in helping exclude a diagnosis of food allergy. The PSTs and serum tests for specific IgE are only moderately specific, and therefore other diagnostic evaluation is typically required. Intracutaneous (intradermal) skin tests for foods are potentially dangerous, overly sensitive (increasing the rate of a false-positive test result), and not recommended. Commercial food extracts (except for some raw fruits and vegetables) typically are adequate to detect specific IgE in most cases of food allergy. In the case of pollen food-related reactions, testing with the fresh food may provide greater sensitivity. For example, for food reactions that involve raw fruits or vegetables, the PST can be performed using liquid foods, by creating an in-house extract, or using a prick-prick technique (pricking the fruit and then the patient, thereby transferring the soluble fruit proteins). These techniques may offer greater sensitivity and hence a higher negative predictive value to exclude food allergy.

5. Even in a patient whose history is suggestive of an IgE-mediated reaction, if testing for food-specific IgE is negative, the patient will likely tolerate the food. In some

cases of atopic dermatitis, particularly in infants, reactions to foods may occur in the absence of detectable IgE. In cases where the reaction to the food was more severe, an open challenge to the negatively tested food may be considered to definitively exclude food allergy. Oral challenges can elicit severe, anaphylactic reactions, so the physician should be prepared with appropriate emergency medications and equipment to promptly treat such a reaction.

6. In patients whose food reaction was that of anaphylaxis and test results for food specific IgE are positive, no further evaluation is typically required. The risk of a potentially severe reaction on food challenge in such a patient warrants a more prudent approach of eliminating the food.

For a few foods, increasingly higher concentrations of food specific IgE antibody, reflected by larger PST responses or high serum IgE antibody concentrations, are correlated with increasing risks for clinical reactions. However, for most foods, types of reactions, and age groups, diagnostic thresholds for clinical correlations have not been established.

7. Once the diagnosis of food allergy has been established, the only proven therapy is strict avoidance of the specific food. Patients and families need to be educated to avoid unintentional ingestion of food allergens. Reading food labels and recognition of the unfamiliar terms used in labeling constituents that may indicate the presence of a given food allergen is essential. Vague or inaccurate labeling of foods and cross-contamination at the time of packaging or during food preparation (especially in restaurant settings) are other potential hazards in food avoidance. Strict food avoidance is usually a complex task and additional educational resources may be required, such as those available through the Food Allergy and Anaphylaxis Network (Fairfax, VA, 1-800-929-4040 or <http://www.foodallergy.org>). For patients with a history of anaphylaxis (or reactions with anaphylactic potential), self-injectable epinephrine should be prescribed and patients should be instructed on its proper use. Additionally, identification of risks by cards or jewelry, such as MedicAlert, should be considered.

8. In patients with a history of anaphylaxis after ingesting a specific food who have specific IgE to that food, food avoidance is recommended. If these patients continue to have anaphylactic reactions despite avoiding the culprit food, further evaluation is required. Detailed food diaries, including specific ingredient lists of prepared meals resulting in anaphylaxis, should be obtained by the patient and reviewed by the physician. Details of other cofactors, such as relationship to exercise, should also be obtained. In many cases, given the complexity of food avoidance, the patient may still be inadvertently ingesting the allergenic food. Inadvertent ingestion of "hidden foods" due to improper or imprecise labeling or cross-contamination is a well-known pitfall in food avoidance. In some cases, patients may be reacting to cross-reacting foods. Proper identification of potential cross-reacting foods and additional avoidance of these foods would also be required. In other cases, the specific IgE detected to the culprit food may have detected sensitization or the presence

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of IgE that is not clinically relevant. Another unidentified food allergen or even idiopathic anaphylaxis may be the true cause of recurrent anaphylaxis.

In patients with persistent symptoms despite strict avoidance of the food, an oral food challenge could be considered to prove or disprove that the culprit food is indeed the causative allergen in the patient's recurrent symptoms. For patients with presumed food induced anaphylaxis, either an open or blinded food challenge could be performed cautiously.

In other IgE-mediated reactions to certain foods, the level of specific IgE or size of the wheal-and-flare reaction on PST in certain instances may add enough diagnostic and prognostic information to warrant food avoidance even in the absence of a history of anaphylaxis. Further evaluation is required in these patients without a history of food anaphylaxis who have been avoiding a food based on a diagnostic test yet continue to have symptoms. Given the complexity of food avoidance, the patient may still be inadvertently ingesting the allergenic food or cross-reacting food(s). In other patients without a history of food anaphylaxis, the diagnostic test, although highly predictive, may not be completely predictive and might give a false-positive result (eg, sensitization without clinical relevance). For example, in a limited number of foods and age groups, a given level of food-specific IgE may yield a 95% likelihood of a positive challenge to that food. However, 5% of patients with this same level of specific IgE may be able to tolerate the food without symptoms.

In patients without a history of food anaphylaxis who have been avoiding a food based on a diagnostic test, oral challenge to that food can also be performed. In these circumstances a blinded food challenge would typically be preferred. In these patients with food specific IgE who remain symptomatic despite avoidance, if the oral challenge result is positive, true food allergy is indicated and usually suggests that food avoidance has not been complete. Rarely, another food may be the causative factor and a food diary may help identify another culprit food allergen. In contrast, if the food challenge result is negative, despite the presence of food specific IgE, other causes of the symptoms should be sought and the negatively challenged food may be added back to the diet.

9. For most patients being evaluated for food allergy, there is neither a history of anaphylaxis nor a highly predictive, diagnostic test result. For these patients, further evaluation is typically required before diagnosing a food allergy simply based on a positive food specific IgE test result. Oral food challenges provide the most definitive means to diagnose an adverse reaction to food and are particularly useful in patients with episodic symptoms suggestive of food allergy. Although oral food challenges offer a more precise method for diagnosing food allergy, the complexities involved with oral food challenges may not be suitable for all clinical situations. In the evaluation of disorders with chronic symptoms where foods may be causal (atopic dermatitis, gastrointestinal symp-

toms), elimination of suspected causal foods may be undertaken to prove the concept that symptoms are diet responsive.

10. Oral food challenges provide the most definitive means to diagnose food allergy. These include open challenges or placebo-controlled blinded challenges in which the food or a placebo is masked in a carrier food or opaque capsules. Blinded challenges can be performed in a single-blind fashion, where the patient is unaware of the content of the test substances, or a double-blind fashion, where neither patient nor physician is aware of the content of the tested substances. Food challenges in patients with specific IgE have the potential to elicit serious reactions, including anaphylaxis. Therefore, these challenges should be performed in a controlled setting where emergency supplies for the treatment of anaphylaxis are readily available. The supplies in this setting are similar to those required for safe administration of allergen immunotherapy (see Practice Parameters for Practice Allergen Immunotherapy).

Open challenges may be preferred in certain situations. Since they are the simplest to perform, in cases where multiple foods are in question, foods tolerated in an open challenge can be excluded. Since the open challenge is most prone to bias, positive results must be viewed with caution. Foods that result in physiologically relevant symptoms can be further investigated in a blinded controlled challenge.

Single-blind challenges offer another method for food challenges. There are several advantages of single-blind food challenges. As opposed to an open challenge, the single-blind challenge helps eliminate patient bias. Single-blind challenges are technically easier to perform, since they do not involve an additional unblinded participant to prepare the placebo and active doses. Single-blind challenges have more flexibility in design, such as the addition of multiple initial placebo doses. This can be particularly helpful in patients in whom food reactions are not causally related to foods.

The double-blind placebo-controlled food challenge remains the gold standard for the diagnosis of food allergy. Although the single-blind challenge helps eliminate patient bias, the individual(s) performing the food challenge have the potential to be biased in the interpretation of the results. Nevertheless, double-blind placebo-controlled food challenges are usually not necessary in most clinical situations but remain an essential tool in food allergy research.

If a double-blind placebo-controlled food challenge result is positive, in most cases this indicates food allergy and food elimination is recommended. In contrast, a positive single-blind or open challenge does not necessarily indicate a true food allergy. In cases of a positive single-blind or open food challenge where doubt exists, a double-blind placebo-controlled challenge could be performed. Especially in cases where the positive challenge result is based on subjective symptoms (eg, pruritus, dyspnea), blinded challenges may need to be performed to help prove causality. In blinded challenges, technical limitations exist, such as quantity of food required for reaction, ability to mask food, and if the test

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food has been eliminated for 2 weeks before the challenge. (see "Diagnosis of Food Allergy" section).

A negative food challenge result indicates that the food-specific IgE is not clinically relevant and the tested food is not responsible for the patient's symptoms. In cases of negative results after blinded food challenges, particularly if foods are encapsulated, an open challenge with the food in its "natural" state may be required to ensure tolerability of the food.

11. Same as Annotation 7.

12. If a patient has no reaction on oral challenge to the incriminated food, the tested food is likely to be well tolerated. Nevertheless, to help exclude false-negative results, it has long been suggested to include an open feeding under supervision of a meal-size portion of the tested food prepared in its usual manner as a follow-up to any negative double-blind, placebo-controlled food challenge. It is also important to appreciate that certain preparation methods (canning, dehydration) may alter the allergens; hence, an open challenge with a meal-size portion of the food prepared in its natural state for consumption following a negative double-blind, placebo-controlled food challenge may be helpful.

13. Because of the poor positive predictive value of food-specific IgE tests, a positive test result does not always equate with clinical food allergy. Trial elimination diets are diagnostic and therapeutic procedures that may be used in patients with presumed food allergy. Elimination diets are particularly helpful in cases where several culprit allergens have been identified based on positive food specific IgE tests, since food challenges would need to be done individually to the multiple foods and can be time-consuming.

14. In patients who have symptoms suggestive of food allergy and specific IgE to a food or foods, improvement or resolution of symptoms following food elimination provides supporting evidence for causality. Nevertheless, a placebo effect should be considered. In cases where diagnostic uncertainty exists, a blinded food challenge may be performed to confirm a true food allergy.

15. Most children allergic to egg, milk, wheat, and/or soy lose their sensitivity within the first 3 to 5 years of life. Although food-specific IgE generally declines with the onset of clinical tolerance, many children who become clinically tolerant of a food may still have specific IgE. Food challenges may also be required to determine if tolerance has developed. Approximately 20% of children with peanut allergy may lose their sensitivity over time. Since peanut is a food frequently associated with anaphylaxis, care must be taken to select patients for peanut challenge.

## PREVALENCE AND EPIDEMIOLOGY

*Summary Statement 27.* The prevalence of food allergy as reported in double-blind studies is not as great as that perceived by the public. It varies between 2% and 5% in most studies, with definite ethnic differences. (B)

The prevalence of food allergy as perceived by the general public is undoubtedly much greater in the public's belief than

has been reported in double-blind studies. The Good Housekeeping Institute, on 2 separate occasions, published the incidence of allergy to food or food additives in mothers with young children as 27.5% and 17%, respectively.<sup>254,255</sup> In another study, 30% of the women reported that they or some member of their family had an allergy to a food product.<sup>256</sup> A British study using a food allergy questionnaire given to 15,000 households reported a 19.9% incidence of food allergy based on the overall response rate of 47%.<sup>257</sup> In a survey of 1,483 Dutch adults, 12.4% claimed to have food allergy. Yet, when food allergy was evaluated by double-blind, placebo-controlled food challenges, only 12 of 73 patients had a positive response, which indicated that there was a 2.4% prevalence of true food allergy, assuming that allergy was equal in participants and dropouts.<sup>258</sup> In a study of 457 adults who took part in a European community respiratory health survey in 1998, 58 adults (13%) claimed sensitization to at least one food allergen, whereas 99 adults (22%) reported illness to foods almost always.<sup>259</sup> However, only 7 subjects who reported illness to foods also had a positive skin prick test result to the same food. Thus, the prevalence of adverse food reactions associated with IgE-mediated food testing was less than 1.5%. The prevalence of seafood allergy in the United States as determined by a random telephone survey of 5,529 households with a census of 14,948 individuals was reported at 5.9%.<sup>260</sup> Since little agreement exists between self-reported perceived illness to foods known to contain the food allergen of interest and positive skin prick test results, it is suggested that most reactions are not due to IgE-mediated food allergies.<sup>259, 260</sup>

*Summary Statement 28.* The prevalence of food allergy is higher in certain subgroups, such as individuals with atopic dermatitis, certain pollen sensitivities, or latex sensitivity. (B)

In general, the prevalence of food allergy in the pediatric population is greater than in adults. In a prospective study of 480 newborns followed up in a general pediatric practice through their third birthday, parents reported that 28% of the infants had food allergy, mainly in their first year of life. When oral challenges were performed in this pediatric population, the confirmed incidence was 8%.<sup>261,262</sup> Cow's milk allergy was confirmed in 2.27% to 2.5% in the first 1 to 2 years of life.<sup>261,262</sup> Prevalence is higher in children with moderate to severe atopic dermatitis, since up to one third of patients experience skin symptoms that are provoked by foods.<sup>262</sup> In fact, the more severe the atopic dermatitis, the more likely it is that the patient has food allergy or that a food contributes to the atopic dermatitis.<sup>263</sup>

### *Cultural, Food-Specific, and Disease-Specific Differences*

In 1,141 randomly selected young adults in Australia, 1.3% had a probable IgE-mediated food allergy, with less than 0.27% for wheat, 0.09% each for cow's milk and egg, 0.53% for shrimp, and 0.61% for peanut.<sup>264</sup> Those with probable IgE-mediated peanut and shrimp allergy were significantly more likely to have recurrent asthma and physician-diagnosed asthma. Wheezing and a history of eczema were also

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associated with peanut allergy, whereas nasal allergies were associated with shrimp allergy.<sup>264</sup>

In another study that used the European Community Respiratory Health Survey, 17,280 adults were evaluated in different countries, and 12% reported food allergy or intolerance.<sup>265</sup> The range was 4.6% in Spain to 19.1% in Australia. There was a higher likelihood for food allergy or intolerance in women who wheezed or had a history of asthma in the past 12 months or were currently taking oral medications. In Italy and Belgium adverse reactions to fruit were most commonly reported. Those from Scandinavia or Germany reported more breathlessness to tree nuts, whereas peanuts were the predominant culprit in the United States.<sup>265</sup> Ethnic and cultural differences must be considered in all studies of food allergies.

In a French study of 33,110 persons who answered a questionnaire, the estimated prevalence of food allergy was 3.24%, of which 57% presented with a history of other atopic diseases.<sup>58</sup> Food allergy lasted more than 7 years in 91% of the adults. The most frequently reported food allergens were the Rosacea family (14%), vegetables (9%), milk (8%), crustaceans (8%), fruit cross-reacting to latex (5%), egg (4%), tree nuts (3%), and peanuts (1%). Sensitization to pollen was significantly correlated with angioedema, asthma, rhinitis, and fruit allergy. Food allergy was more frequent in patients who had latex allergy. Atopic dermatitis was the main manifestation of food allergy in subjects younger than 6 years; asthma in subjects between 4 and 6 years of age; and anaphylactic shock in adults older than 30 years. Anaphylactic shock was correlated with alcohol or nonsteroidal anti-inflammatory drug intake.<sup>58</sup>

#### *Food-Specific Considerations*

Population-based investigations of cow's milk allergy confirmed by challenge in infants and young children reported a 1.9% to 3.2% prevalence.<sup>6,7,266, 267</sup> The cumulative prevalence of egg allergy from birth to age 2.5 years is 2% to 6%.<sup>268</sup> Population-based questionnaires estimate tree nut allergy to be 0.5%<sup>25</sup> and peanut allergy to be 0.5% to 0.6%,<sup>25,269</sup> which amount to approximately 1.5 million people in the United States.<sup>25,270</sup> A single study showed a strong genetic influence for peanut allergy, with a concordance rate of 64% in identical twins compared with 7% in fraternal twins.<sup>271</sup> Roasting of peanuts apparently confers more resistance to digestion and greater allergenicity than frying or boiling.<sup>272,273</sup> This finding might partly account for the relatively low prevalence of peanut allergy in China, where boiled peanuts are widely consumed.

#### *Deaths Secondary to Food Allergy*

In a retrospective analysis of 13 million children 0 to 15 years old in Britain, 8 children died of food allergy during a 10-year period.<sup>274</sup> Milk caused 4 of those deaths. No child younger than 13 years died of peanut allergy. In an analysis of the last 2 years of this study, there were 6 near-fatal reactions (none caused by peanut) and 49 severe reactions (10 caused by peanuts), yielding incidences of 0.02 and 0.19, respectively,

per 100,000 children. Coexisting asthma strongly correlated with a severe reaction. Five percent of the childhood population was reported to have food allergy. Based on these data, the risk of fatality for a food allergic child is approximately 1:800,000 per year.<sup>274</sup> Data are lacking regarding the risk of fatal food allergic reactions in adults. In summary, according to a recent review, food allergy affects up to 6% to 7% of children younger than 3 years and approximately 4% of the general population. Furthermore, the prevalence appears to be increasing.<sup>275</sup>

#### **NATURAL HISTORY OF FOOD ALLERGY**

*Summary Statement 29.* Although sensitivity to most food allergens such as milk, wheat, and eggs tends to remit in late childhood, persistence of certain food allergies such as peanut, tree nut, and seafood most commonly continues throughout one's lifetime. (B)

The most common food allergens in children in the United States are egg, milk, peanut, soy, and wheat. In a prospective study of adverse reactions to foods in infants, 80% of confirmed symptoms developed in the first year of life.<sup>261</sup> Sensitivity of some food allergens (especially cow's milk, wheat, and egg) tends to remit in late childhood. For example, most infants who are sensitive to cow's milk lose their sensitivity by 2 years of age.<sup>276</sup> However, persistence of childhood food allergies is common with certain foods, especially to peanuts, tree nuts, and seafood.<sup>277</sup> Children diagnosed as having food allergy after 3 years of age are less likely to lose this sensitivity.<sup>27,261</sup> Furthermore, children who develop one IgE-mediated food allergy have an increased risk of developing allergies to other foods and inhalant allergens.<sup>19</sup>

The notion that peanut allergy is permanent was derived from studies on school-aged children.<sup>27</sup> However, several studies that followed up young children with peanut allergy to school age (ie, 5 years) document a resolution rate of approximately 20%.<sup>28,29,278</sup> The features that are favorable for a child having outgrown the allergy include small (<6 mm to negative) skin test results, a period of 2 or more years with no reactions, a history of only mild reactions, and few additional atopic diseases. Tolerance is also associated with low levels of peanut-specific serum IgE antibody. More than 50% of school-aged children with specific IgE to peanut less than 5 kIU/L had negative oral food challenges.<sup>279,280</sup> Long-term follow-up on individuals who outgrew their peanut allergy has not been published. It appears that patients may rarely redevelop this allergy.<sup>30</sup> This phenomenon has thus far been described in persons who originally had not routinely ingested peanut following negative oral food challenges, so families must be warned about this potential.

Small amounts of egg may be tolerated when egg is used as an ingredient in the preparation of foods. Although most children will outgrow their egg allergy by school age and lose their positive skin test reactivity, a clue to continued sensitivity is the persistence of a positive skin test result.<sup>19</sup>

In a population-based study, there was an incremental loss of milk hypersensitivity in children when followed up for 3

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years; most children lose their milk allergy by this time, with 50% losing the sensitivity by 1 year of age, 70% by 2 years of age, and 85% by 3 years of age.<sup>7,263</sup> A negative skin prick test result at 1 year of age had a good prognostic value, since all such children lost their milk sensitivity by 3 years of age. Yet, 25% of those who had positive skin test results remain milk allergic at the end of their third year.<sup>7</sup> By contrast, in studies of children under the care of allergists, which may represent a more severe form of milk allergy, there was a much greater percentage of persistence of milk allergy at the completion of the study.<sup>19</sup> Typically, in children, adverse reactions to fruits, vegetables, and cereal grains are short lived and may represent irritant or intolerant reactions rather than true allergies, but that is not necessarily true in adults.<sup>1,19,281-283</sup> Allergies to tree nuts, fish, shellfish, and seeds are usually not outgrown.<sup>45,275</sup> In one study of 26 patients with tree nut allergy, none of them lost this sensitivity after a 2- to 5-year follow-up period. In a study of 32 children with fish allergy, 5 seemed to lose their allergy.<sup>282</sup> In a report that described 11 patients with shrimp allergy during a 2-year period, there was no significant change in allergen specific antibody levels during this period.<sup>283</sup> In addition, foods that are not tolerated when eaten raw may be ingested without difficulty when they are completely cooked or autoclaved<sup>150,151</sup> and vice versa.

*Summary Statement 30.* The natural history of specific foods varies considerably. (C)

It is understandable that a discussion of the natural history of food allergy should include children, since food allergies are acquired at an early age and may persist into adulthood. The most common food sensitivities in adults include peanut, fish, shellfish, and tree nuts, most of which have persisted since childhood.

One study in adults looked at the effect of avoidance on confirmed food sensitivity.<sup>284</sup> Twenty-three adults with allergies to a variety of foods underwent baseline double-blind, placebo-controlled food challenges, in which clear reactions occurred in 10 patients of a total of 13 foods that were identified. After strict dietary avoidance of the offending food for 1 to 2 years, they were rechallenged. Five (38%) of the 13 previously offending foods were well tolerated, including milk in 2 patients and wheat, egg, and tomato in 1 patient each. The 2 patients with nut allergy continued to react, as did 2 patients with milk allergy and 1 patient each with allergies to rice, garlic, and potato.

It is still not understood why some individuals outgrow food sensitivity and others do not. A positive skin test result or serum test for food specific IgE does not necessarily mean that food allergy has not been outgrown, since these tests can remain positive even when the patient is no longer clinically sensitive. A skin test result that becomes negative, however, is more likely to be associated with loss of clinical sensitivity. An oral food challenge under the direction of a specialist usually will be necessary to prove that food allergy is no longer present. Although there is a widespread belief that strict avoidance increases the chance of outgrowing the food

allergy and may hasten the process, few data are available to support this notion.<sup>284,285</sup> Food allergy may be the first manifestation of allergy in early childhood as a harbinger of additional food allergies and inhalant allergens. Early recognition has practical immediate value, as well as the potential for improving our understanding of the natural history of food allergy.

The mechanism involved in abrogation of food sensitivity is unknown. It could be associated with gut maturation and accompanying immune maturation and decreased gut permeability. Tolerance can also be associated with specific regions on proteins (epitopes) to which IgE binds. With egg and milk, for example, persistence to allergy seems to be associated with IgE binding to epitopes that are composed of sequential amino acids compared with epitopes that are dependent on folding confirmation.<sup>286,287</sup>

## **RISK FACTORS AND PREVENTION OF FOOD ALLERGY**

*Summary Statement 31.* The rate of observed food allergy in children born to families with parental asthma was approximately 4-fold higher than expected when compared with an unselected population. (B)

Like other medical disorders, both genetic and environmental influences affect the phenotypic expression of food allergy. Studies to identify risk factors for atopy are often aimed toward infants and children, because potential prevention strategies are greatest in this group. Most studies have considered asthma, allergic rhinitis, or atopic dermatitis rather than food allergy.<sup>288</sup> In regard to genetic influences, male sex in children appears to be a risk factor for atopic disease.<sup>289</sup> Linkage studies have identified a number of chromosomal regions that contain genes for HLA class II and cytokines that influence atopic disease (IgE, asthma, rhinitis).<sup>290-293</sup> Genetics studies of food allergy are few. For peanut allergy, the influence of HLA class II genes has been demonstrated.<sup>294</sup>

Although currently no genetic tests are available to identify persons at risk of food allergy, a family history of atopy, or food allergy in particular, appears to be the best current screening test.<sup>295-297</sup> The rate of observed food allergy in children born to families with a strong parental (50%) or biparental (50%) history of atopy was approximately 4-fold higher than expected when compared with an unselected population.<sup>298</sup> For peanut allergy in particular, a significantly higher concordance rate for this allergy exists among monozygotic twins (64%) compared with dizygotic twins (7%); the rate of allergy in a sibling of an affected person is approximately 10-fold higher than the rate in the general population.<sup>271</sup> Thus, a family history of atopy, possibly of a specific food allergy in particular, is the best current screening test to identify an individual at risk of food allergy.

Food allergy is a complex trait influenced not only by polygenetic inheritance but also by environmental factors. Major environmental factors that have been identified to influence atopic disease in children, investigated primarily

for respiratory disease, include a protective effect of breastfeeding<sup>299–301</sup> and detrimental effect of exposure to environmental tobacco smoke.<sup>302</sup> In regard to food allergy, numerous possible risk factors have been investigated or presumed to be influential, with variable and often controversial results. Factors under consideration include maternal diet during pregnancy and breastfeeding, age at solid food exposure, age at introduction of allergenic foods, exposure to indoor and outdoor allergens or pollutants, birth order, race/ethnicity, cesarean section, maternal age, and others.<sup>289,296,303–307</sup> For example, soy formula feeding (odds ratio, 2 to 6) and complaint of rash consistent with atopic dermatitis (odds ratio, 2.6 to 5.2) were independently associated with development of peanut allergy (as was use of peanut-containing topical lotions, although these are not used in the United States), but maternal diet was not associated.<sup>308</sup> The newborn child, particularly one genetically predisposed to atopic disease, is often considered vulnerable to becoming sensitized to foods based on an “immature” immune system biased toward T<sub>H</sub>2 responses,<sup>308</sup> increased gut permeability, and other aspects of digestive immaturity that may promote systemic sensitization.<sup>309–311</sup> In one prospective study, these hypotheses are possibly demonstrated by a direct linear relationship between the number of solid foods introduced into the diet by 4 months of age and the subsequent development of atopic dermatitis.<sup>312</sup>

Microbial agents may also have an important effect on atopic sensitization and induction of tolerance.<sup>313</sup> Microbial exposure of infants during the neonatal period may influence postnatal maturation of the T-cell system toward the T<sub>H</sub>1 cell line. Estonian and Swedish children exhibit qualitative differences in intestinal microflora in early life.<sup>314–317</sup> In Estonia, the typical microflora includes more lactobacilli and fewer clostridia, which has been associated with a lower prevalence of atopic disease. Infants with milk allergy and atopic dermatitis have exhibited milder symptoms and fewer markers of intestinal inflammation when milk formula was fortified with lactobacilli,<sup>315</sup> suggesting a salutary effect of adding probiotics to infant formula. All of these observations have led to increasing efforts to prevent atopy and food allergy through alteration of the environment, usually directed to persons “at risk.”

*Summary Statement 32.* Food allergy prevention strategies include breastfeeding, maternal dietary restrictions during breastfeeding, delayed introduction of solid foods, delayed introduction of particular allergenic foods, and the use of supplemental infant formulae that are hypoallergenic or of reduced allergenicity. The effectiveness of these strategies for safeguarding against the development of food allergies has not been established. (B)

The apparent increase in atopic disease, including food allergy, has focused attention toward prevention strategies. Promotion of breastfeeding and avoidance of tobacco smoke are general consensus recommendations, although the data are not conclusive at this time.<sup>295</sup> The Committee on Nutrition of the American Academy of Pediatrics (AAP)<sup>296</sup> and a joint

committee from the European Society for Pediatric Allergology and Clinical Immunology (ESPACI) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition<sup>318</sup> presented recommendations for the prevention of food allergy in “at risk” infants. The provisional statements (some by consensus) from the AAP have a stricter interpretation of “at risk” infants, as well as making specific maternal dietary recommendations during breastfeeding and steps for the addition of supplementary foods. The ESPACI/ESPGHAN committee concluded that there was a lack of convincing studies to make such broad recommendations. The AAP specified that their statements did not constitute an exclusive recommendation or an absolute standard of medical care (Tables 3 and 4).

Although breastfeeding is recommended<sup>296,318</sup> and has been associated with protection against development of atopic dermatitis,<sup>299–300</sup> it has not consistently and convincingly been shown to safeguard against development of food allergy (see “Mucosal Immune Responses Induced by Foods” section).<sup>87</sup> The utility of dietary avoidance (which does not exclude essential foods) by the mother during pregnancy for prevention of food allergy, particularly during the last trimester, has not clearly been established.<sup>319</sup> The comparative efficacy of “hypoallergenic” or “reduced allergenic” infant formula for supplementation or weaning in infants at risk for atopy is under study.<sup>320</sup> Using probiotics to promote non-T<sub>H</sub>2 responses is also under study.<sup>321</sup> A secondary preventive technique concerns workers exposed to food allergens by inhalation. Removal of these workers from exposure may prevent subsequent development of food allergy.<sup>24,322–325</sup>

Table 3. Recommendations for Prevention of Allergy by the American Academy of Pediatrics Committee on Nutrition, 2000

Infants at high risk of developing allergy, identified by a strong (biparental, parent, and sibling) family history of allergy may benefit from exclusive breastfeeding or a hypoallergenic formula or possibly a partial hydrolysate formula. Conclusive studies are not yet available to permit definitive recommendations. However, the following recommendations seem reasonable at this time:

- Breastfeeding mothers should continue breastfeeding for the first year of life or longer. During this time, for infants at risk, hypoallergenic formulas can be used to supplement breastfeeding. Mothers should eliminate peanuts and tree nuts (eg, walnuts) and consider eliminating eggs, cow’s milk, fish, and perhaps other foods from their diets while breastfeeding. Solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age.
- No maternal dietary restrictions during pregnancy are necessary with the possible exception of excluding peanuts.
- Breastfeeding mothers on a restricted diet should consider the use of supplemental minerals (calcium) and vitamins.



Table 4. Recommendations for Prevention of Allergy by the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), 1999

Infants at high risk of developing allergy, identified by a strong (biparental, parent, and sibling) family history of allergy may benefit from exclusive breastfeeding or a hypoallergenic formula or possibly a partial hydrolysate formula. Conclusive studies are not yet available to permit definitive recommendations. However, the following recommendations seem reasonable at this time:

- Exclusive breastfeeding during the first 4–6 months of life might greatly reduce the incidence of allergic manifestations and is strongly recommended.
- Supplementary foods should not be introduced before the fifth month of life.
- In bottle-fed infants with a documented hereditary atopic risk (affected parent or sibling), the exclusive feeding of a formula with a confirmed reduced allergenicity is recommended because it can reduce the incidence of adverse reactions to food, especially to cow's milk protein.
- More studies comparing the preventive effects of formulas that have highly reduced allergenicity with formulas that have moderately reduced allergenicity are needed.
- Dietary products used for preventive purposes in infancy need to be evaluated carefully with respect to their preventive and nutritional effects in appropriate clinical studies.
- There is no conclusive evidence to support the use of formulas with reduced allergenicity for preventive purposes in healthy infants without a family history of allergic disease.

## CROSS-REACTIVITY OF FOOD ALLERGENS

*Summary Statement 33.* Recent studies with molecular biological techniques have characterized a variety of cross-

reacting allergens among foods: (1) tropomyosins in crustaceans (shrimp, lobster, crab, crawfish) arachnids (house dust mites), insects (cockroaches), and mollusks (squid); (2) parvalbumins in fish; (3) bovine IgG in beef, lamb, venison, and milk; (4) lipid transfer protein LTP in peach, apricot, plum, apple, cereals, peanut, walnut, pistachio, broccoli, carrot, celery, tomato, melon, kiwi, and beer; (5) profilin in pear, cherry, plums, celery, birch pollen, zucchini, and latex; (6) class I chitinases in latex, banana, avocado, kiwi, chestnut, papaya, tomato, cherimoya, passion fruit, mango, and wheat; and (7) phenylcoumarin benzylic ether reductase and isoflavonoid reductase in birch pollen, apple, peach, orange, lychee fruit strawberry, persimmon, zucchini, and carrot. (C)

Recent studies with molecular biologic techniques have characterized a variety of cross-reacting allergens among different classes of foods (Tables 5 and 6).<sup>326</sup> Panallergens, such as tropomyosin, are proteins in food, pollen, or plants that contain homologous IgE-binding epitopes across species. Allergenic tropomyosins are found in invertebrates such as crustaceans (shrimp, lobster, crab, crawfish), arachnids (house dust mites), insects (cockroaches), and mollusks (eg, oysters, squid), whereas mammalian tropomyosins are non-allergenic.<sup>326,327</sup> Paralbumins are another example of a panallergen, accounting for cross-reactivity among fish.

Bovine IgG has been identified as a major cross-reactive vertebrate meat allergen in beef, lamb, venison, and milk.<sup>328</sup>

Lipid transfer protein (LTP) is a panallergen in plant-derived foods, including the fruit of the Rosaceae and subfamilies of Prunoideae (peach, apricot, plum) and Pomoideae (apple). In addition, IgE antibodies to Rosaceae LTPs react to a broad range of vegetable foods, including almond, cereals, peanut, walnut, pistachio, broccoli, carrot, celery, tomato, melon, and kiwi,<sup>329</sup> and beer.<sup>330</sup>

Table 5. Classification of Foods From Animal Sources

Mollusks	Crustaceans		Fish
Abalone	Crab	Sturgeon	Sole
Mussel	Crawfish	Hake	Pike
Oyster	Lobster	Anchovy	Flounder
Scallop	Shrimp	Sardine	Drum
Clam		Herring	Mullet
Squid	<b>Reptiles</b>	Haddock	Trout
	Turtle	Bass	Mackerel
<b>Amphibians</b>		Pompano	Tuna
Frog	<b>Birds</b>	Salmon	Bluefish
	Chicken	Whitefish	Snapper
<b>Mammals</b>	Duck	Scrod	Sunfish
Beef	Goose	Shad	Swordfish
Pork	Turkey	Eel	Grouper
Goat	Guinea hen	Carp	Plaice
Mutton (lamb)	Squab	Codfish	
Venison	Pheasant	Halibut	
Horsemeat	Partridge	Catfish	
Rabbit	Grouse		
Squirrel			

Table 6. Classification of Foods From Plant Sources\*

<b>Grain family</b> Wheat Graham flour Gluten flour Bran Wheat germ Rye Barley Malt Corn Oats Rice Wild rice Sorghum Cane	<b>Tea family</b> Tea	<b>Birch family</b> Hazelnut	<b>Mint family</b> Mint Peppermint Spearmint Thyme Sage Marjoram Savory
<b>Mustard family</b> Mustard Cabbage Cauliflower Broccoli Brussels sprouts Turnip Rutabaga Kale Collard Celery cabbage Kohlrabi Radish Horseradish Watercress	<b>Pedalium family</b> Sesame seed	<b>Mulberry family</b> Mulberry Fig Hop Breadfruit	<b>Gourd family</b> Pumpkin Squash Cucumber Cantaloupe Muskmelon Honeydew melon Persian melon Casaba Watermelon
<b>Ginger family</b> Ginger Turmeric Cardamon	<b>Arum family</b> Taro	<b>Maple family</b> Maple syrup	<b>Rosaceae/apple family</b> Apple Pear Quince
<b>Pine family</b> Juniper Pine nut	<b>Buckwheat family</b> Buckwheat Rhubarb	<b>Pomegranate family</b> Pomegranate	<b>Poppy family</b> Poppy seed
<b>Orchid family</b> Vanilla	<b>Potato/nightshade</b> Potato Tomato Eggplant Red pepper Green pepper Chili pepper	<b>Ebony family</b> Persimmon	<b>Rosaceae/plum family</b> Plum Prune Cherry Peach Apricot Nectarine Almond
<b>Madder family</b> Coffee	<b>Gooseberry family</b> Gooseberry Currant	<b>Banana family</b> Banana Plantain	<b>Laurel family</b> Avocado Cinnamon Bay leaf
<b>Olive family</b> Green olive Ripe olive Red pepper Green pepper Bell pepper Chili Tabasco Pimento	<b>Honeysuckle family</b> Elderberry	<b>Grape family</b> Grape Raisin	<b>Walnut family</b> English walnut Black walnut Butternut Hickory nut Pecan
<b>Lily family</b> Asparagus Onion Garlic Leek Chive Aloe	<b>Citrus family</b> Orange Grapefruit Lemon Lime Tangerine Kumquat	<b>Myrtle family</b> Allspice Cloves	<b>Cashew family</b> Cashew Pistachio Mango
<b>Goosefoot family</b> Beet Spinach Swiss chard	<b>Pineapple family</b> Pineapple	<b>Legume family</b> Navy bean Kidney bean Lima bean String bean Soybean Lentil Black-eyed peas Pea Peanut Licorice Acacia Senna	<b>Beech family</b> Beechnut Chestnut
	<b>Papaw family</b> Papaya	<b>Morning glory family</b> Sweet potato Yam	<b>Fungi family</b> Mushroom Yeast
	<b>Parsley family</b> Parsley Parsnip Carrot Celery Celeriac Caraway Anise Dill Coriander Fennel Cumin	<b>Sunflower family</b> Jerusalem artichoke Sunflower seed	<b>Sterculia family</b> Cacao Chocolate (processed from cacao)
	<b>Heath family</b> Cranberry Blueberry	<b>Pepper family</b> Black pepper	
	<b>Legythis family</b> Brazil nut	<b>Nutmeg family</b> Nutmeg	
	<b>Composite family</b> Leaf lettuce Head lettuce Endive Escarole Artichoke Dandelion Chicory Guava		

\*Reprinted with permission from Metcalfe DD. The diagnosis of food allergy: theory and practice. In: Spector SL, ed. *Provocative Challenge Procedures: Background and Methodology*. Mt Kisco, NY: Futura Publishing Co; 1989.

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Profilin is a panallergen that is recognized by approximately 20% of patients allergic to plant food (pear, Pyre 4; cherry, Pru av 4; and celery, Api g 4) and birch pollen (Bet v 2)<sup>331</sup> and zucchini.<sup>332</sup> Profilin is a low-molecular-weight protein involved in the organization of the mammalian and protozoan cytoskeleton and in signal transduction.<sup>333</sup> Various *Hevea brasiliensis* latex profilins are cross-reactive allergens of latex, plant foods, and pollen.<sup>334,335</sup>

Class I chitinases are other panallergens responsible for many of the cross-reactions in the latex-fruit syndrome, including avocado, banana, chestnut, kiwi, papaya, tomato, cherimoya, passion fruit, mango, and wheat.<sup>336</sup>

Phenylcoumarin benzylic ether reductase and isoflavonoid reductases are newly discovered classes of cross-reacting allergens in birch pollen and apple, peach, orange, lychee fruit, strawberry, persimmon, zucchini, and carrot.<sup>337</sup>

*Summary Statement 34.* In vitro cross-reactivity to multiple shared carbohydrate food allergens is common, but clinical correlation of the cross-reactivity is variable. (C)

Cross-reactive carbohydrate determinants are commonly found in many foods, but they are usually of little clinical relevance.<sup>4</sup>

#### *Cow's Milk*

*Summary Statement 35.* Cow's milk allergy is a common disease of infancy and childhood. Goat's milk cross-reacts with cow's milk. Ninety percent of cow's milk allergic patients will react to goat and/or sheep's milk. (A)

Cow's milk allergy is a common disease of infancy and childhood. Most patients allergic to cow's milk cannot tolerate milk from other mammals (goat),<sup>10</sup> except mare's milk.<sup>338</sup> Ten percent of patients with cow's milk allergy may have a reaction to beef.<sup>339</sup> A variety of milk substitutes have been evaluated with mixed results.<sup>340-347</sup> Only extensively hydrolyzed and amino acid-derived formulas have been shown to be nonallergenic.<sup>344-347</sup>

#### *Hen's Egg*

*Summary Statement 36.* Hen's egg allergens cross-react with certain avian egg allergens, but the clinical implications of such cross-reactivity are unclear. (B)

Extensive in vitro IgE inhibition studies have demonstrated identical patterns of cross-reactivity between bird dander and hen's egg proteins, livetins being the major cross-reacting antigens.<sup>348,349</sup> Chicken albumin (Gal d 5) is a partially labile allergen that may cause respiratory and food allergy symptoms in patients with the bird-egg syndrome.<sup>350</sup>

Livetins are the major cross-reacting antigens between hen's egg protein and bird dander.<sup>345,349</sup> Various bird egg whites (turkey, duck, goose, and seagull) contain proteins that cross-react with allergens in hen's egg white.<sup>350-352</sup> Several proteins that cross-react with allergens in hen's egg white are also detected in egg yolk, hen sera, and meat.<sup>350</sup>

#### *Soy*

*Summary Statement 37.* In vitro cross-reactivity between soybean and other legume foods is extensive, but oral food

challenges demonstrate that clinical cross-reactivity to other legumes in soy bean sensitive children is uncommon and generally transitory. (B)

Although extensive cross-reactivity among the legume foods (peanut, soybean, lima beans, pea, garbanzo bean, green bean) has been demonstrated by in vitro IgE inhibition testing, results of oral food challenges demonstrate that clinically important cross-reactivity to legumes in children is uncommon and generally transitory.<sup>353-356</sup> Therefore, clinical hypersensitivity to one legume does not routinely warrant dietary elimination of all legumes.<sup>357</sup>

#### *Peanut*

*Summary Statement 38.* Patients with peanut allergy generally tolerate other beans (95%), even soy. Evaluation of legume allergy in a patient with peanut allergy should be individualized, but avoidance of all legumes is generally unwarranted. (B)

Peanut and soybean are members of the legume family and share several common antigenic fractions. Patients allergic to one of these foods have serum IgE antibodies that immunologically cross-react with other legumes. Nevertheless, ingestion of other legumes generally does not induce an allergic reaction, suggesting that the cross-reacting antibodies in this case are not clinically relevant.<sup>357</sup>

Peanut allergic patients do not generally have clinically relevant reactions to other legumes.<sup>358-360</sup> However, there is a high risk of cross-reactions with lupin flour antigens.<sup>360</sup> *Lupinus albus*, in the form of flour or bran, is used as a wheat flour additive in Europe, and Australia. Double-blind oral challenge tests were performed with lupin flour and peanut in 8 patients. Challenge test responses were positive in 7 of 8 subjects at the same doses as peanut. The homolog of Ara h 2, a major peanut allergen, is also present in lupine seeds. The risk of crossed peanut-lupine allergy is high, contrary to the low risk to other legumes.<sup>361</sup>

#### *Fish*

*Summary Statement 39.* There is significant cross-reaction between different species of fish, including salt and fresh water. Significant in vitro and clinical cross-reactivity between fish species has been demonstrated. (B)

Allergic reactions to fish are common in many areas of the world where fish is a major source of protein.<sup>362</sup> There is significant cross-reactivity between different types of fish, but these types of investigation have been limited. Cod, mackerel, herring, and plaice share a common antigenic structure,<sup>46,363</sup> which corresponds to sarcoplasmic parvalbumins.<sup>364</sup> Some fish-sensitive patients have specific IgE antibody to fish gelatin (type I collagen).<sup>365</sup> Negating the notion that there is a difference in salt water and fresh water fish allergy is the evidence that species that live in both environments have cross-reacting parvalbumin (eg, salmon, trout, perch, carp, and eel).<sup>366,367</sup>

In vitro serum IgE inhibition testing has demonstrated significant cross-reactivity among pollack, salmon, trout, and

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tuna, as well as between mackerel and anchovy.<sup>368</sup> Skin prick and/or in vitro-positive adults with a history of an immediate reaction following fish ingestion have been challenged with 17 different fish species using double-blind, placebo-controlled food challenges. Of the total of 19 double-blind, placebo-controlled fish challenges performed, 14 challenges (74%) resulted in the induction of objective signs that were consistent with an IgE-mediated response. The most common sign observed was emesis (37%); the most prevalent symptom reported was itching of the mouth or throat (84%). Three patients reacted to at least 3 fish species and 1 patient reacted to 2 species tested. Based on a positive challenge result, predictive accuracy for skin prick testing was 84% and 78% for serum specific IgE.<sup>361</sup> Other studies have demonstrated similar findings.<sup>368,369</sup> Fish allergic patients may be clinically sensitive to more than one species of fish. Skin test reactivity to fish by itself is not an adequate criterion for confirmation of clinically relevant fish allergy. Therefore, fish allergic patients with a specific IgE to any fish should exercise caution when eating fish of another species until lack of reactivity to that species can be demonstrated.<sup>368</sup>

#### *Shellfish*

*Summary Statement 40.* Crustaceans, such as shrimp, crab, crawfish, and lobster, are a frequent cause of adverse food reactions, including life-threatening anaphylaxis. There is considerable risk of cross-reactivity between crustaceans. Less well defined is cross-reactivity between mollusk and crustaceans. (C)

The panallergen invertebrate tropomyosin is highly homologous in the *Crustacea*, such as shrimp, crab, and lobster; in mollusks, such as oyster, scallop, and squid; in fish muscle parasites, such as *Anisakis*; and in insects, such as cockroach, grasshopper, storage mite, and dust mites.<sup>48</sup> Vertebrate (mammalian) tropomyosins are nonallergenic.<sup>326</sup> Crustaceans, such as shrimp, crab, crawfish, and lobster, are a frequent cause of adverse food reactions, including life-threatening anaphylaxis. Patients with proven allergy to crustacean species should be cautious about ingestion of other crustaceans. Cross-reactivity between mollusks and crustaceans is not well defined.<sup>48,50</sup>

In one study evaluating sera from 31 shrimp-sensitive individuals, 77% reacted to extracts of both white shrimp and brown shrimp; 1 reacted only to white shrimp and 2 only to brown shrimp, indicating there are isolated instances of species specific shrimp allergens that do not cross-react.<sup>370</sup> Seafood allergens aerosolized during food preparation are a source of potential respiratory and contact allergens. A well-documented case of a restaurant seafood handler with IgE-mediated occupational asthma and contact urticaria to both shrimp and scallops, with demonstrated in vitro cross-reactivity, has been described.<sup>129</sup>

*Summary Statement 41.* Crustaceans do not cross-react with vertebrate fish. (B)

Contrary to public perception, crustaceans (shrimp, crab, and lobster) do not cross-react with vertebrate fish.

*Summary Statement 42.* Seafood allergy is not associated with increased risk of anaphylactoid reaction from radiocontrast media. (F)

Despite the common belief that individuals with seafood allergy have a higher risk of radiocontrast media reactions, no convincing data exist to support this, and it has no theoretical basis. Individuals with seafood allergy have specific IgE directed against specific proteins, not iodide. The mechanism for anaphylactoid reactions to radiocontrast media is not due to the iodide but to physiochemical properties of the radiocontrast media complex itself. In fact, low-ionic radiocontrast media have a lower incidence of reactions despite containing more iodide per dissolved particle.<sup>371</sup>

A surveillance study of factors associated with adverse reaction to contrast media infusion described an association of "seafood allergy" with greater rate of adverse reaction. This study had several methodologic weaknesses: (1) no corroborative testing was performed to confirm true seafood allergy, and subjects were classified as having "seafood allergy" by self-report; (2) self-reported "allergy" to other foods was also more common in individuals who had contrast media reactions: a reaction rate of 15% was found among those with "allergy" to seafood or shellfish compared with 14.6% among patients with "allergy" to egg, milk, chocolate; and (3) patients who experienced anaphylactoid reaction were not distinguished from those who experienced chemotoxic or other adverse reactions. For these reasons, a clear association between seafood allergy and greater risk for anaphylactoid reaction from contrast infusion was not established by these data.<sup>372</sup>

#### *Wheat*

*Summary Statement 43.* Patients with wheat allergy alone show extensive in vitro cross-reactivity to other grains that is not reflected clinically. Therefore, elimination of all grains from the diet (ie, wheat, rye, barley, oats, rice, corn) of a patient with grain allergy is clinically unwarranted and may be nutritionally detrimental. (B)

Patients with wheat allergy alone showed extensive in vitro cross-reactivity to other grains that is not reflected clinically. Of 145 patients with positive skin prick test responses to one or more cereal grains (wheat, rye, barley, oat, rice, corn), only 21% had symptoms in response to double-blind, placebo-controlled challenges, and most of these (80%) occurred in response to only one cereal grain (76% of positive responses were to wheat).<sup>42</sup>

Therefore, elimination of all grains from the diet (ie, wheat, rye, barley, oats, rice, corn) of a patient with a single grain allergy is clinically unwarranted and may be nutritionally detrimental.<sup>42</sup> In wheat-dependent, exercise-induced asthma, the major allergen associated with these reactions is identified as an  $\omega$ -5 gliadin. A study shows that gamma-70 and gamma-35 secalins in rye and gamma-3 hordein in barley cross-react with  $\omega$ -5 gliadin, suggesting that rye and barley may elicit symptoms in patients with wheat-dependent exercise-induced asthma.<sup>373</sup>

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### Tree Nuts

*Summary Statement 44.* Evaluation of cross-reactivity among tree nuts (walnut, hazelnut, Brazil nut, pecan) is characterized by shared allergens among tree nuts and between tree nuts and other plant-derived foods and pollen. Clinical reactions to tree nuts can be severe and potentially fatal and can occur from the first exposure to a tree nut in patients allergic to other tree nuts. In most cases, elimination of all tree nuts from the diet is appropriate. (C)

Evaluation of cross-reactivity among tree nuts (walnut, hazel nut, Brazil nut, pecan) is characterized by shared allergens among tree nuts and other plant-derived foods and pollens,<sup>48</sup> such as vicilin storage proteins in cashew,<sup>374</sup> English walnut,<sup>375</sup> and a variety of seeds. Clinical reactions to tree nuts can be severe,<sup>376</sup> can be potentially fatal, and can occur from the first exposure to a tree nut in patients allergic to other tree nuts.<sup>13</sup> Serologic studies have indicated a high degree of IgE binding to multiple tree nuts presumably because of cross-reacting allergens.<sup>55,377</sup> Some tree nut allergens are highly homologous and cause clinical cross-reactions (eg, between pistachio and cashew).<sup>378</sup> Because of the frequency of severe reactions, no comprehensive studies have been performed to determine clinically relevant cross-reactivity to tree nuts.<sup>48</sup> Allergy to multiple tree nuts has been described in more than a third of 34 patients evaluated for tree nut allergy,<sup>376</sup> but it is not clear that this represents multiple individual allergies or cross-reactivity. Considering the potential severity of allergic reactions to tree nuts, the difficulty with accurate identification of particular tree nuts in prepared foods and the potential for cross-reactivity, total elimination of tree nuts in a patient with allergy to tree nuts is recommended. Total elimination of tree nuts may not be necessary if it can be clearly established that a patient can tolerate tree nuts other than the one responsible for the reaction and can obtain such nuts without any risk of cross-contamination.<sup>48</sup> The ubiquity of nuts in the diet makes avoidance difficult and unintentional ingestions with reactions common.<sup>379</sup>

### Cacao Nut

*Summary Statement 45.* Since the proteins of cacao nut undergo extensive modification into relatively nonallergenic complexes during the processing of commercial chocolate, clinical sensitivity to chocolate is vanishingly rare. (D)

Special note should be made of cacao, which is actually a tree nut. Some sequence homology has been found between cacao vicilin seed storage protein and walnut vicilin (Jug r 2).<sup>375</sup> However, cacao seeds undergo extensive processing, with the end result being that in commercial chocolate the proteins exist in an insoluble, complex form.<sup>380</sup> IgE-mediated chocolate allergy, as opposed to allergy to components of chocolate confections, including traces of other tree nuts or peanut, is vanishingly rare and has not been reported in the modern literature in any study that used double-blind, placebo-controlled food challenges. Previous publications relied on subjective reports and positive skin prick test results with cacao extract, an extract that should not be routinely used in

the evaluation of food allergy. Cacao extract is not reflective of processed chocolate but is usually made from raw cacao seeds. This extract is appropriate for the evaluation of workers exposed to cacao seeds or flour in an occupational setting. Otherwise, irrelevant cross-reactive IgE is certain to be detected in some atopic patients based on conserved panallergens (eg, profilins), plant defense proteins, or clinically irrelevant homology among seed storage proteins. However, new forms of gourmet chocolate that have undergone less processing are now coming onto the market, eg, products using cacao nibs (pieces of raw or roasted cacao nut). It is unknown if such products have significant allergenicity or the potential for any relevant cross-reactivity with other tree nuts.

### Fruits and Vegetables

*Summary Statement 46.* Although IgE-mediated reactions to fruits and vegetables are commonly reported, clinically relevant cross-reactivity resulting in severe reactions is uncommon. (C)

IgE-mediated reactions to fruits and vegetables are the most common types of food allergy reported by questionnaire in Europe, where consumption is high.<sup>58</sup> Clinically relevant cross-reactivity resulting in severe reactions among fruits and vegetables is uncommon. In the United States, allergy to ragweed species is often associated with oral allergy symptoms to melon and banana.<sup>381</sup> The most important conditions linked to melon allergy are pollen allergy (100%), allergy to an unrelated fruit, mainly peach (up to 62%), and latex sensitivity (up to 23%).<sup>382</sup>

Allergenic cross-reactivity among peach, apricot, plum, and cherry has been demonstrated in patients with the oral allergy syndrome.<sup>383,384</sup> In a study designed to evaluate IgE-mediated hypersensitivity to melon (*Eucumis melo*) confirmed by double-blind, placebo-controlled food challenge, actual clinical reactivity of 53 patients was confirmed in 19 (36%).<sup>385</sup> The most frequent symptom was oral allergy syndrome, but 2 patients experienced life-threatening reactions, including respiratory symptoms and hypotension. Forty-five reactions to 15 other foods (including avocado, kiwi, banana, chestnut, latex, pollen, and others) were confirmed in 18 patients. The most common foods associated with melon allergy were avocado, banana, kiwi, watermelon, and peach.<sup>385</sup>

### Cross-Reactions Between Food and Latex

*Summary Statement 47.* The latex-fruit syndrome is the result of cross-reactivity between natural rubber latex proteins and fruit proteins. Class 1 chitinases (Hev b 6, hevein-like proteins), profilins (Hev b 8),  $\beta$ -1, 3-gluconases (Hev b 2), and other cross-reactive polypeptides have been implicated. The most commonly reported cross-reactive foods include banana, avocado, kiwi, and chestnut, but many other fruits and some nuts have been identified in cross-reactivity studies. (D)

In the last 2 decades of the 20th century, latex allergy has reached epidemic proportions.<sup>386</sup> The main risk groups for developing clinical allergy to cross-reactive latex determi-

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nants in food are atopic persons, children with spina bifida, individuals who require frequent surgical instrumentation, health care workers, and all persons who have regular contact with latex products.<sup>387,388</sup>

Epidemiologic studies demonstrate that 3% to 25% of health personnel are allergic to latex and 30% to 50% of all individuals allergic to natural rubber latex are sensitive to some plant-derived foods.<sup>389</sup>

The *Hevea brasiliensis* latex profilin is cross-reactive with allergens of plant foods and pollen. The commonly reported cross-reactive foods include banana, avocado, kiwi, and chestnut. The group of defense-related plant proteins, class 1 chitinases, cross-react with the panallergen hevein. Cross-reactivity with these proteins is noted with banana, avocado, kiwi, chestnut, papaya, tomato, cherimoya, passion fruit, mango, and wheat.<sup>390–392</sup>

Prohevein (Hev b 6) behaves as a major allergen, since it reacts to IgE in most of the sera of patients with latex allergy.<sup>386</sup> Others have reported that in latex-sensitive adults, hevein (Hev b 6), rubber elongation factor (Hev b 1), and Hev b 5 are major allergens, whereas in children with spina bifida, the Hev b 1 proteins are important allergens.<sup>393</sup> Hev b 8, the *Hevea brasiliensis* latex profilin, is a cross-reactive allergen of latex, plant foods, and pollen.<sup>334</sup>

Mugwort, ragweed, and timothy grass pollen share IgE epitopes with glycoprotein latex allergens as studied by immunoblot inhibitions and quantitative competition experiments, but the clinical relevance is unknown.<sup>394</sup>

### Seeds

*Summary Statement 48.* Seed storage proteins appear to be the main allergens in the edible seeds, in particular, 2S albumin family proteins (part of the cereal prolamin superfamily) have been demonstrated as allergens in sesame, mustard, sunflower, and cottonseed. Cross-reactivity has not been well studied. (E)

As in legumes and tree nuts, seed storage proteins are emerging as the main allergens in the other edible seeds and have been associated with cases of anaphylaxis. Vicilin (Cupin family) and legumin group protein allergens have been described in sesame, and unidentified allergens have been documented in many seeds.<sup>52,53,395,396</sup> However, 2S albumins are major allergens in sesame, mustard, sunflower, and cottonseed.<sup>51,53,397–400</sup> Many spices are seeds, including poppy seed, coriander, nutmeg, dill seed, caraway, fennel seed, cumin, and anise seed. There are reports of pollen-food syndrome related to Bet v 1–like and profilin allergens in poppy seed and among the parsley and carrot spice family (caraway, coriander, dill, fennel, anise) (also known as Apiaceae).<sup>395,396</sup> Additionally, there are reports of in vitro cross-reactivity between poppy seed and sesame and among poppy, sesame, kiwi, hazel nuts, and rye.<sup>395</sup> The clinical relevance of such in vitro cross-reactivity is not clear.

## ADVERSE REACTIONS TO FOOD ADDITIVES

*Summary Statement 49.* The number of additives used by the food industry is extensive. Only a small number of additives have been implicated in IgE-mediated or other (immunologic or nonimmunologic) adverse reactions. Adverse reactions to food additives, therefore, are rare. (C)

The number of additives used by the food industry is extensive and includes antioxidants, flavoring and coloring substances, preservatives, sweeteners, thickeners, and many others. Only a small number of additives have been implicated in IgE-mediated or other (immunologic or nonimmunologic) adverse reactions. Many reported adverse reactions to additives have been anecdotal and/or based on poorly controlled challenge procedures.<sup>401</sup> Adverse reactions to food additives, therefore, are rare.

*Summary Statement 50.* Food additives may cause anaphylaxis, urticaria or angioedema, or asthma. These reactions can be severe or even life-threatening; fatalities have been described. (C)

Adverse reactions, including urticaria or angioedema, asthma, or anaphylaxis, to many additives have not been described and must be extremely rare if they occur at all.<sup>401</sup> Recent controlled studies imply that sensitivity to food additives monosodium glutamate (MSG), nitrates, benzoates, parabens, sulfites, butylated hydroxyanisole [BHA], butylated hydroxytoluene [BHT], tartrazine [FD&C yellow No. 5], sunset yellow [FD&C yellow No. 6] in patients with chronic urticaria or angioedema is uncommon. Several case reports have described anaphylaxis from sulfites, erythritol, annatto, saffron, and carmine. In individuals with asthma, the potential for provocation of bronchospasm has been observed in a subgroup with sensitivity to sulfites; rare cases of asthma provoked by benzoate, MSG, and tartrazine have also been reported.

*Summary Statement 51.* Tartrazine (FD&C yellow No. 5) sensitivity has been reported; based on current evidence, tartrazine may be a rare cause of bronchospasm in patients with asthma. (C) There is no convincing evidence to support the contention that tartrazine “cross-reacts” with cyclooxygenase-inhibiting drugs. (B)

Many of the Food Dye and Coloring (FD&C)–approved dyes are coal tar derivatives, which contain aromatic rings. In addition to tartrazine (FD&C yellow No. 5), azo dyes (containing N:N-linkages) include ponceau (FD&C red No. 4), which was banned from use in the United States based on claims of carcinogenicity in 1975. Non-azo dyes include brilliant blue (FD&C blue No. 1), erythrosine (FD&C red No. 3), and indigotin (FD&C blue No. 2). The use of FD&C-approved dyes is ubiquitous in foods and beverages. Although several dyes have been reported to produce anaphylaxis, urticaria or angioedema, and/or asthma,<sup>401,402</sup> the prevalence of reactions to food additives (eg, tartrazine) is unknown, not because of an inadequate number of studies, but rather because of the lack of properly controlled studies. In part, this relates to problems inherent in challenging pa-

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tients with asthma and/or chronic urticaria or angioedema. Many early reports described “false-positive” reactions; that is, prior withdrawal of medications (for asthma or urticaria or angioedema) resulted in reappearance of disease activity at the time of additive challenge. Variability in activity of chronic conditions that may wax or wane with time, as well as other potential confounders, should be managed by maintaining routine medications and using double-blind, placebo-controlled challenge protocols.<sup>403,404</sup>

Critical review of the medical literature supports the contention that sensitivity to tartrazine (FD&C yellow No. 5) in asthmatic patients is, at best, extremely unusual.<sup>405</sup> Well-designed, double-blind, placebo-controlled studies found no tartrazine sensitivity among approximately 50 adults<sup>406</sup> and 50 children<sup>407</sup> in each report with chronic, often steroid-dependent, asthma. Although tartrazine is not a cyclooxygenase inhibitor,<sup>408</sup> tartrazine sensitivity in aspirin-sensitive asthmatic patients was described by several investigators.<sup>409–412</sup> In a more recent report, using double-blind, placebo-controlled challenge protocols in aspirin-sensitive asthmatic patients, no adverse reactions were found in 165 aspirin-sensitive asthmatic patients challenged to a dose of 50 mg of tartrazine.<sup>405</sup> These data do not support any “cross-reaction” of tartrazine with cyclooxygenase-inhibiting drugs or that tartrazine should be avoided in aspirin-sensitive asthmatic patients.

*Summary Statement 52.* Cases of urticaria or angioedema and of bronchospasm from MSG have been reported; however, blinded placebo-controlled MSG challenges in properly selected patients have not confirmed these associations. Based on current evidence, MSG may be a rare cause of urticaria or angioedema and a rare cause of bronchospasm in patients with asthma. (B)

MSG is a nonessential dicarboxylic amino acid. MSG is added to food as a flavor-enhancer, particularly in Asian foods, and has been commonly reported to produce a variety of symptoms,<sup>413</sup> including headache, myalgia, backache, neck pain, nausea, diaphoresis, tingling, flushing, and chest heaviness (MSG symptom complex, also known as Chinese restaurant syndrome). Urticaria was attributed to MSG in one report,<sup>414</sup> but the potential for exacerbation of chronic urticaria with MSG has not been demonstrated in carefully performed, placebo-controlled challenges.<sup>415</sup> One case has been reported of angioedema with onset 16 hours after ingestion of 250 mg of MSG, confirmed by single-blind, placebo-controlled challenge.<sup>416</sup> MSG has also been associated with provocation of asthma in several reports<sup>417,418</sup>; however, this association has not been supported in more recent studies characterized by double-blind, placebo-controlled MSG challenges in asthmatic subjects,<sup>419,420</sup> in which no reactors were found.

*Summary Statement 53.* Sulfites produce bronchospasm in 5% of the asthmatic population, in most cases due to generation of sulfur dioxide in the oropharynx. (A) Sulfite-induced anaphylaxis has also been described. (B)

Sulfites have been widely used for centuries to freshen and prevent oxidative discoloration (browning) of foods.<sup>421</sup> Sul-

fites are also used as sanitizers and to inhibit the growth of undesirable microorganisms in the fermentation industry. Sulfiting agents include sulfur dioxide and sodium or potassium sulfite, bisulfites, and metabisulfites. High levels of sulfites are found in dried fruits (eg, apricots), potatoes, wine, and some seafood items.

The published reports demonstrating a causal association between sulfites and adverse reaction are more methodologically sound than studies of any other additive. In double-blind controlled studies, sulfites have clearly been shown to be the cause of serious and potentially life-threatening asthmatic reaction.<sup>421,422</sup> Although the incidence of sulfite-sensitive asthma remains unknown, reports suggest that as many as 5% of the asthmatic population may experience adverse reaction ranging from mild wheezing to severe bronchospasm following ingestion of sulfite-containing foods or beverages.<sup>423</sup> Attenuation of sulfite-induced bronchospasm has been described with inhaled sodium cromolyn,<sup>423</sup> oral cromolyn at dose of 200 mg,<sup>424</sup> cyanocobalamin,<sup>425</sup> and inhaled anticholinergic agents<sup>426</sup>; doxepin may also block bronchospastic response, at least in part due to its potent anticholinergic properties.<sup>427</sup> Although the mechanism of sulfite sensitivity is not fully understood, most sulfite-sensitive asthmatic patients react via inhalation of sulfur dioxide generated from sulfite solutions in an acidic environment.<sup>421</sup> In several reports of sulfite sensitivity, positive skin test results to sulfites were described, implicating IgE-mediated pathogenesis and implying anaphylactic potential.<sup>428–431</sup> Some asthmatic patients with severe reactions to sulfites may have low levels of the enzyme sulfite oxidase, which is necessary to oxidize sulfite into inactive sulfate.<sup>421</sup> These asthmatic patients and skin test–positive asthmatic patients may respond to low amounts of sulfite ingested in capsule form; others react only to challenge with sulfite-containing solutions (generating sulfur dioxide). There are isolated case reports of nonasthmatic reactions to sulfites, including urticaria or angioedema<sup>432,433</sup>; however, rigorously controlled double-blind, placebo-controlled challenges have either not been performed or have not provoked adverse reaction in these individuals.<sup>401,421</sup> Three reports evaluated sulfite sensitivity in subjects with idiopathic anaphylaxis: in one, 1 subject among 130 challenged was found to be sulfite sensitive<sup>434</sup>; in another, 1 subject experienced a systemic reaction following a sulfite skin test<sup>122</sup>; and in yet another, no sulfite sensitivity was found.<sup>435</sup>

#### *Other Chemical Additives*

There has been only one individual described in the medical literature as being sodium benzoate sensitive. In a double-blind, placebo-controlled study of additive-provoked asthma,<sup>436</sup> an asthmatic patient was described who was benzoate sensitive but not aspirin sensitive; this patient did not experience amelioration of asthma symptoms while following a benzoate-free diet.

BHA and BHT are antioxidants commonly used in breakfast cereals and other grain products to maintain crispness and prevent rancidity. There is one well-documented report of

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chronic urticaria, confirmed by double-blind, placebo-controlled challenges, exacerbated by these agents.<sup>437</sup> Sensitive subjects also exhibited improvement in urticaria after dietary elimination of BHA and BHT. A case of possible urticarial vasculitis related to BHT in chewing gum has also been reported.<sup>438</sup>

Nitrates and nitrites are widely used as preservatives in processed meats (frankfurters, salami, etc). These agents have not been associated with anaphylactic or anaphylactoid, asthmatic, or urticarial reactions but can provoke vascular headache; their metabolic products (nitrosamines) are known carcinogens.<sup>401</sup>

Aspartame (Nutrasweet), a dipeptide of aspartic acid and phenylalanine, is a low-calorie artificial sweetener 180 times sweeter than sucrose.<sup>439</sup> Two cases of aspartame-induced urticaria, confirmed by placebo-controlled, double-blind challenge, have been reported,<sup>440</sup> and additional cases by the same author have also been described<sup>441</sup>; however, other investigators have encountered difficulty recruiting subjects with adverse reactions to aspartame and have found that such individuals do not have reproducible reactions.<sup>442,443</sup> Reports of aspartame-provoked headaches have been variable, with both positive and negative findings depending on study design.<sup>444,445</sup>

A single case has been described of abdominal pain and hives attributed to FD&C yellow No. 6.<sup>446</sup> The legitimacy of this diagnosis is questionable, because 4 isolated episodes of hives during a 2-year period occurred despite continuing exposure to this dye. A single-blind challenge provoked abdominal pain and urticaria, whereas a double-blind challenge was associated with pain without urticaria.

Although hyperactivity in children has been suspected to be due to "additives,"<sup>447</sup> well-controlled studies have failed to support this hypothesis.<sup>401</sup>

*Summary Statement 54.* "Natural" food additives, including annatto, carmine, and saffron, as well as erythritol (ERT; 1,2,3,4-butanetetrol), a sweetener, may be rarer causes of anaphylaxis. (C)

"Natural" color additives are derived from plant or animal sources by extraction or other physical processes, in contrast to "synthetic" additives, which are chemically synthesized.<sup>448</sup> Anaphylaxis has been reported rarely to "natural" food additives,<sup>448</sup> including annatto, carmine, and saffron,<sup>449-451</sup> as well as erythritol (ERT; 1,2,3,4-butanetetrol), a sweetener.<sup>452</sup> Annatto is a natural yellow food coloring used in a variety of foods, including cereal, cheese, ice cream, popcorn, margarine, oils, and beverages. Annatto dye extract is produced from the pericarp of the fruit of the tropical annatto tree, *Bixa orellana*. Carmine is a natural dark red food dye derived from the dried bodies of females of the tropical American insect *Coccus cacti*, used in foodstuffs such as candy, ice cream, cookies, pastries, syrups, liqueurs, vinegar, cheese, butter, delicatessen meats, jam, and caviar. Saffron is produced from dried stigmas and the style of the flower *Crocus sativa*. It is used as a spice and also as a coloring in soups, bouillabaisse, sauces, rice dishes (eg, paella), cheeses, cakes, and liqueurs.

Erythritol is a 4-carbon sugar alcohol prepared from glucose by fermentation that is used as a sweetener and may occur naturally in foods such as wine, beer, soy, cheese, mushroom, grape, and watermelon.

*Summary Statement 55.* Adverse reactions (anaphylaxis, urticaria or angioedema, or bronchospasm) from food additives should be suspected when symptoms after food or beverage consumption occur some but not all the time, suggesting that the reaction occurs only when an additive is present. (C)

The knowledge about which foods and beverages contain particular additives is important for corroborating the possibility that symptoms are being provoked by consumption of a food additive. Patients with sensitivity to an additive exhibit a tendency for adverse reaction in association with foods or beverages that is inconsistent, in the sense that they may consume a specific food item and experience untoward reaction and at other times tolerate the food item without any problem. For instance, a sulfite-sensitive asthmatic patient may consume fresh apricots that are not sulfited without problem but then experience severe bronchospasm in association with dried apricots that contain substantial amounts of sulfites.<sup>401</sup> For proper diagnosis and management of such patients, it is critical for the allergist-immunologist to be aware of food and beverage items that do and do not contain specific additives.

*Summary Statement 56.* Management entails avoiding foods and beverages that contain the implicated additive and using self-injectable epinephrine for life-threatening reactions, especially for individuals who are sulfite sensitive. (B)

Management of food additive allergy is similar to allergy due to more common food items, such as egg, peanut, and shrimp. Avoidance is the key aspect of management. Patients should be advised to carry self-injectable epinephrine, because inadvertent exposure to the additive may occur and lead to unexpectedly severe reaction. Although aqueous epinephrine solutions are sulfited, their sulfite content is only 0.3 mg per usual dose. This is below the level at which known sulfite-sensitive individuals will react<sup>421</sup>; for this reason, epinephrine should not be withheld from sulfite-sensitive patients and should be used to treat anaphylaxis (see The Diagnosis and Management of Anaphylaxis: An Updated Practice Parameter).

## GENETICALLY MODIFIED FOODS

*Summary Statement 57.* Many of the major food groups have undergone modification by gene manipulation or replacement, and several of these food products are currently on grocery store shelves. (C)

For almost 3 decades, agricultural scientists have directly manipulated DNA to rapidly improve specific plant, animal, or bacterial characteristics (Tables 5 & 6). Recombinant-based proteins and genetically engineered microorganisms have been used by the agricultural industry to improve the food supply, increase agricultural productivity, and reduce the adverse effects of agricultural practices on the environ-



ment (ie, use of herbicides and pesticides).<sup>453</sup> Similar techniques are proposed for commercial production of enzymes, pharmaceutical peptides, and proteins (eg,  $\beta$ -glucuronidase, insulin, trypsin), some of which are known allergens.<sup>454</sup> All of the major food groups have undergone modification by gene manipulation or replacement.<sup>453</sup> Five years ago, several examples of these food products were on grocery store shelves in the United States.<sup>455</sup>

*Summary Statement 58.* The possibility exists that transgenic plant proteins in genetically modified foods could cause severe food allergy, including anaphylactic shock, if allergenic determinants (amino acid sequences) in the transgenic proteins share a high degree of homology to those of known food allergens. (E)

Despite potential nutritional and therapeutic advantages, there has not yet been complete acceptance of novel genetically modified (GM) foods. One of the concerns by consumer groups is the potential allergenicity of novel GM foods, particularly those containing encoded proteins to which human beings have not been previously exposed. This has become a contentious issue not only for consumers but also for food technology scientists and allergists-immunologists.

Allergists-immunologists have raised the possibility that transgenic plant proteins could cause severe allergic reactions, including anaphylaxis, if amino acid sequences in the transgenic proteins resemble those of known food allergens.<sup>456</sup> This theoretical concern is supported by an instance in which soybeans were engineered to express a previously known food allergen (Brazil nut 2S storage albumin).<sup>457</sup> This manipulation was performed to improve the protein composition of soybean and increase its biologic value in animal feed and other soybean products. Fortunately, reactivity of the 2S storage albumin was quickly detected in serum IgE from patients sensitized to Brazil nuts and this transgenic soybean was promptly withdrawn from market consideration.

*Summary Statement 59.* As illustrated by recent introduction of corn engineered to contain a pesticide,  $\delta$  endotoxin (derived from *B thuringiensis*), into the human food chain, food allergy to such engineered foods could occur in workers previously exposed and sensitized to this endotoxin or in other highly susceptible atopic patients. (A)

The possibility of GM food allergy was further intensified in 1999 when it was learned that Cry9C transfected corn, which the Environmental Protection Agency had approved only for animal feed, had inadvertently appeared in consumer food products. Cry9C is a crystal body endotoxin derived from *B thuringiensis kurstaki* and is closely related to *B thuringiensis kurstaki* Cry1A endotoxin that was shown to induce IgE sensitization in migrant workers.<sup>458,459</sup> Soon after Cry9C was detected in the human food chain, multiple consumer complaints were received and evaluated by the FDA. Specific Cry9C IgE antibodies were not detected in any of these consumers, but similar tests were not conducted in workers previously sensitized to a Cry1A-related protein.<sup>459</sup> This group of workers might be particularly susceptible since a recent review of occupational asthma due to inhaled food

allergens revealed that approximately 30% of workers sensitized by inhalant food allergens ultimately develop allergic reactions after ingestion of the same food.<sup>322-325</sup>

*Summary Statement 60.* The potential allergenicity of newly developed genetically modified foods should be investigated on a case-by-case basis by individual commercial developers and appropriate regulatory agencies. (D)

In the future, possible sensitization to transgenic foods should be evaluated in susceptible populations, including workers previously sensitized by inhalation and/or atopic subsets of patients. The recent transgenic Cry9C corn episode illustrates that allergenicity to GM foods should be investigated on a case-by-case basis, particularly since many potential allergenic proteins (eg, trypsin, insulin) may be produced commercially in the near future and therefore constitute a source of inhalant and ingestant exposures to workers and consumers, respectively, who may be at increased risk of developing allergy to genetically modified foods as listed in Table 7.

## DIAGNOSIS OF FOOD ALLERGY

*Summary Statement 61.* The primary tools available to diagnose adverse reactions to foods include history (including diet records), physical examination, skin prick or puncture tests, serum tests for food specific IgE antibodies, trial elimination diets, and oral food challenges. (B)

The general aims of diagnosis are to determine if food is causing the disorder under evaluation and, if so, to identify specific causal food(s). A proper diagnosis will allow the patient to receive instructions regarding avoidance of problematic foods. Equally as important, a specific diagnosis will prevent unnecessary and potentially deleterious dietary restrictions when a suspected food allergy is not present. The diagnostic tools available to the clinician include simple and relatively inexpensive tests, such as the clinical history, physical examination, skin prick or puncture tests, and serum tests for food specific IgE. Additional tests (oral food challenges) are more involved timewise, may be more expensive, and may carry additional risks. The rational selection and interpretation of diagnostic tests require an appreciation for the utility of the tests themselves and an evaluation of the level of certainty required for the diagnosis

Table 7. Patients Possibly at Increased Risk of Developing Allergy to Genetically Modified Foods\*

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Atopic patients with single or multiple IgE-mediated allergy to foods
Patients with atopic dermatitis and proven allergy to one or more foods
Workers previously sensitized by inhalant exposure to related food proteins
Atopic patients previously sensitized by inhalant exposure to consumer products containing food related proteins
Atopic neonates being breastfed

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\* From Bernstein et al.<sup>23</sup>

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*Summary Statement 62.* A detailed dietary history, at times augmented with written diet records, is necessary to determine the likelihood that food is causing the disorder, identify the potential triggers, and determine the potential immunopathophysiology. (D)

The history is the starting point where the clinician must decide on the possibility that food is a potential cause of a disorder or reaction and whether the pathophysiology of the disorder may be IgE mediated or associated or not (thereby guiding further diagnostic evaluation). Historical points of interest include age of the patient; a list of suspect foods, ingredients, or labels for manufactured products; the amount of food necessary to elicit a reaction; the route of exposure eliciting a reaction; the typical interval between exposure and onset of symptoms; clinical manifestations of reaction(s) following exposure to each food; duration of symptoms; ancillary events (exercise, use of nonsteroidal anti-inflammatory drugs, alcohol); treatment of reactions and patient response; and the consistency with which a reaction occurs on exposure.

As indicated in the differential diagnosis section, key points in the history, such as symptoms and timing of onset following ingestion, may identify reactions likely to be dependent on demonstrable IgE antibody (eg, sudden reactions such as anaphylaxis) and those that are associated with IgE to particular foods in many but not all cases (eg, chronic disorders such as atopic dermatitis).<sup>253,460</sup> The history may also suggest those that are immune mediated but are not associated with food specific IgE antibody (eg, gastrointestinal disorders such as food protein-induced enterocolitis syndrome)<sup>461</sup> and those that are not likely to be immune mediated (eg, lactose intolerance).

In addition to identifying a pathophysiologic basis, the history may indicate specific food triggers and a starting point to estimate the probability that a particular food is causal.<sup>462,463</sup> Diet records, including review of labels from packaged foods, may facilitate identification of specific triggers by food challenges.<sup>403,464</sup> Careful review is often needed, since labels may include terms that are unfamiliar to the patient or ambiguous (eg, casein, "spices") and unsuspected causes may be revealed.<sup>465</sup> Common reasoning would indicate that a food previously tolerated on a routine basis is less likely to be a trigger than one eaten rarely. Similarly, for a person with a previously confirmed food allergy to a ubiquitous food (eg, milk, peanut) who reacts to a specific meal, consideration that the previously identified allergen may be present as a hidden ingredient or contaminant should be entertained. Age is important since the epidemiology of food allergy indicates a higher probability of reactions to cow's milk, egg, wheat, and soy in infants; peanuts, tree nuts, seafood, and raw fruits in older children and adults; and a predilection of certain food-related disorders in infants and children (atopic dermatitis, enterocolitis).<sup>1,2,264</sup> Symptom duration is important because acute urticaria is more likely associated with food allergy than chronic urticaria.<sup>466</sup> Consistent reactions, particularly acute ones, to a specific food raise the probability that the

food is causal. The history is notoriously poor (approximately 30% verified) in identifying causal foods for chronic disorders such as atopic dermatitis.<sup>467,468</sup>

*Summary Statement 63.* A physical examination may reveal the presence of atopic disorders, such as asthma, atopic dermatitis, and allergic rhinitis, that indicate an increased risk for food allergy or reveal alternative diagnoses that may reduce the likelihood of food allergy. (C)

The physical examination may reveal stigmata of atopy (asthma, allergic rhinitis, atopic dermatitis) that indicate an increased risk for food allergy on an epidemiologic basis<sup>462,463</sup> or reveal a disorder or complaint not typically associated with food allergy (psoriasis, joint pain, behavioral disorders). Overall, these points should allow a decision regarding the utility of performing tests for IgE antibodies or other routes of investigation.

*Summary Statement 64.* Tests for food specific IgE antibody include percutaneous skin tests (prick/puncture, PST) and serum assays. These tests are highly sensitive (generally >90%) but only modestly specific (approximately 50%) and therefore are well suited for use when suspicion of a particular food or foods is high. They are not effective for the purpose of screening (eg, using panels of tests without consideration of likely causes). (B)

Modalities to determine the presence of IgE antibody to specific foods include PSTs and serum assays. Both techniques merely detect the presence of antibody (sensitization) and do not necessarily indicate, by themselves, that ingestion would result in clinical reactions. The technique of skin prick or puncture testing was reviewed in a previous practice parameter.<sup>469</sup> Even infants can be tested.<sup>470</sup> Some workers prefer fresh extracts, particularly when testing fruits and vegetables that are prone to degradation.<sup>153</sup> Results of PSTs are considered positive if there is a mean wheal diameter of 3 mm or greater, after subtraction of the saline control, because this provides acceptable sensitivity (approximately 75% to 95%) and specificity (approximately 30% to 60%).<sup>471,472</sup> Reviews of medical records concerning skin prick or puncture testing with foods indicate a low rate of systemic reactions (0 of 1,000,000 tests; 95% confidence interval, 0–109), although such reactions may occur.<sup>473</sup> These systemic reactions may be more likely in infants when fresh foods are used.<sup>474</sup>

Another means to detect food specific IgE is in vitro assays to determine the presence of food specific IgE antibodies in the serum. There are a variety of manufacturers, substrates, and manners of reporting results: classes (class 1 to 5 or 6), counts, percentages, or units of concentration (kIU/mL) (see Glossary).

The clinical utility of PST and serum food specific IgE have been evaluated in various referral populations. The results are most valuable when they are negative, since the high sensitivity makes them approximately 95% accurate for ruling out IgE-mediated reactions.<sup>468</sup> However, a positive test result is associated with true clinical reactions only approximately 50% of the time.<sup>279,404,471,475–477</sup> In addition, the test results may also remain positive some time after clinical

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reactivity has resolved. The serum assay for specific IgE is generally considered less sensitive than skin prick tests, but in some cases the sensitivity is similar. Panels of food allergy tests should not be performed without consideration of the history, because one may be faced with numerous irrelevant positive results. For example, in patients with grass pollen allergy, there is a significant likelihood that skin tests or specific IgE assays will be falsely positive for grains.<sup>42</sup> Although the size of the PST or concentration of food specific IgE antibody by in vitro assay may be related to the likelihood of a clinical reaction, neither is useful in predicting the type or severity of a reaction.<sup>472,478,479</sup> Similar to stratification by RAST Unicap test levels, a recent study by Sporik and David<sup>480</sup> demonstrated similar predictive values using skin prick or puncture test wheal sizes. During a 9-year period, children referred to a tertiary allergy clinic for the evaluation of suspected food allergy were studied prospectively by comparing skin prick or puncture tests and open food challenges. In the case of cow's milk, hen's egg, and peanuts, it was possible to identify skin wheal diameters at and above which negative reactions did not occur (cow's milk, 8 mm; hen's egg, 7 mm; peanut, 8 mm). Data of this sort will enable future applications of likelihood ratios for confirmation of clinical sensitivity.<sup>480</sup>

*Summary Statement 65.* Intracutaneous (intradermal) skin tests for foods are potentially dangerous, overly sensitive (increasing the rate of a false-positive test result), and not recommended. (D)

Intracutaneous allergy skin tests with food extracts give an unacceptably high false-positive rate, can elicit systemic reactions (rarely an issue for prick tests), and should not be used.<sup>475</sup>

*Summary Statement 66.* Results of PSTs and serum tests for food-specific IgE antibody may be influenced by patient characteristics (eg, age), the quality and characteristics of reagents (eg, variations in commercial extracts, cross-reacting proteins among food extracts), and techniques (eg, assay types, skin test devices, location of test placement, mode of measurement). (B)

Like any laboratory test, the reagents and the techniques selected for food allergy testing influence the results. Standardized food extracts are not currently available despite a recognized need.<sup>481</sup> Commercial extracts are usually prepared as glycerinated extracts of 1:10 or 1:20 dilution. With the lack of standardized extracts, it is well recognized that variations exist in allergen distribution and concentration between lots and companies.<sup>482</sup> Additionally, protein stability must be considered. Labile proteins in raw fruits and vegetables may not be present in commercial extracts, and so testing with them for pollen-food-related reactions may be insensitive (although stable proteins associated with systemic reactions may be preserved).<sup>152</sup> For the evaluation of allergy to fresh fruits and vegetables, and possibly other foods, it is helpful to use fresh foods.<sup>470</sup> The PST can be performed using liquid foods, by creating an in-house extract, or alternatively by using a prick-prick technique (pricking the fruit or vegetable and then

the patient, thereby transferring the soluble allergenic protein).<sup>153</sup> Presumably, such in-house reagents are more concentrated and may increase the risk for a systemic reaction from the test itself.<sup>473</sup> The impact of allergen concentration on wheal size is somewhat tempered by the fact that wheal size increases by a factor of 50% for each log increase in concentration.<sup>483,484</sup> Composition of reagents also affects serum tests, since the available display of proteins may vary. Cross-reactive carbohydrate determinants are commonly found in many foods, but they usually are of little clinical relevance.<sup>485,486</sup>

Prick or puncture test device selection and technique may influence results, since the more allergen introduced, the larger the expected skin response. Therefore, the configuration of the device, the pressure applied by the operator, and the time over which pressure is applied must be considered.<sup>469</sup> Test results also vary according to the location on the body on which they are placed. For example, the back is approximately 20% more reactive than the arm.<sup>487</sup> Studies that evaluate histamine reactivity indicate that wheals become detectable in early infancy and increase in size with age until adulthood.<sup>488,489</sup> These physical and patient variables become relevant when comparing study results and for clinical decision making. Noting the time of day of testing is suggested, since PST response size may vary by circadian rhythms.

Another variation concerning PSTs is the timing at which they are read and the manner in which they are measured and reported. The histamine test peaks at 10 minutes, whereas allergen wheal size generally peaks at 15 to 20 minutes.<sup>469</sup> The preferred method of measurement is to determine the greatest wheal (or flare) diameter, its perpendicular maximum diameter, and the mean of these 2 measurements reported in millimeters for the allergens and controls.<sup>469</sup> It is not recommended to report test results categorically (eg, 1+, 2+, etc), because there is no universal standard for these categories.

*Summary Statement 67.* Increasingly higher concentrations of food-specific IgE antibodies (reflected by increasingly larger PST response size and/or higher concentrations of food-specific serum IgE antibody) correlate with an increasing risk for a clinical reaction. (C)

Studies in children support the notion that increasingly higher concentrations of food specific IgE antibody, reflected by larger PST responses or high serum IgE antibody concentrations, are correlated with increasing risks of clinical reactions.<sup>479,490,491</sup> Thus, instead of considering a test result for IgE as positive or negative with one decision point (positive-negative), additional clinical utility may be achieved through consideration of PST size and serum antibody concentration. Various studies have correlated reaction likelihood with test results in this regard, but it is clear that absolute values may vary by technique, food involved, age group studied, and the disorder under consideration. Workers have published skin test sizes or levels at or above which clinical reactions are highly likely within the context of the patient population evaluated. For example, the concentration of specific IgE

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antibody measured using a particular method (CAP-RAST FEIA or UniCap reported in arbitrary units [kIU/L]) was compared with outcomes of double-blind, placebo-controlled food challenges in children with atopic dermatitis evaluated at a mean age of 5 years.<sup>472</sup> IgE antibody concentrations of 6 kIU/L or higher to egg, 32 kIU/L or higher to milk, 15 kIU/L or higher to peanut, and 20 kIU/L or higher to codfish were 95% predictive for a reaction. It must be emphasized that clinical correlations such as these are undetermined for most other foods, allergic disorders, and age groups. A prospective study of children not selected for atopic dermatitis (only 61% with the disorder) found the 95% diagnostic cutoff point to be slightly lower for milk (15 kIU/L).<sup>479</sup> Additional studies have demonstrated that concentrations of specific IgE antibody with high predictive capacity are lower in younger infants and children.<sup>477,490,491</sup> Some laboratories report categorical interpretations of their test results, for example, “Class 2 or higher is indicative of allergy”; the studies mentioned herein clearly indicate that this practice is incorrect. Similar to studies using serum tests, a study using PSTs in young children revealed that large wheals ( $\geq 8$  mm for milk and peanut and  $\geq 7$  mm for egg) were predictive for clinical reactions,<sup>480</sup> but this is not a universal experience.<sup>477</sup>

*Summary Statement 68.* A trial elimination diet may be helpful to determine if a disorder with frequent or chronic symptoms is responsive to dietary manipulation. (D)

In the evaluation of disorders with chronic symptoms where foods may be causal (eg, atopic dermatitis, gastrointestinal symptoms), elimination of suspected causal foods may be undertaken to determine whether symptoms are diet responsive.<sup>253</sup> There are no studies to define the utility of this approach. Factors that may complicate interpretation of such a trial (eg, a trial failure when the disorder is truly food responsive) include the following: incomplete removal of causal foods, selection of the wrong foods to eliminate, inadequate time allowed for resolution of chronic inflammation (eg, atopic dermatitis), and additional triggers that may be causing symptoms (eg, skin infection in atopic dermatitis). The underlying pathophysiology is not a significant consideration in using elimination trials. Selection of foods to eliminate may be based on a variety of items including historical features, results of tests, and epidemiologic considerations. Information concerning strict adherence to the diet must be carefully reviewed, similar to what is needed for treatment of food allergy following a more definitive diagnosis. Diets may vary from directed ones (removal of one or a few targeted foods), extreme ones with elimination of most allergenic foods (eg, a prescribed diet without major allergens and limited numbers of allowed foods) or even more restricted ones with essentially no source of potential allergen (eg, use of amino acid-based formula alone or with a few other foods proven safe). Response to elimination diet should not be construed as a definitive diagnosis unless there is compelling supportive evidence regarding specific foods. Another use of an elimination diet is before undertaking oral food challenges; the response to oral food challenge is po-

tentially definitive but must be performed for each food under consideration.<sup>476</sup> Severe reactions have occurred when previously tolerated, IgE antibody-positive foods were added back into the diet after they had been removed from the diet for a period.<sup>492</sup>

*Summary Statement 69.* Graded oral food challenge is a useful means to diagnose an adverse reaction to food. (B)

The oral food challenge is performed by having the patient ingest increasing amounts of the suspected food under physician observation for hours or days.<sup>403,476</sup> This represents a definitive test for tolerance since ingestion of a relevant amount of the food with no reaction excludes the diagnosis of an adverse reaction to the tested food. The test is open to misinterpretation when not done in a masked manner. Therefore, procedures to reduce this possibility need to be implemented, such as masking the challenge substance (blinding) and using placebos.<sup>404</sup>

The challenge procedure and its risks and benefits must be discussed with the patient and/or caregiver. Several factors are considered, including the evaluation of the likelihood that the food will be tolerated, the nutritional and social needs for the food, and the ability of the patient to cooperate with the challenge. In limited circumstances, the food could be administered with potential adverse reactions monitored at home by the patient or parents. This may be considered if the expected adverse reactions are delayed in onset, non-IgE mediated, atypical (eg, headache, behavioral issues), mild gastrointestinal, and not potentially anaphylactic. On the other hand, if there is a reasonable potential for an acute and/or severe reaction or if there is strong patient anxiety, physician supervision is recommended.

Except in the uncommon circumstances described previously, oral food challenges are undertaken under direct medical supervision.<sup>403</sup> A risk evaluation must be made regarding location of challenge (office, hospital, intensive care unit) and preparation (eg, with or without an intravenous line in place). These decisions are based on the same types of data evaluated for the consideration of food allergy in the early diagnostic process: the history, PST results, and so on. In any setting, it must be appreciated that oral challenges can elicit severe, anaphylactic reactions, so the physician must be immediately available and comfortable with this potential and be prepared with emergency medications and equipment to promptly treat such a reaction. In most circumstances, the materials, medications, and equipment that are generally available to treat anaphylaxis in settings where injections for allergen immunotherapy are administered should suffice for oral food challenges.<sup>471,493,494</sup>

If the challenge is considered “high risk” (eg, positive test result for food specific IgE antibodies, previous severe reaction, asthmatic patient), then it is best to perform the challenge in a more controlled setting where additional interventions to support and reverse anaphylactic shock are available (eg, hospital). In high-risk challenges, it may also be prudent to have intravenous access before commencing challenges.<sup>494</sup> Even non-IgE antibody-mediated food allergic reaction can

be severe, such as food protein–induced enterocolitis syndrome,<sup>461,495,496</sup> which may include lethargy, dehydration, and hypotension, and may be complicated by acidosis and methemoglobinemia.<sup>497</sup> Food challenges for patients with this syndrome are typically performed with 0.15 to 0.6 g/kg of the causal protein (usually cow’s milk or soy), and reactions of profuse vomiting and diarrhea typically begin 2 to 4 hours after the ingestion and are accompanied by a rise in the absolute neutrophil count of more than 3,500 cells/mm<sup>3</sup>. Because of these characteristics and the potential for shock, intravenous access should be obtained in advance to allow for fluid resuscitation. With this disorder, the challenge is best performed in a hospital setting.

Before oral food challenges, patients should avoid the suspected food(s) for at least 2 weeks, antihistamine use should be discontinued according to its elimination half-life, and long-term asthma medications such as  $\beta$ -agonists should be reduced as much as possible. Patients should be evaluated carefully before challenge to confirm that they are not already having chronic symptoms; for example, it would not be prudent to undertake a challenge in an individual with mild wheezing (or other uncontrolled disorder) for both the ability to properly interpret a reaction and for safety reasons. For severe atopic dermatitis, hospitalization may be necessary to treat acute disease and establish a stable baseline before challenges.

Challenges can be done “openly,” with the patient ingesting the food in its natural form; “single-blind,” with the food masked and the patient unaware if the test substance contains the target food; or double-blind and placebo-controlled, where neither the patient nor the physician knows which challenges contain the food being tested. In the latter 2 formats, the food must be hidden in some way, such as in another food or opaque capsules. There are several factors that weigh in deciding which type of challenge to use. Al-

though the open challenge is most prone to bias, it is easy to perform, since no special preparation is needed to mask the food. Indeed, if the patient tolerates the ingestion of the food, there is little concern about bias. It is only when symptoms, especially subjective ones, arise that the issue of bias comes into play.<sup>498,499</sup> Therefore, open challenges are a good option for screening when several foods are under consideration, and if a food is tolerated, nothing further is needed. If there is a reaction to an open challenge used in the clinical setting, and there is concern that the reaction may not have been physiologic, the format could be altered to include blinding and controls. Patient-blind challenges prevent patient bias and may be an option over double-blind, placebo-controlled challenges for convenience. No consensus has been reached on a uniform protocol for performing oral food challenges.<sup>403,500</sup> Suggestions regarding the dosing and administration of oral food challenges are delineated in Table 8 and the Appendix—Suggested Oral Challenge Methods).

Preparations for a double-blind, placebo-controlled food challenge are more complicated than for open or single-blind challenges. Although the procedure is more labor intensive, it can be performed in an office setting if the challenge is not high risk.<sup>403</sup> The procedure still introduces graded doses, but in this case either a challenge food or a “placebo” food is administered. The aid of a third party is needed to prepare the challenges so that the observer and patient are kept unaware of whether a true or placebo challenge is being undertaken. A “coin flip” can be used by the third party to randomize the order of administration. The food is hidden either in another food or in opaque capsules. Certain preparation methods (canning, dehydration) may alter the allergens; hence, an open challenge with a meal-size portion of the food prepared in its natural state for consumption following a negative double-blind, placebo-controlled food challenge result may be necessary. It is preferable not to use fatty foods as vehi-

Table 8. Food Challenge Procedure Form

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History of previous reaction(s) suspected due to food.  
 Date: \_\_\_\_\_  
 Symptoms: \_\_\_\_\_  
 Time from ingestion to initial symptoms: \_\_\_\_\_  
 Estimated amount of food that caused reaction(s) \_\_\_\_\_  
 Treatment received for reaction: \_\_\_\_\_  
 Food specific IgE test results: Food(s) \_\_\_\_\_  
 Skin test: \_\_\_\_\_ Serum specific IgE: \_\_\_\_\_  
 Positive negative Positive negative  
 Relevant past history (asthma, urticaria, etc): \_\_\_\_\_  
 Current medications: \_\_\_\_\_  
 Challenge substance: \_\_\_\_\_  
 Carrier food/encapsulated: \_\_\_\_\_  
 Type of challenge:      Open                              Single-blind                              Double-blind  
 Baseline:                      B/P: \_\_\_\_\_                      P: \_\_\_\_\_                      RR: \_\_\_\_\_                      FEV<sub>1</sub>  
 Pertinent physical findings: \_\_\_\_\_

Time given	Dose	Time evaluated	B/P*	FEV <sub>1</sub> *	Reaction (symptoms/signs)
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Abbreviations: B/P, blood pressure; FEV<sub>1</sub>, forced expiratory volume in 1 second; P, pulse; RR, respiratory rate.

\* Measurement of B/P and/or FEV<sub>1</sub> optional and as clinically indicated based on anticipated reaction.

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cles, since they can delay gastric emptying and intestinal absorption.

The double-blind, placebo-controlled food challenge is the gold standard for diagnosing food allergy.<sup>403,404,464,468</sup> The false-positive and false-negative rates for the double-blind, placebo-controlled food challenge, which are based primarily on studies in children with atopic dermatitis, are 0.7% and 3.2%, respectively.<sup>501,502</sup> To help exclude false-negative results, it has long been suggested to include an open feeding under supervision of a meal-size portion of the tested food prepared in its usual manner as a follow-up to any negative double-blind, placebo-controlled food challenge result.<sup>500,503,504</sup> When one is evaluating subjective symptoms, there is a greater likelihood that false-positive or false-negative determinations would occur. Increasing the number of challenges (additional placebo and true foods) helps to diminish the possibility of a random association, but this can be a labor-intensive approach.<sup>505</sup> Although the double-blind, placebo-controlled food challenge can elucidate the relationship of symptoms to foods, it is not specific for food allergy. Any adverse reaction to food (intolerance, pharmacologic effect) can potentially be evaluated, so demonstration of an immunologic explanation is still needed to label a reaction as a food allergy. Oral challenges are almost the only method to adequately evaluate reactions to food additives (coloring and flavoring agents and preservatives).<sup>506</sup> The same can be said for symptoms not likely to be associated with food allergy (eg, behavior).

*Summary Statement 70.* A number of additional diagnostic tests are under investigation, including atopy patch tests, basophil activation assays, and tests for IgE binding to specific epitopes. (E)

Various additional diagnostic tests are under evaluation and are at various stages of acceptance or still under research scrutiny. Patch tests, classically used to evaluate cell-mediated responses to various chemical sensitizers, have been investigated for food allergy. They are performed by applying whole food proteins in a similar manner in a format termed the atopy patch test. Although workers use varying regimens, the tests are generally performed by applying the suspected agent to the surface of the skin in a metal cup (Finn chamber) under an occlusive dressing and leaving this in place for 24 hours. The test site is evaluated at the time of removal and 1 to 2 days later for evidence of inflammation that can be scored by severity. Controls are applied to compare for possible irritant reactions. The atopy patch test can hypothetically induce T-cell responses, reflecting those that occur in subacute and chronic atopic dermatitis<sup>507</sup> or perhaps in gastrointestinal food hypersensitivity.<sup>460</sup> Early studies of the atopy patch test in cow's milk allergy in infants showed improved utility for determining delayed responses to oral food challenges,<sup>508-510</sup> but one subsequent study reported the test to be of modest utility with a wide range of sensitivities and specificities in various settings.<sup>511</sup> Another study of children with atopic dermatitis revealed that the atopy patch test had the highest positive predictive value for allergy to egg

and milk compared with PST or food specific serum IgE antibody tests for both immediate and delayed reactions.<sup>512</sup> However, the results vary widely among workers, since much lower positive predictive accuracy (40% to 63%) and specificities (71% to 87%) have been reported.<sup>74,509,511</sup> The variety of results using atopy patch tests may reflect variations in patient populations (age, type of atopic disorder), definition of positive test results, reagents, and study techniques. Because of the low and variable predictive accuracy and lack of standardized approach to testing, the atopy patch test is not currently indicated for routine use.

The following tests are being evaluated on a research basis but are not available for routine use. The identification of and purification of specific proteins in foods or segments (epitopes) of proteins to which IgE binding correlates with a high risk for clinical reactions may prove useful to enhance the diagnostic value of PSTs and serum tests for food specific IgE antibodies.<sup>59,508</sup> The measurement of inflammatory markers in blood and stool that predict reaction would be convenient but has met with mixed success.<sup>513-515</sup> The quantification of IgE-positive cells in the gastrointestinal tract or evaluation of gut mucosal responses to allergen instillation during endoscopy may improve diagnostic capabilities but are relatively invasive.<sup>516,517</sup> Recent studies of activation markers on basophils may provide another modality for in vitro testing.<sup>518</sup>

*Summary Statement 71.* Some tests, including provocation neutralization, cytotoxic tests, IgG antibodies directed to foods, and hair analysis, are either disproved or unproven; therefore, they are not recommended for the diagnosis of food allergy. (C)

There are a host of tests that have been touted for the diagnosis of food allergy but have never been found useful in blinded studies.<sup>519</sup> Provocation neutralization (by intracutaneous testing) has been evaluated in 2 randomized, controlled, clinical studies and found to rely on the placebo response.<sup>520</sup>

Other tests have not been adequately studied in the diagnosis of food allergy. These include measurement of food specific total IgG or IgG4 antibody, immune complexes, hair analysis, cytotoxic tests to foods that use automated machinery, and applied kinesiology (muscle strength testing).<sup>157</sup> These tests should not be used for the diagnosis of food allergy.<sup>469</sup>

*Summary Statement 72.* Ancillary tests may be needed to confirm the diagnosis of food intolerance or immune reactions to foods, such as breath hydrogen tests for lactose intolerance or gastrointestinal biopsy to determine eosinophilic inflammation or atrophic villi. (D)

When the history and testing indicate that a non-IgE-mediated (cell-mediated) adverse immune response to food or a nonimmunologic reaction to food is possible, ancillary testing may be required. The diagnosis of eosinophilic gastroenteropathies or celiac disease requires biopsy evidence, for example.<sup>521,522</sup> Breath hydrogen tests may be useful for evaluation of lactose intolerance. Celiac disease evaluation may include biopsies of the small intestine and serologic tests

for gliadin and endomysial antibodies (tissue transglutaminase).<sup>523</sup> In many cases, elimination and challenge can act to confirm the relationship of adverse reactions to the suspected triggers.

*Summary Statement 73.* The rational selection, application, and interpretation of tests for food specific IgE antibodies require consideration of the epidemiology and underlying immunopathophysiology of the disorder under investigation, the importance of making a definitive diagnosis, estimation of prior probability that a disorder or reaction is attributable to particular foods, and an understanding of the test utility. (D)

Tests for food allergy, like other medical tests, are neither 100% sensitive nor 100% specific. The diagnostic utility of a test is influenced by (1) the possibility of the disease existing in the individual being tested (prior probability) and (2) the characteristics of the test itself (sensitivity, specificity). These involve the use of predictability indices and likelihood ratios, the principles of which are elaborated in greater detail in Table 9.

The sensitivity and specificity of a test provide information about its ability to identify a known condition. Sensitivity refers to the proportion of patients with an illness who test positive, and for IgE-mediated food allergy, the sensitivity of the PST and serum tests for some foods is usually high (greater than 80%). Specificity refers to the proportion of individuals without the disorder who test negative, and for IgE antibody-mediated food allergy, specificity of the IgE tests is usually lower than the sensitivity but usually better than 50%.<sup>153,471,511</sup> Sensitivity and specificity are affected by intrinsic properties of the test as discussed previously, but the clinical question of import to the physician concerns the probability that a patient has food allergy if the test result is positive (positive predictive value) or does not have food allergy if the test result is negative (negative predictive value). The predictive value is affected by the prevalence of the disorder in the population being tested (or, as applied to the individual, the prior probability that persons being tested have the disorder). In studies using referred atopic dermatitis patients with an increased probability of disease and a definition of positive PST result as one with a mean wheal diameter of 3 mm or greater, PSTs have an excellent negative predictive value (approximately 95%), but the positive predictive value is on the order of only 50%.<sup>468</sup>

Table 9. Food Specific IgE Values at/or Above Which There Is a 95% Risk of Clinical Allergy

Food	Serum IgE (kIU/L) for 95% PPV
Egg (child)	≥7
Egg (age <2 y)	≥2
Cow's milk (child)	≥15
Cow's milk (age <2 y)	≥5
Peanut	≥14
Fish	≥20

Abbreviation: PPV, positive predictive value.

The definition used to indicate a positive test result (or degree of positive) will additionally affect the positive predictive value and negative predictive value. For example, increasing skin test size correlates directly with increasing IgE antibody and the risk of clinical reactions. Therefore, if one were to analyze skin test sizes (rather than just labeling them categorically as positive or negative at a mean wheal size of 3 mm), there would be variation in sensitivity and specificity with each incremental change in size. In general, because the definition of a positive test result requires a larger wheal, specificity increases and sensitivity decreases. This is illustrated by a study that revealed that positive oral challenge results to cow's milk, hen's egg, and peanut always occurred at PST wheal values of 8 mm or larger, 7 mm or larger, and 8 mm or larger, respectively.<sup>480</sup> As cutoff for positive increases, so does the positive predictive value, whereas the negative predictive value simultaneously decreases. Since these indices of predictive value are population dependent, the predictive value drops (illness is overestimated) when results obtained in a referral center (high prevalence) are applied to unselected individuals. Table 9 gives the values of food specific IgE antibody measured by Unicap-System Fluorescent Enzyme Immunoassay (in kIU/L) at or above which there is a 95% risk for an allergic reaction in children based on studies in referral populations (eg, these values may affect a decision to defer oral food challenges).<sup>479,491</sup> The application of these values is thus far limited to studies in children for just a few foods.

#### FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS (EIA)

*Summary Statement 74.* Individuals with food-dependent EIA develop neither anaphylaxis with ingestion of food without subsequent exercise nor anaphylaxis after exercise without temporally related ingestion of food. (A)

Foods associated with food-specific EIA include crustaceans,<sup>524</sup> cephalopods,<sup>525</sup> celery,<sup>526,527</sup> grapes,<sup>528</sup> chicken,<sup>529</sup> wheat,<sup>529,530</sup> buckwheat,<sup>531</sup> tomato,<sup>529</sup> dairy products,<sup>532</sup> and matsutake mushrooms.<sup>533</sup> One case has been described in which the sequence was reversed in that anaphylaxis was provoked by food consumption *preceded by exercise*.<sup>526</sup> Cases of food-dependent EIA requiring prior consumption of 2 foods,<sup>534</sup> related to contamination of food with *Penicillium lanoso caeruleum*,<sup>535</sup> and occurring in the postprandial period unrelated to a specific food or beverage<sup>536</sup> have also been reported. An epidemiologic survey of 279 individuals with EIA, either food dependent or non-food dependent, revealed that jogging was the most frequent exercise precipitating episodes of EIA.<sup>532</sup> However, a variety of activities, including tennis or racquetball, basketball, skiing, dancing, aerobics, bicycling, and even less strenuous activities such as yard work or walking, were also implicated in provoking EIA episodes.<sup>532</sup> Factors associated with episodes of food-dependent EIA include phase of menstrual cycle,<sup>530,531</sup> use of aspirin or aspirin-like drugs,<sup>529,532,537,538</sup> the amount of food ingested,<sup>528,539</sup> season,<sup>529,532,540</sup> and climactic conditions such as

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ambient temperature and humidity.<sup>532</sup> EIA may occur in individuals with cholinergic urticaria (see The Diagnosis and Management of Anaphylaxis, Diagnosis and Management of Urticaria: A Practice Parameter, and The Diagnosis and Management of Anaphylaxis: An Updated Practice Parameter) as a manifestation of aberrant thermoregulatory mechanisms during exercise.<sup>541,542</sup>

*Summary Statement 75.* Two subsets of patients with food-dependent EIA have been described: (1) one subset may develop anaphylaxis when exercising in temporal proximity to ingestion of *any type of food*; (2) another subset may experience anaphylaxis with exercise in conjunction with ingestion of a *specific food*. (A)

Food-dependent EIA has been associated with mast cell degranulation and elevated plasma histamine levels.<sup>524,543,544</sup> Several hypotheses to explain this syndrome have been proposed.<sup>525,544–547</sup> A mast cell secretagogue may be elaborated during exercise in the postprandial state in affected individuals. The interaction of specific IgE antibody with food antigen may lower the mast cell releasability threshold to the physical stimulus of exercise. In patients with food-dependent EIA, the physical stimulus of exercise in the postprandial state may enhance the potential for release of histamine and other mediators from mast cells or basophils and/or may encourage altered mucosal enzyme activity or barrier function, thereby promoting intestinal absorption of food antigens.

When a specific food is suspected by history, significant wheal-flare reaction on PST (or in vitro detection of specific IgE antibodies) can confirm the potential for IgE-mediated reaction to the suspected food. Exercise challenge with and without prior consumption of the relevant food may also be useful in establishing this diagnosis.

*Summary Statement 76.* Management of food-dependent EIA entails avoiding exercising in proximity to food consumption, carrying self-injectable epinephrine, exercising with a “buddy,” and wearing medic-alert jewelry. (C)

Individuals in whom the diagnosis of EIA is confirmed should be advised to avoid exercising in close proximity to (specific) food consumption. The length of time that affected individuals should not exercise following food consumption is controversial. However, a waiting period of 4 to 6 hours is generally recommended. Provocation of EIA with a latency following food consumption of 24 hours has been reported.<sup>537</sup> For this reason, it is prudent to individualize this management recommendation, particularly for individuals with postprandial (non-food specific) EIA. No data are available to support the effectiveness of prophylactic medication use (including antihistamine, oral cromolyn, or oral corticosteroid) to reliably safeguard against food-dependent EIA. When exercising, EIA patients should be accompanied by a designated individual who is aware of their condition, carries a cellular telephone if available, and is able to treat anaphylaxis if it should occur. Self-injectable epinephrine should be prescribed, and medical identification jewelry should be worn describing this condition. Individuals with food-dependent

EIA should also be advised to modify exercise on warm, humid days, avoid concomitant use of aspirin and aspirin-like drugs, and cease exercising at the earliest occurrence of premonitory symptoms of anaphylaxis such as pruritus or flushing.

Emergency management of an episode of food-dependent EIA is similar to the management of other types of anaphylaxis (see Anaphylaxis Practice Parameter).

## DIFFERENTIAL DIAGNOSIS OF ADVERSE REACTIONS TO FOODS

### Introduction

Adverse reactions to foods can be due to immunologic or nonimmunologic pathogenic mechanisms. Immunologic reactions to foods can be IgE mediated or non-IgE mediated. Immunologic reactions to foods have a characteristic clinical presentation and need to be separated from nonimmunologic reactions to foods, as well as reactions that are consistent with reactions to foods but are not caused by food exposure. Food reactions of uncertain immunologic etiology include (1) food-dependent, EIA, a variant of EIA, and (2) reactions to food additives.

*Summary Statement 77.* Non-IgE-mediated immunologic reactions to foods have been implicated in such entities as (1) food-induced enterocolitis and colitis; (2) malabsorption syndromes (eg, celiac disease); (3) cow’s milk-induced syndromes; and (4) dermatitis herpetiformis. (C)

A wide spectrum of adverse reactions may occur after ingestion of food. These are typically classified on the basis of the underlying pathogenesis (Table 10), which is relevant to the management of patients with adverse reactions to food. Adverse food reactions can be divided on the basis of immunologic and nonimmunologic mechanisms. The clinical presentation of the latter may mimic immunologic reactions. The former may include IgE-mediated and non-IgE-mediated reactions. In addition, there are conditions, not related consistently to food ingestion, such as irritable bowel syndrome or inflammatory bowel disease, symptoms of which may mimic reactions to food. These conditions are important to recognize because patients may have an incorrect opinion as to whether a clinical condition is due to food ingestion. In particular, patients with psychological disorders often attribute their reactions to foods. Physicians must be aware that this is a frequent occurrence in adult patients and food allergy may not be the major cause of their symptoms. Although this document is focused on food-induced IgE-mediated reactions, it is essential that the practicing physician be able to identify and separate food-induced IgE-mediated reactions from other types of reactions to food.

Reactions to foods may also result from non-IgE-mediated immunologic mechanisms, and in such cases, a correlation between food ingestion and the reaction may be less obvious, particularly with gastrointestinal reactions. Non-IgE-mediated immunologic food reactions can be gastrointestinal,



Table 10. Primary Considerations in the Differential Diagnosis of Adverse Reactions to Foods

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- A. Immunologic
1. IgE-mediated reactions (anaphylaxis)
    - a. Systemic IgE-mediated reactions (anaphylaxis)
      - i) Immediate-onset reactions
      - ii) Late-onset reactions
    - b. IgE-mediated gastrointestinal reactions
      - i) Oral allergy syndrome
      - ii) Immediate gastrointestinal allergy
    - c. IgE-mediated respiratory reactions
      - i) Rhinitis
      - ii) Asthma secondary to ingestion of food
      - iii) Asthma secondary to inhalation of food (e.g. occupational asthma)
    - d. IgE-mediated cutaneous reactions
      - i) Immediate onset reactions
        - (a) Acute urticaria or angioedema
        - (b) Contact urticaria
      - ii) Late-onset reactions
        - (a) Atopic dermatitis
  2. Non-IgE-mediated immunologic food reactions
    - a. Gastrointestinal reactions
      - i) Food-induced enterocolitis
      - ii) and Malabsorption syndromes colitis
      - iii) Celiac disease
      - iv) Infantile colic
    - b. Cutaneous reactions
      - i) Dermatitis herpetiformis
      - ii) Allergic contact dermatitis
    - c. Pulmonary reactions
      - i) Cow's milk-induced pulmonary hemosiderosis
- B. Nontoxic, nonimmunologic
1. Intolerance
    - a. Enzymatic or metabolic
      - i) Lactose intolerance
      - ii) Carbohydrate malabsorption
- C. Food reactions of uncertain immunologic etiology
1. Food-dependent exercise-induced anaphylaxis
  2. Food-additive reactions
  3. Eosinophilic esophagogastronteropathy
- D. Toxic
1. Bacterial (eg, food poisoning)
  2. Pharmacologic (eg, scombroid poisoning)
- E. Reactions not consistently related to food ingestion
1. Irritable bowel syndrome
  2. Inflammatory bowel disease
- 

cutaneous, or pulmonary and include such entities as (1) food-induced enterocolitis or colitis; (2) food-induced malabsorption syndromes (eg, celiac disease); (3) a variety of cow's milk-induced conditions; (4) dermatitis herpetiformis; and (5) allergic contact dermatitis. In addition, food-dependent EIA may be associated with a non-IgE-mediated immunologic reaction (see "The Clinical Spectrum of Food Allergy" section).

Food reactions of uncertain immunologic etiology include (1) food-dependent EIA, a variant of EIA; and (2) reactions to food additives

*Summary Statement 78.* Food-induced enterocolitis and colitis are most commonly seen in infants several hours after ingestion of food proteins, most notably those in cow's milk or soy formulas. Infants with food-induced enterocolitis develop severe protracted vomiting and diarrhea compared with infants with food-induced colitis who usually appear healthy. Both groups of patients present with blood and eosinophils in the stool, although colitis more often presents with gross blood. (C)

Food-induced enterocolitis frequently presents in infants between 1 week and 3 months of age (although it can occur in older children) with symptoms developing several hours after ingestion of food proteins (eg, milk, soy). These infants develop severe protracted vomiting and diarrhea, not infrequently resulting in dehydration and hypotension. Food protein-induced enterocolitis is generally seen in infants using cow's milk or soy protein formulas but occasionally is seen in breast fed infants, presumably from allergens passed in maternal milk.<sup>461,495,548</sup> Approximately one third of infants with severe diarrhea resulting from food-induced enterocolitis develop acidosis and transient methemoglobinemia.<sup>497</sup> Similar symptoms have been reported in older children and adults after ingestion of egg, rice, wheat, oat, tree nuts, chicken, turkey, fish, and peanut.<sup>549,550</sup> Occult blood, eosinophils, and neutrophils are generally present in the stools. On oral challenge, there is an increase in the peripheral blood neutrophil count, but IgE antibodies to provoking foods have not been demonstrated. Approximately 15% of challenges have been reported to result in hypotension<sup>551</sup> and therefore should be performed in a setting that allows for rapid response with appropriate treatment if such a reaction occurs. Jejunal biopsy specimens reveal patches of flattened villi, edema, and increased numbers of lymphocytes, eosinophils, and mast cells. However, the diagnosis of enterocolitis must be made on the basis of the patient's clinical presentation, since findings such as increased IgA- and IgM-containing plasma cells in intestinal biopsy specimens and increased intraepithelial lymphocytes are nonspecific.<sup>552</sup> Most children with food-induced enterocolitis will recover from this condition by their third birthday.<sup>548</sup>

Food-induced colitis also presents in the first few months of life and is generally secondary to cow's milk or soy protein hypersensitivity but also may occur in exclusively breastfed infants.<sup>553-558</sup> These children generally appear healthy and are discovered only because of the presence of gross or occult blood in their stool. Sigmoidoscopic findings are variable but range from areas of patchy, mucosal injection to severe friability with small aphthoid ulcerations and bleeding. Mucosal edema and a prominent eosinophilic infiltrate in the crypt epithelium and lamina propria are seen on biopsy specimens. Focal increases in the number of eosinophils in the mucosa is seen histologically<sup>553,558-560</sup> as are polymorphonuclear neutrophils in patients who have severe lesions with

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crypt destruction.<sup>561</sup> Infants with food-induced colitis have been reported as being able to tolerate the responsible allergens after 6 months to 2 years of allergen avoidance, although no systematic studies have been performed to confirm this observation.

*Summary Statement 79.* Immune-mediated malabsorption syndromes that result in diarrhea and weight loss (or lack of weight gain) may occur secondary to intolerance to a variety of food proteins, including those in cow's milk, soy, wheat, other cereal grains, and eggs. (C)

Immune-mediated malabsorption syndromes that result in diarrhea and weight loss (or poor weight gain) may be secondary to intolerance to a variety of food proteins, including cow's milk, soy, wheat and other cereal grains, and eggs.<sup>562</sup> Symptoms may include protracted diarrhea, vomiting, and failure to thrive. These patients may have increased fecal fat with steatorrhea, decreased absorption of carbohydrates, and often iron-deficiency anemia and hypoproteinemia due to damage to the jejunal mucosa. A patchy villous atrophy similar to celiac disease but generally less severe is seen on endoscopy. Biopsy of the intestinal wall reveals a prominent lymphocytic infiltrate of the epithelium with an increase in IgA- and IgM-containing cells and a small number of eosinophils in the lamina propria. Isolated cells have been shown to have increased secretion of interferon- $\gamma$ .<sup>563</sup>

*Summary Statement 80.* Celiac disease is a severe form of malabsorption characterized by total villous atrophy and extensive cellular infiltrates due to an immunologic reaction to gliadin, a component of gluten found in wheat, oat, rye, and barley. The diagnosis of the disease is crucial, since the removal of gluten from the diet can lead to reversal of histopathologic changes and recovery of gastrointestinal function. (C)

Celiac disease is a severe form of malabsorption due to extensive enteropathy with total villous atrophy, marked increase in crypt-villous ratio, and extensive cellular infiltrates secondary to an immunologic reaction to gliadin, a component of gluten found in wheat, rye, and barley.<sup>564-570</sup> Celiac disease is characterized by IgA antigliadin and IgA antiendomysial (tissue transglutaminase) antibodies,<sup>569</sup> as well as prominent numbers of CD8<sup>+</sup> lymphocytes in the jejunal mucosa and the peripheral blood.<sup>570</sup> An excellent correlation has been demonstrated between the presence of antiendomysial antibodies and villous atrophy.<sup>571</sup> The diagnosis of the disease is critical, since the removal of gluten from the diet can result in total recovery of gastrointestinal function and reversal of the histopathologic changes.<sup>565,572</sup> Life-long elimination of gluten-containing foods is necessary to prevent recurrence of symptoms.

*Summary Statement 81.* In a subset of infants, colic and gastroesophageal reflux disease have been attributed to adverse reactions to cow's milk. However, an immunologic basis for these conditions has not been clearly established. (A)

Infantile colic is seen in 15% to 40% of infants younger than 4 months<sup>573</sup> and is characterized by crying, irritability,

abdominal distention, and excess flatus. Only rarely has an immunologic basis for infantile colic been implicated.<sup>574-576</sup> although double-blind studies in bottle-fed and breastfed infants indicate that IgE-mediated hypersensitivity may be a pathogenic factor in some infants.<sup>572-580</sup> In addition, infantile colic has been linked to carbohydrate malabsorption.<sup>581</sup> Although the diagnosis is important, specific treatment for this condition has been limited but includes elimination of suspected foods.<sup>582-584</sup> An immunologic basis for this condition has not been clearly established.<sup>585</sup> Gastroesophageal reflux in the first year of life has been attributed, in a subset of infants, to cow's milk allergy or intolerance.<sup>586,587</sup> The prevalence of this association is controversial and has been estimated to be 16% to 42%.<sup>180,588-590</sup>

*Summary Statement 82.* Dermatitis herpetiformis is characterized by a chronic, intensely pruritic, papulovesicular rash symmetrically distributed over the extensor surfaces of the extremities and the buttocks associated with gluten ingestion and often with gluten-sensitive enteropathy. Direct immunofluorescence or specific immunologic assays may be helpful in making the diagnosis. (B)

Dermatitis herpetiformis is a cutaneous non-IgE-mediated condition associated with food ingestion, which is characterized by a chronic, intensely pruritic, papulovesicular rash symmetrically distributed over the extensor surfaces of the extremities and the buttocks.<sup>591</sup> Many, but not all, patients with dermatitis herpetiformis have gluten-sensitive enteropathy.<sup>591,592</sup> Both involved and uninvolved skin are infiltrated with neutrophils and contain deposits of IgA and C3 that typically accumulate at the dermoepidermal junction, although histologic findings may be nonspecific.<sup>593</sup> Therefore, direct immunofluorescence or specific immunologic assays may be helpful in making the diagnosis.<sup>594</sup> The histologic features of the intestinal lesion are virtually identical to that seen in celiac disease, although villous atrophy and inflammatory infiltrates are less pronounced.<sup>595</sup> Epidermal transglutaminase autoantigens have been demonstrated in dermatitis herpetiformis,<sup>596</sup> in addition to circulating tissue transglutaminase autoantigens, which have also been implicated in celiac disease.<sup>597-600</sup>

*Summary Statement 83.* Cow's milk-induced pulmonary hemosiderosis (Heiner syndrome) is an extremely rare condition in infants that also may be related to egg or pork hypersensitivity and for which the immunopathology is poorly understood. It is characterized clinically by recurrent episodes of pneumonia associated with pulmonary infiltrates, hemosiderosis, gastrointestinal blood loss, iron-deficiency anemia, and failure to thrive. The presence of precipitating antibodies to the responsible antigen is necessary but not sufficient to make the diagnosis. (C)

Cow's milk-induced pulmonary hemosiderosis (Heiner syndrome) is an extremely rare non-IgE-mediated pulmonary hypersensitivity.<sup>601</sup> There have also been reports of hypersensitivity to egg and pork as a cause of this condition.<sup>602</sup> It usually occurs in infants and is characterized by chronic cough, wheezing, recurrent lung infiltrates, hemosiderosis,

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gastrointestinal blood loss, failure to thrive, and microcytic hypochromic anemia. In affected patients' sera, precipitins to cow's milk proteins are detectable and have been thought to be related to the pathogenesis of this disease.<sup>603</sup> However, the immunopathology of this condition is not completely understood.<sup>604</sup> The presence of peripheral blood eosinophilia, including precipitating antibodies to the responsible antigen, is considered necessary but not sufficient to make a diagnosis. Removal of cow's milk protein can result in symptomatic improvement, and reintroduction of cow's milk protein can result in symptom recurrence and worsening of the clinical course. In infants who present with pulmonary infiltrates, the presence of severe anemia should suggest the possibility of a cow's milk-induced origin.

*Summary Statement 84.* Toxic food reactions, bacterial contamination of food, and pharmacologic food reactions may mimic IgE-mediated reactions and should be considered early in the differential diagnosis because of the serious nature of such reactions. (C)

Food poisoning is an adverse reaction that occurs as a result of bacterial contamination of food, usually due to contamination during handling, and may occur immediately after ingestion of the contaminated food, such as with *Staphylococcus exotoxin* and *Escherichia coli* enterotoxin. There may also be a delay after eating the contaminated food before the onset of the reaction if the contaminating microorganism causes an infection, such as with *Salmonella* or *E coli*. In many cases, an adverse food reaction may be mistakenly attributed to a gastrointestinal virus unless multiple individuals at a given site develop symptoms, suggesting a common food source as the cause.

*Summary Statement 85.* Pharmacologic adverse food reactions occur after ingestion of foods with pharmacologically active substances, such as vasoactive amines, in particular histamine (scombroid poisoning), and produce a wide range of clinical manifestations, especially gastrointestinal and central nervous system in nature. Patients may present with flushing, sweating, nausea, vomiting, diarrhea, headache, palpitations, dizziness, swelling of the face and tongue, respiratory distress, and shock. (C)

Pharmacologic adverse food reactions occur on ingestion of foods with pharmacologically active substances. A variety of foods contain vasoactive amines and other substances capable of inducing a wide range of manifestations, most notably gastrointestinal and central nervous system manifestations. Vasoactive amines include tyramine, tryptamine, phenylethylamine, dopamine, norepinephrine, serotonin, and histamine. Histamine may occur naturally in foods, such as strawberries, tomatoes, spinach, and other foods<sup>605-607</sup> and can also be produced by bacteria that decarboxylate histidine. In the latter situation, the ingestion (and perhaps even inhalation<sup>607</sup> of foods with a high histamine content, most often scombroid fish (tuna and mackerel) but also skipjack, bonito, mahi-mahi, bluefish, amberjack, herring, sardines, anchovies, and in some countries primarily smoked fish<sup>608</sup> as well as cheese, can lead to immediate anaphylactoid reactions (ie,

within 1 hour after ingestion). When these reactions occur, patients may present with flushing, sweating, nausea, vomiting, diarrhea, headache, palpitations, dizziness, and occasionally swelling of the face and tongue, respiratory distress, and shock.<sup>609-615</sup>

*Summary Statement 86.* Enzymatic food reactions are caused by the ingestion of normal dietary amounts of foods in individuals susceptible to such reactions because of medications, disease states, malnutrition, or inborn errors of metabolism (eg, lactose intolerance). (C)

Enzymatic metabolic food reactions are caused by the ingestion of normal dietary amounts of foods in individuals susceptible to such reactions because of medications they are taking, disease states, malnutrition, or inborn errors of metabolism. The most frequent type of metabolic food reaction is lactose intolerance, which occurs in individuals with deficiency of the enzyme lactase. Decreased levels or lack of this enzyme results in fermentation of lactose to lactic acid and a resultant osmotic effect in the gastrointestinal tract, leading to symptoms of malabsorption and diarrhea. Other enzyme deficiencies include disaccharidase deficiency (sucrase-isomaltase, glucose-galactose), galactosemia, and phenylketonuria.

*Summary Statement 87.* Reactions not related to specific food ingestion but due to the act of eating that can be misdiagnosed as reactions to foods include gustatory or vasomotor rhinitis, carcinoid syndrome, idiopathic anaphylaxis, systemic mastocytosis, inflammatory bowel disease, and irritable bowel syndrome. (C)

The presence of food in the stomach can stimulate the formation of gastrin and the nonspecific release of histamine.<sup>616</sup> The auriculotemporal syndrome (Frey syndrome, gustatory flushing syndrome) is characterized by a transient, nonpruritic vascular flush, usually unilateral, on the cheek along the distribution of the auriculotemporal nerve that occurs with strong salivation. The flush may mimic a food allergic reaction because of the timing with ingestion of tart or spicy foods.<sup>617</sup> Furthermore, there are reactions that mimic food reactions but that are not specifically caused by ingestion of food. Gustatory rhinitis without flushing is a manifestation of vasomotor rhinitis. Carcinoid syndrome may cause intestinal symptoms and flushing with or without food ingestion and is diagnosed by the presence of elevated levels of urinary 5-hydroxyindoleacetic acid. Idiopathic anaphylaxis, systemic mastocytosis, and hereditary angioedema are other disorders that may be confused with food allergy. Irritable bowel syndrome, essentially a diagnosis of exclusion, may also be associated with abdominal complaints after ingestion of food.

*Summary Statement 88.* Conditions incorrectly identified as being related to food ingestion include multiple sclerosis, attention-deficit disorder, autism and other behavioral conditions, chronic fatigue syndrome, and the "yeast connection." (C)

Attention-deficit disorder with or without hyperactivity, autism, and other behavior problems have never been convincingly demonstrated to be related to ingestion of food. In

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addition, there is no evidence that chronic fatigue or multiple sclerosis is associated with food ingestion. Foods that contain yeast have been suspected of causing a multitude of constitutional symptoms (the so-called yeast connection), although there is no evidence for the validity of such a connection. A connection between food ingestion and arthritis, vascular headaches, and convulsive disorders has been suspected.<sup>618,619</sup>

## GENERAL MANAGEMENT OF FOOD ALLERGY

In general, there are 4 approaches to the management of allergic conditions: avoidance, education, pharmacotherapy, and immunotherapy. Avoidance measures, education, and pharmacotherapy, as they relate specifically to food allergy, will be discussed herein. Immunotherapy with food allergens has not been shown to be consistently effective or safe in the management of patients with food allergy.<sup>404,620,621</sup>

*Summary Statement 89.* The key to the management of patients with food allergy is avoidance of foods known to have or suspected of having caused a reaction. (F)

Patients should make every effort to avoid foods to which they have previously had a reaction. After a correct diagnosis of food allergy has been confirmed, complete avoidance of the implicated food(s) is the only proven form of prophylactic management currently available. This is not always an easy undertaking, especially if the patient is extremely sensitive to a food allergen, the food is ubiquitous, and/or the food is difficult to avoid. Labeling may be misleading, small amounts of the food allergen may be present in tolerated foods, and there may be hidden cross-contamination. Patients can often tolerate a particular food in another form (eg, raw vs cooked).

*Summary Statement 90.* Since elimination diets may lead to malnutrition or other serious adverse effects (eg, personality change), every effort should be made to ensure that the dietary needs of the patient are met and that the patient and/or caregiver(s) are fully educated in dietary management (D).

Since elimination diets may lead to malnutrition or other serious adverse effects,<sup>622-624</sup> every effort should be made to ensure that the dietary needs of the patient are met and that the patient and/or caregiver(s) are fully educated in dietary management. Elemental diets such as EleCare, Neocate, or Vivonex may be useful in some patients who have multiple food allergies. Hydrolysates may be useful in young children.<sup>344</sup> It is important to determine the specific foods to which a patient is allergic because of the serious consequences of malnutrition or eating disorders, if a large number of foods are being eliminated from the diet during an extended period.<sup>622,624</sup> Even the elimination of an important food such as cow's milk can lead to deficiencies in protein, calcium and vitamins. A local dietician or the Food Allergy Network (<http://www.foodallergy.org> or e-mail [faan@foodallergy.org](mailto:faan@foodallergy.org) or telephone 1-800-929-4040) may provide additional educational and supportive input.

*Summary Statement 91.* In some cases, severe allergic reactions may be seen in patients who only inhale or come in

contact with food allergens, thereby making avoidance even more difficult. (D)

Severe allergic reactions may be seen in some patients who only inhale or come in contact with food allergens.<sup>625-627</sup> Some patients may experience symptoms on inhalation of a food allergen but not experience symptoms after ingestion of the same food allergen (eg, baker's asthma).<sup>628</sup> Therefore, it may be necessary to avoid food exposure by routes other than ingestion.

Patients allergic to eggs may react to allergens released when eggs are cooked. Theoretically, patients who are extremely allergic to peanuts might have a reaction at a ball game when peanut particles from husking are blown in the wind and inhaled by that individual and in airplanes when another passenger is eating peanuts. Patients allergic to fish or shellfish may react to aerosolized proteins from these foods when they are cooked. Reactions that occur in such patients can be severe and sometimes fatal. Therefore, patients who have this marked sensitivity require special avoidance education. However, most patients with food allergies do not experience symptoms after inhalational exposure. Allergic reactions to foods have been reported in highly sensitized individuals from kissing, receiving allografts, or exposure to seminal fluid that contains the food allergen.<sup>629-631</sup>

*Summary Statement 92.* The successful avoidance of food allergens relies on (1) identification in each patient of the specific food that caused the reaction; (2) recognition of cross-reacting allergens in other foods; (3) education of the patient and/or caregiver about avoidance measures, with particular emphasis on hidden food allergens or additives; and (4) willingness of the educated patient and/or caregiver to read labels carefully, inquire at restaurants, and take other measures to prevent inadvertent exposure to known or suspected allergens. (D)

Patients, family members, and other individuals responsible for the care of the patient should be taught to scrutinize food labels to detect potential sources of food allergens.<sup>632</sup> Severe reactions, including anaphylaxis, may result from ingestion of unrecognized (hidden) foods.<sup>13,633-635</sup> Consumption of hidden food ingredients is one of the greatest challenges and dangers facing the patient with food allergy, as well as the physician and/or dietary professional. Elimination of even one food may require extensive education of the patient and/or patient's advocate.<sup>339</sup> For example, multiple names for milk or milk-containing products (eg, casein, whey, caseinate, lactalbumin, hydrolyzed protein) may be present on a food label without a listing for milk. A recent study to determine the accuracy of label reading among parents of food allergic children concluded that with current labeling practices, most parents are unable to identify common allergenic food ingredients.<sup>634</sup> Investigation into the source of exposure may be necessary.

High-risk environments may need to be avoided if the patient is highly allergic and particularly if the patient has reacted to airborne food allergens. High-risk environments may include common eating places such as school cafeterias,

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lunchrooms, other individual's homes, some restaurants, for example, those that large amounts of peanuts in dishes, receptions, ice cream shops, and yogurt shops.

*Summary Statement 93.* In selected cases, reevaluation of patients with food allergy may be important to determine if food allergy has been lost over time. (F)

Patients with food allergy, especially younger patients allergic to eggs, milk, or wheat, may need to be reevaluated if it is important to determine whether food allergy has been lost. Monitoring of food specific IgE antibody levels may be helpful in determining the time that would be appropriate for food challenge and/or reintroduction of a food into the patient's diet. Peanut, tree nut, fish, and shellfish allergy are more likely to persist throughout the patient's life.<sup>29,261,279,636</sup> Food allergens trigger atopic dermatitis more commonly in young infants and children than adults (see Disease Management of Atopic Dermatitis: A Practice Parameter). Patients who have pollen- or food-related syndrome (oral allergy syndrome) should avoid foods that trigger the reaction, although the likelihood that more severe reactions will occur in such patients is minimal. Symptoms consistent with food allergy may be manifestations of psychological problems. The management of such patients is challenging and may require specific treatment focusing on this aspect of their condition. Every attempt should be made to rule out nonallergic conditions that might produce allergic-type symptoms.

*Summary Statement 94.* If there is a history of suspected or proven IgE-mediated systemic reactions to foods, injectable epinephrine should be given to patients and/or caregivers to carry with them and they should be instructed in its use. (F)

Inadvertent ingestion of a food by individuals who know that they are allergic to that food is not uncommon. For example, during a 3- to 4-year period, patients allergic to peanuts have a 35% to 50% chance of unintentional ingestion of peanuts.<sup>637,638</sup> Not only do patients experience allergic reactions to foods after unexpected exposure but the characteristics of reactions to foods may vary. For example, patients who experience anaphylaxis from ingestion of a food may experience an acute and/or delayed reaction.<sup>26,113</sup> As a result, prolonged observation after anaphylaxis is often indicated. Patients may experience a severe reaction after exposure to a food without having more than a mild reaction when previously exposed to that food.

The pharmacotherapy of food allergies revolves around emergency treatment for patients who are inadvertently exposed to food allergens to which they have previously had a reaction. Epinephrine is the treatment of choice for anaphylactic reactions, in general, and food-induced anaphylaxis in particular (see The Diagnosis and Management of Anaphylaxis: An Updated Practice Parameter). Therefore, injectable epinephrine and instructions on its use should be given to any patient who has a history of an immediate systemic IgE-mediated reaction to a food. Epinephrine should be administered early in the treatment of an anaphylactic reaction. In addition, the patient should immediately seek appropriate medical care if they develop a systemic reaction to a food.

The health care professional should know the potential pharmacologic benefits, risks, and routes of administration of epinephrine.

*Summary Statement 95.* Prophylactic medications have not been shown to be effective in consistently preventing severe, life-threatening reactions to foods and may mask a less severe IgE-mediated reaction to a food, knowledge of which could prevent a more severe reaction to that food in the future. (D)

Medications taken before food ingestion will not reliably protect patients from anaphylactic reactions to foods.<sup>637,638</sup> Antihistamines may mask a less severe IgE-mediated reactions to a food, knowledge of which could lead to future avoidance of that food. On the other hand, antihistamines may be helpful in the treatment of anaphylaxis. Antihistamines should never, however, be considered a substitute for epinephrine in the management of anaphylaxis.

There are insufficient data to indicate whether H<sub>2</sub>-receptor antagonists or other mediator antagonists have any effect on preventing reactions after exposure to foods.<sup>639</sup> Oral cromolyn has not consistently been effective in preventing reactions to food allergens.<sup>640</sup> Oral corticosteroids are *not* effective in preventing the immediate phase of anaphylaxis, including that induced by food exposure.

## MANAGEMENT IN SPECIAL SETTINGS AND CIRCUMSTANCES

Implementing a food allergy treatment strategy is simplest within the patient's home, where there is both control over meal preparation and also a strong likelihood that an emergency plan will be available and familiar to family members. Patients have an increased risk for unintentional food allergen exposure in a number of special settings and circumstances. These include, but are not limited to, schools, childcare centers, restaurants, hospitals, summer camps, public transportation modalities such as commercial airlines, and behaviors such as kissing and coitus. There are no controlled studies that prove that a specific intervention reduces the mortality or morbidity associated with food reactions in these special settings and circumstances, although standards have evolved based on clinical experience.

*Summary Statement 96.* Fatal and near-fatal food anaphylactic reactions tend to occur away from home after an unintentional ingestion of a food allergen by individuals with a known allergy to the same food. (C)

*Summary Statement 97.* Delay in the administration of injectable epinephrine is a common feature of fatal food allergic reactions. (C)

*Summary Statement 98.* Peanut and tree nuts account for most fatal and near-fatal food allergic reactions in the United States. (C)

Three separate retrospective US studies have described a total of 52 fatal or near-fatal cases of food-induced anaphylaxis.<sup>13,26,641</sup> Most (85%) of these events occurred away from home, and almost all (98%) of the subjects had a prior history of food allergy. Epinephrine was administered promptly in only 12% of cases. Peanut and tree nuts accounted for 54%

and 33% of these reactions, respectively. Nearly half of the fatalities (43%) occurred at either a school or an eating establishment.

*Summary Statement 99.* Allergic reactions that result from direct skin contact with food allergens are generally less severe than reactions due to allergen ingestion. Reactions that result from inhalation of food allergens are generally less frequent and less severe than reactions caused by either direct skin contact or ingestion. Exceptions to these generalizations are more likely in occupational environments and other settings in which food allergen sensitization occurred via either inhalation or skin contact. (B)

Patients with food allergies may report symptoms with direct skin contact or ambient exposure to the offending food.<sup>625,642-647</sup> These reactions are frequently reported to occur in schools and daycare centers with peanut butter craft projects.<sup>643</sup> There are also several uncontrolled reports of systemic or severe local reactions that occurred with cutaneous contact,<sup>625</sup> kissing,<sup>625,647</sup> coitus,<sup>630</sup> or inhalational<sup>628</sup> exposures to food in severely allergic patients. One controlled inhalational food challenge study<sup>645</sup> has documented both early- and late-phase asthmatic responses in selected food allergic children with asthma. Despite this, both individual patient reports<sup>642,644</sup> and additional controlled challenges<sup>645,646</sup> suggest that severe reactions due to noningestion exposures are rare.

*Summary Statement 100.* Schools and childcare centers should have policies for facilitating food allergen avoidance, including staff education regarding label reading and cross-contamination, prohibition of food or utensil sharing, and increased staff supervision during student meals. (D)

*Summary Statement 101.* Schools and childcare centers should have policies ensuring prompt treatment of food anaphylaxis, including a requirement for physician-prescribed treatment protocols for food allergic students, staff education regarding recognition and treatment of anaphylaxis, and the ready availability of injectable epinephrine. (D)

Allergic reactions to foods in schools and daycare centers are not rare events.<sup>643,648</sup> Peanut, milk, and tree nuts account for most of these reactions,<sup>643,648</sup> although reactions at school to other foods have also been reported.<sup>648</sup> Treatment delays of food allergic reactions in schools occur due to failure to recognize reactions promptly, calling parents, failure to follow emergency management plans, and incorrect technique when administering epinephrine.<sup>643</sup> Table 11 lists recommended avoidance and treatment standards for schools<sup>649</sup> and is based, in part, on a Position Statement issued by the American Academy of Asthma, Allergy and Immunology in 1998.<sup>650</sup>

*Summary Statement 102.* It is important to inform workers in a restaurant or other food establishment about a history of a systemic food allergic reaction, although this does not ensure that the meal will be free of the offending food. (C)

In the United States, most fatal food allergy reactions in restaurants or other food establishments are caused by unintentional ingestion of peanuts or tree nuts.<sup>13</sup> More than 10%

Table 11. Avoidance and Treatment Strategies for Food Allergies in Schools\*

Avoidance
· Increased supervision during meals and snacks (perhaps allergy free table)
· No food, container, or utensil sharing
· Cleaning of tables, toys
· Substitution of causal food during craft, cooking, science projects
· Handwashing before and after food handling and eating
· Avoidance of exposure to food during preparation and cooking
· Provision of safe substitute foods
· Foods brought in should have ingredient labels
· Instruction of staff on issues of
Careful label reading
Cross-contamination
Technical and scientific word(s) for the food(s)
Treatment
· Physician-prescribed treatment protocols in place, periodic review of protocols
· Epinephrine available for potentially life-threatening reactions (readily available, not locked)
· Education of supervising personnel on:
recognizing signs of an allergic reaction
technique of medication administration
basic first aid and resuscitation

\* Reproduced with permission from Bock et al.<sup>13</sup>

of patients with peanut or tree nut allergy report experiencing reactions in restaurants or other food establishments.<sup>642</sup> These reactions frequently require epinephrine treatment and occur more often in Asian restaurants, bakeries, or ice cream shops. Patients frequently neglect to inform food establishment personnel of their food allergy, although errors also occur, despite warnings.

*Summary Statement 103.* Allograft transplant recipients may acquire specific food allergic sensitivities from organ donors. (B)

Immediate anaphylactic reactions have been reported to peanut<sup>651,652</sup> and tree nuts<sup>652</sup> in liver transplant recipients without previous histories of food allergy. In these cases the organ donors' cause of death was anaphylaxis to the same foods, and there had been a prior history of allergy to these foods. There are also reports that recipients of a bone marrow<sup>653,655</sup> transplant may acquire specific food allergies from organ donors.

*Summary Statement 104.* Patients with latex allergy have an increased risk of experiencing IgE-mediated food-induced symptoms, including anaphylaxis, particularly when ingesting banana, avocado, kiwi, or chestnut. (C)

Clinical reactions to natural rubber latex allergens have become an increasingly important problem, and approximately 50% of patients with latex allergy also have clinical food allergies.<sup>655-657</sup> The most commonly implicated foods include banana, avocado, kiwi, and chestnut, and these appear to cross-react with natural rubber latex via class I chiti-

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nases.<sup>658</sup> Multiple additional fruits and vegetables cross-react with one or more latex proteins, although some latex allergic patients are allergic to foods without known cross-reactivity with natural rubber latex.

## FUTURE DIRECTIONS

*Summary Statement 105.* Future strategies for diagnosis, treatment, and prevention of food allergy will involve the use of new molecular and immunologic techniques. (B)

Future strategies for diagnosis, treatment, and prevention of food allergy include the following: (1) exploration of other possible routes of sensitization (eg, respiratory and/or skin) as possible sources of food sensitization; (2) identification of food allergy phenotypes by single nucleotide polymorphisms and specific haplotypes; (3) synthesis of bioengineered peptides lacking B-cell-specific food allergen epitopes with the potential to induce autotolerance in food allergic patients; (4) use of CD4<sup>+</sup> CD25<sup>+</sup> positive regulatory T cells or their secretory products (TGF- $\beta$  or IL-10) for induction of tolerance or immune deviation after food sensitivity is established; (5) the role of commensal bacteria in preventing systemic immunity as a potentially useful adjunct in the management of food allergy; (6) development of genetically modified, non-IgE-binding mutants of the most highly allergenic foods that would not induce allergy even in highly susceptible individuals; and (7) investigation of the anti-allergic pharmacologic properties of certain Chinese herbal remedies for treatment of food allergy. (B)

*Summary Statement 106.* Although there is no evidence at this time to justify the use of humanized anti-IgE monoclonal antibody for preventing severe food allergy responses, future research will determine the clinical feasibility of such an approach and the use of short-chain Fc $\epsilon$ RI peptides antagonistic to the Fc $\epsilon$ RI  $\alpha$ -chain. (B)

Future research focus areas of special interest to food allergy will depend on mechanistic progress in mucosal immunity and tolerance, as well as the unique sensitization patterns of food allergens themselves. As the complex functional interactions among epithelial, dendritic, CD4<sup>+</sup>, and CD8<sup>+</sup> lymphocytes, mast cells, and their respective cytokines within gut-associated lymphoid tissue (GALT) become more clearly delineated, novel preventive or therapeutic strategies may become apparent.<sup>659-663</sup> In particular, it is anticipated that several subsets of mucosal regulatory CD4<sup>+</sup>, CD25<sup>+</sup> cells (secreting TGF- $\beta$  or IL-10) could be up-regulated to induce peripheral tolerance after food sensitization has occurred.<sup>664,665</sup>

Inductive or inhibitory signals between innate (Toll-like) and adaptive immune receptors in GALT should define the respective roles of commensal gut bacteria vis-à-vis pathogens in preventing or enhancing systemic immunity.<sup>660,662,663</sup> In this regard, several recent clinical trials have demonstrated that probiotic bacteria may alleviate intestinal inflammation, thereby suggesting their potential usefulness as adjuncts in the treatment of food allergy.<sup>666,667</sup> Apart from possible specific receptor and/or signaling alterations within the cellular

milieu of GALT, several nonspecific immunologic approaches are under current investigation.

Treatment of peanut-sensitive patients with a humanized IgG1 monoclonal antibody against an epitope in the CH<sub>3</sub> domain of IgE achieved a significant increase of oral challenge thresholds in a dose-dependent manner.<sup>668</sup> Patients who received 450 mg of the monoclonal antibody were able to tolerate 8 peanuts compared with 1 or 2 peanuts before the treatment. Thus, this treatment may effectively prevent anaphylactic reactions in the event that small amounts of peanut are inadvertently ingested as contaminants of other foods. In addition to neutralizing almost all peanut-specific circulating IgE, the monoclonal antibody masks the CH<sub>3</sub> site responsible for binding to both Fc $\epsilon$ RI and Fc $\epsilon$ R2, thereby preventing the binding of IgE to Fc $\epsilon$ RI on mast cells and basophils and Fc $\epsilon$ R2 on eosinophils, monocytes, macrophages, and platelets. However, it does bind to membrane-associated IgE on differentiated B cells. Other investigators have defined the functional region of the Fc $\epsilon$ RI  $\alpha$ -chain by interactions with a series of synthetic antagonistic Fc $\epsilon$ RI peptides.<sup>669</sup> One of these peptides successfully inhibited IgE binding in the area of the CH<sub>3</sub> domain. This could serve as the basis for future abrogation of food reactions under the protective cover of short chain recombinant synthetic peptides.<sup>669</sup>

Several allergen-dependent aspects of sensitization should receive considerable attention. Both single nucleotide polymorphisms and general susceptibility patterns will undoubtedly be investigated with increasing frequency.<sup>81,670,671</sup> The route(s) of sensitization by foods is not exclusively oral. For example, it has been known for some time that a significant proportion of workers sensitized to food proteins by the inhalant route will subsequently develop food allergy symptoms.<sup>23</sup> In a recent long-term epidemiologic survey of 15,000 near-term pregnant women and their recently delivered children, the use of baby skin creams that contained peanut oil, presumably with traces of peanut protein, was found to be a significant risk factor for subsequent occurrence of peanut allergy.<sup>462,672</sup> These creams were applied when the children were experiencing rashes and preceded the onset of peanut allergy. Thus, there will be heightened awareness about the possibility of respiratory and/or skin as routes of food sensitization. This will be particularly relevant for those inhalant allergens with known cross-allergenic determinants to specific classes of foods (eg, concomitant house dust mite and shellfish allergy; concomitant birch pollen and food allergy).<sup>673-675</sup>

In the past decade, major IgE-binding determinants have been identified for most of the common food allergens, and more recently, synthetic recombinant forms of these peptides have been produced.<sup>74</sup> Current and future research in this area will be to develop non-IgE-binding mutants of these recombinant proteins by site-directed mutagenesis.<sup>74</sup> Theoretically at least, if this could be accomplished for all the major allergens in a particular food, it would be possible to produce a genomically modified strain of that food that would not induce allergy even in highly susceptible individuals. An-

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other possible application of such engineered peptides would be to use their immunotherapeutic potential, because these mutants retain T-cell immunoregulatory activities without the possibility of anaphylactic reactions due to the lack of IgE B-cell epitopes.<sup>676</sup> Thus, genetic engineering of food allergens may enable new immunotherapeutic approaches and offer the possibility of hypoallergenic foods for patients with food allergy.

*Summary Statement 107.* New approaches in evidence-based medicine aim to more precisely define the potential clinical outcomes reflected in test results through mathematical calculations of data derived through clinical studies, such as the application of likelihood ratios. (D)

The choice of which diagnostic test to perform depends in part on the performance characteristics of the various tests. Such characteristics include the positive and negative predictive values and the likelihood ratios (LRs) for each test. The latter is a measure of the likelihood that a positive test result is present in someone who actually has the disease. The LR is simply the ratio of the odds that the patient whose test results fall within a particular range has the disease divided by the odds that they do not. The formula can most conveniently be expressed as  $LR = \text{sensitivity}/(1 - \text{specificity})$  as applies to a positive test result. To be useful, a LR needs to be determined for each diagnostic test used in evaluating the probability of food allergy. Unfortunately, this is not available for most food allergy tests. When the LR is known, a "pretest" probability (based for example on the medical history) is estimated and a nomogram can be used to determine the posttest probability that a person has the disorder.

Although LRs are not calculated for most tests of food allergy, the concept of LR and pretest probability has practical implications for routine practice. Consider, for example, 3 individuals: (1) a child with 3 severe allergic reactions to peanut requiring epinephrine, (2) a child with chronic atopic dermatitis who eats peanuts but has no history of a reaction to peanut, and (3) a nonatopic child who sometimes has headaches on days he eats peanut. Each patient is tested by PST to peanut and has a 4-mm wheal, a positive test result with modest sensitivity (approximately 50%), and good specificity (approximately 90%). The meaning of a 4-mm wheal to peanut when there has been recurrent anaphylaxis in patient 1 (high prior probability of peanut allergy, virtually 100%) is that it confirms reactivity and no food challenge should be undertaken. In a chronic condition like atopic dermatitis in patient 2, a modest size skin test may reflect clinical reactivity in only approximately half of patients (depending also on age) and may be a relevant positive result in this scenario, needing confirmation by other means (oral food challenge) or additional testing to increase diagnostic accuracy (serum test). The test result in patient 3 with headaches is most likely of no clinical concern, since the pretest probability is essentially zero. Considering again the patient with multiple episodes of peanut-related anaphylaxis, if there were no wheal response to peanut, the clinician would not be likely to trust the result because the pretest probability is so high that the

correct course of action would be to repeat the test and consider a supervised oral food challenge if the test result were negative. Similarly, one could argue that a test for peanut causing migraines is not necessary, since the prior probability is so low. Thus, one test (eg, PST) can provide pretest probability for another test (eg, oral food challenge).

More specific calculations may become possible once the tests are studied more for a variety of foods, age groups and diagnoses.<sup>479</sup> The need to confirm a diagnosis also weighs in the decision to proceed with tests at any given risk evaluation (eg, confirmation of an allergy may be more important for certain foods as mentioned previously).

## APPENDIX: SUGGESTED ORAL CHALLENGE METHODS

In diagnostic oral food challenges, the food is given in gradually increasing amounts. The physician or health care professional records the dose given, the time of administration, vital signs, and any symptoms that arise during the challenge.<sup>403</sup> Frequent assessments are made for symptoms that affect the skin, gastrointestinal tract, respiratory tract, and/or cardiovascular system. Challenges may be done with the food unhidden (open), disguised but known by the physician to contain the test food (single-blind), or double-blind and placebo-controlled. The rationale for selection of the test format is reviewed in the "Diagnosis of Food Allergy" section of this parameter. No fatalities have been described from supervised oral food challenges despite decades of use for diagnostic purposes, but reactions elicited can be severe. For example, in a report of 513 positive oral food challenge results in 196 children, 48% of reactions included respiratory symptoms, 10% of reactions were graded as severe, and 11% of reactions that developed on the first dose were severe.<sup>478</sup> As indicated elsewhere in these Parameters, oral challenges can elicit severe, anaphylactic reactions, so the physician should be prepared to treat with appropriate emergency medications and equipment.

Despite discussions to make a uniform international protocol for performing oral food challenges, no consensus has been reached.<sup>468,499,500,677,678</sup> Comprehensive manuals that describe the procedure, including discussions of dosing, methods to disguise foods, examples of flow sheets that can be used to document the procedure, and consideration for informed consent, have been published.<sup>403,678</sup> These published resources also discuss the potential need to individualize dosing and time frame of administration according to the clinical history. One approach<sup>403,476,478,679</sup> is to administer a total of 8 to 10 g of the dry food or 100 mL of wet food (double the weight for meat or fish) in gradually increasing doses at 10- to 15-minute intervals for approximately 90 minutes followed by a larger, meal-size portion of food a few hours later. The protein content of foods vary, so absolute protein content is not equivalent for different foods. In research protocols, dry forms of foods are often used (eg, milk, eggs, and peanut flour), and so the grams used 8 to 10 g may not match the protein content of ingested foods in their



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natural form. Thus, the powdered forms with a weight of 8 to 10 g are approximately equivalent to 100 mL of skim milk, 1 egg, and 20 mL of peanut butter, respectively. The whole challenge may be distributed, for example, in portions such as 1%, 4%, 10%, 20%, 20%, 20%, and 25% of the total. For example, 1% of the milk challenge is 1 mL. However, a variety of other challenge regimens have been used (lower starting doses including 10-fold lower doses for potentially highly sensitive persons, variations in the degree of dosing increases, different intervals, etc).<sup>679,680</sup> It is important to follow negative blinded challenges with an open feeding of a meal-size portion of the food prepared in the manner relevant to the patient's history (eg, cooked or raw) to confirm that the food is tolerated. If such an open feeding induces a reaction, consideration may be given to repeat a blinded challenge better simulating the actual ingestion (eg, cooked or raw) and portions using larger doses.

To be particularly cautious in persons who may be extremely sensitive based on clinical judgment (eg, a patient with asthma who seems to have experienced a severe reaction to a small amount of a food under consideration for oral food challenge), one could argue for starting doses that begin under the thresholds reported to induce reactions. Unfortunately, the published thresholds vary by logarithmic differences among studies and data are not available for most foods. However, reactions are usually not reported for less than 0.25 mg of protein for peanut (approximately 1 in 1,000 of 1 mL of peanut butter), 0.13 mg for egg (similar to the volume of peanut), and 0.6 mg for milk (approximately 0.02 mL).<sup>681</sup> Clearly, these trace doses cannot be easily measured or administered. Labial food challenge has been suggested as a safe starting point for oral challenges by some researchers. This procedure begins with placing the food extract on the lower lip for 2 minutes and observing for local or systemic reactions in the ensuing 30 minutes.<sup>679,682</sup> The development of a contiguous rash of the cheek and chin, edema of the lip with conjunctivitis or rhinitis, or a systemic reaction is considered a positive test result.<sup>682</sup> Negative labial challenges are generally followed by an oral food challenge. However, the utility of this approach has not been extensively studied.

## ACKNOWLEDGMENTS

Published Practice Parameters of the Joint Task Force on Practice Parameters for Allergy & Immunology include the following:

1. Practice parameters for the diagnosis and treatment of asthma. *J Allergy Clin Immunol.* 1995;96:S707–S870.
2. Practice parameters for allergy diagnostic testing. *Ann Allergy Asthma Immunol.* 1995;75:543–625.
3. Practice parameters for the diagnosis and management of immunodeficiency. *Ann Allergy Asthma Immunol.* 1996;76:282–294.
4. Practice parameters for allergen immunotherapy. *J Allergy Clin Immunol.* 1996;98:1001–1011.
5. Disease management of atopic dermatitis: a practice parameter. *Ann Allergy Asthma Immunol.* 1997;79:197–211.

6. The diagnosis and management of anaphylaxis. *J Allergy Clin Immunol.* 1998;101:S465–S528.

7. Algorithm for the diagnosis and management of asthma: a practice parameter update. *Ann Allergy Asthma Immunol.* 1998;81:415–420.

8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol.* 1998;81:S463–S518.

9. Parameters for the diagnosis and management of sinusitis. *J Allergy Clin Immunol.* 1998;102:S107–S144.

10. Stinging insect hypersensitivity: a practice parameter. *J Allergy Clin Immunol.* 1999;103:963–980.

11. Disease management of drug hypersensitivity: a practice parameter. *Ann Allergy Asthma Immunol.* 1999;83:S665–S700.

12. Diagnosis and management of urticaria: a practice parameter. *Ann Allergy Asthma Immunol.* 2000;85:S521–S544.

13. Allergen immunotherapy: a practice parameter. *Ann Allergy Asthma Immunol.* 2003;90:S1–S54.

14. Symptom severity evaluation of allergic rhinitis: part I. *Ann Allergy Asthma Immunol.* 2003;91:105–114.

15. Disease management of atopic dermatitis: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2004;93:S1–S21.

16. Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol.* 2004;113:869–886.

17. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol.* 2005;115:S482–S523.

18. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol.* 2005;94:S1–S63.

19. Attaining optimal asthma control: a practice parameter. *J Allergy Clin Immunol.* 2005;116:S3–S11.

20. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol.* 2005;116:513–547.

These parameters are also available on the Internet at [www.jcaai.org](http://www.jcaai.org).

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