Practice parameter

Food allergy: A practice parameter update—2014

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This parameter was developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI). The AAAAI and the ACAAI have jointly accepted responsibility for establishing "Food Allergy: A practice parameter update—2014." This is a complete and comprehensive document at the current time. The medical environment is a changing one, 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. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Disclosure of potential conflict of interest: H. A. Sampson has received research support from the National Institute of Allergy and Infectious Diseases (NIAID; AI44236 and AI66738), the National Institutes of Health (NIH; RR026134), and Food Allergy Research and Education (FARE); has received travel support as the chair of PhARF Award review committee; has consultant arrangements with Allertein Therapeutics, Regeneron, and the Danone Research Institute; and has received payment for lectures from Thermo Fisher Scientific, UCB, and Pfizer. S. Aceves is a member of the medical advisory panel for the American Partnership for Eosinophilic Disorders; has received research support from the National Institutes of Health (NIAID AI092135), the Department of Defense, and the American Academy of Allergy, Asthma & Immunology (AAAAI)/American Partnership for Eosinophilic Disorders; has a patent held by University of California–San Diego for OVB licensed to Meritage Pharma; and has received travel support from the NIH and the Falk Foundation. S. A. Bock is on the medical advisory board for FARE. S. Jones has received research support from the NIH (COFAR), the NIH/NIAID Immune Tolerance Network (A1-15416), and Food Allergy Research and Education. D. Lang is a speaker for Genentech/Novartis, GlaxoSmithKline, and Merck; has consultant arrangements with GlaxoSmithKline, Merck, Aerocrine; and has received research support from Genentech/Novartis and Merck. A. Nowak-Wegrzyn is a speaker for Thermo Fisher Scientific, is on the advisory board for Nutricia, is on the Data Safety Monitoring Board for Merck, and has received research support from Nestlé (grant 0955), Nutricia, and the NIH. J. Oppenheimer has received research support from AstraZeneca, GlaxoSmithKline, Merck, Boehringer Ingelheim, Novartis, and MedImmune; has provided legal consultation/expert witness testimony in malpractice defense cases; is chairman of the American Board of Allergy and Immunology; and has consultant arrangements with GlaxoSmithKline, Mylan, Novartis, and Sunovion. C. Randolph is a member of the Board of Regents for the American College of Allergy, Asthma & Immunology (ACAAI); has consultant arrangements with AstraZeneca and Genentech; has received payment for lectures from GlaxoSmithKline, AstraZeneca, Genentech, and TEVA; and has received travel support from TEVA. S. H. Sicherer has received research support from the NIAID, is a member of the American Board of Allergy and Immunology, has consultant arrangements with Novartis and FARE; and receives royalties from UpToDate. R. A. Simon has provided expert testimony for various law firms; has received payment for lectures from Merck, Novartis, and CSL-Behring; holds patents for the use of surfactants in chronic rhinosinusitis and asthma; has received royalties from Wiley Blackwell and UpToDate; and has stock options in URXmobile. B. P. Vickery has received research support from the NIH/NIAID (AI099083) and the Foundation of the ACAAI. R. Wood has consultant arrangements with the Asthma and Allergy Foundation of America, is employed by Johns Hopkins University, has received research support from the NIH, and receives royalties from UpToDate. The rest of the authors declare that they have no relevant conflicts of interest.

We thank Anne Munoz-Furlong for review and helpful comments to "Section IX: Management in special settings."

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Received for publication February 7, 2014; revised May 2, 2014; accepted for publication May 6, 2014.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.05.013

Key words: *Food allergy, food allergen, cross-reactivity, adverse food reactions, IgE-mediated food allergy, eosinophilic esophagitis*

Previously published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology are available at http://www.JCAAI.org or http://www.allergyparameters.org.

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The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Recommendation rating scale

Statement	Definition	Implication
Strong recommendation (StrRec)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B).* In some clearly identified circumstances, strong recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate (Mod)	A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C).* In some clearly identified circumstances, recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Weak (Weak)	An option means that either the quality of evidence that exists is suspect (grade D)* or that well-done studies (grade A, B, or C)* show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they might set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is both a lack of pertinent evidence (grade D)* and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

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 quasiexperimental study
- III Evidence from nonexperimental descriptive studies, such as comparative studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation*

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated recommendation from category I evidence
- C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
- LB Laboratory based
- NR Not rated

SUMMARY OF CONFLICT OF INTEREST DISCLOSURES

The following is a summary of interests disclosed on workgroup members' conflict of interest disclosure statements (not including information concerning family member interests). Completed conflict of interest disclosure statements are available on request.

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Resolution of nondisqualifying interests

The Joint Task Force recognizes that experts in a field are likely to have interests that could come into conflict with development of a completely unbiased and objective practice parameter. A process has been developed to prevent potential conflicts from influencing the final document in a negative way to take advantage of that expertise.

At the workgroup level, members who have a potential conflict of interest either do not participate in discussions concerning topics related to the potential conflict, or if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is reviewed by the Joint Task Force, and any apparent bias is removed at that level. Finally, the practice parameter is sent for review both by invited reviewers and by anyone with an interest in the topic by posting the document on the Web sites of the ACAAI and AAAAI.

The practice parameter on food allergy was last updated in 2006[1] and focused primarily on IgE-mediated food allergy. In the ensuing years, there have been considerable advances in the field in many areas, including our basic understanding of food allergens, diagnostic testing, non–IgE-mediated disorders, and management of various food-induced allergic reactions. In 2010, the NIAID "Guidelines on the diagnosis and management of food allergy" were published, providing a comprehensive review of the scientific literature and expert opinion on food allergy.[2] Given the many advances in the field, the Joint Task Force on Practice Parameters appointed a working group to review and update the standing practice parameters. The working group relied heavily on the NIAID Guidelines and focused on advances since the publication of that landmark document.

THE JOINT TASK FORCE ON PRACTICE PARAMETERS

The Joint Task Force on Practice Parameters (JTF) is a 13-member task force consisting of 6 representatives assigned by the AAAAI, 6 by the ACAAI, and 1 by the Joint Council of Allergy and Immunology. This task force oversees the development of practice parameters, selects the workgroup chair or chairs, and reviews drafts of the parameters for accuracy, practicality, clarity, and broad utility of the recommendations for clinical practice.

FOOD ALLERGY: A PRACTICE PARAMETER UPDATE—2014 WORKGROUP

The Food Allergy: A Practice Parameter Update 2014 Workgroup was commissioned by the JTF to develop a practice parameter that addresses recent advances in the field of food allergy and the optimal methods of diagnosis and management based on an assessment of the most current literature. The Chair (Hugh A. Sampson, MD) invited workgroup members to participate in the parameter development who are considered to be experts in the field of food allergy. Workgroup members have been vetted for financial conflict of interest by the JTF, and their conflicts of interest have been listed in this document and are posted on the JTF Web site at http://www.allergyparameters.org.

The charge to the workgroup was to use a systematic literature review in conjunction with consensus expert opinion and workgroup-identified supplementary documents to develop a practice parameter that evaluates the current state of the science regarding food allergy.

PROTOCOL FOR FINDING EVIDENCE

The NIAID guidelines were used to identify previously identified impactful studies on these topics. Additional Clinical reports were reviewed to ensure parity of expert opinion (AAP and ICON). Additional PubMed searches were performed primarily to identify items in the literature after September 2009 that were pertinent to update these topics. Meta-analyses were always selected when available. Grading of each reference was performed as applicable (see the reference list), and overall grades and strengths of recommendations were placed after the summary statements. Search terms include food allergy, food allergen, and each of the specific conditions reviewed in this parameter.

SUMMARY STATEMENTS

Summary Statement 1: Evaluate the patient for possible food allergy with the understanding that a relatively small number of allergens cause a high proportion of food allergy (eg, cow's milk, hen's egg, soy, wheat, peanut, tree nuts, fish, and shellfish). See Summary Statement 48 for management. [Strength of recommendation: Strong; B Evidence]

Summary Statement 2: Advise patients who are allergic to certain specific foods about the risk of ingestion of similar cross-reacting foods. Examples include ingestion of other tree nuts in patients with tree nut allergy (eg, walnut and pecan or pistachio and cashew), Crustacea in patients with crustacean seafood allergy, vertebrate fish in patients with fish allergy, and other mammalian milks in patients with cow's milk allergy. [Strength of recommendation: Strong; C Evidence]

Summary Statement 3: Avoid other mammalian milks, such as goat's milk or sheep's milk, in patients with cow's milk allergy because of highly cross-reactive allergens. [Strength of recommendation: Strong; B Evidence]

Summary Statement 4: Advise patients with seafood allergy that they are not at increased risk of a reaction to radiocontrast media. There is no documented relationship between non–IgE-mediated anaphylactic reactions to radiocontrast media and allergy to fish, crustacean shellfish, or iodine. [Strength of recommendation: Strong; D Evidence]

Summary Statement 5: Test for IgE antibodies specific for the immunogenic oligosaccharide galactose-alpha-1, 3-galactose (alpha-gal) in patients who report a delayed systemic reaction to red meat or unexplained anaphylaxis, particularly if they have a history of previous tick bites. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 6: Avoid all mammalian meats in patients with alpha-gal allergy because this oligosaccharide antigen is widely expressed in mammalian tissues. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 7: Evaluate patients with latex allergy for the possibility of cross-reactivity to banana, avocado, kiwi, chestnut, potato, green pepper, and other fruits and nuts. Individualized management is recommended because clinical reactions caused by this cross-reactivity can range from mild to severe. [Strength of recommendation: Strong; C Evidence]

Summary Statement 8: Advise patients not to be concerned about ingesting genetically modified foods given the current state of knowledge and the US Food and Drug Administration's screening requirements to rule out allergenicity of genetically modified foods. [Strength of recommendation: Weak; D Evidence]

Summary Statement 9: Manage non–IgE-mediated reactions to foods with appropriate avoidance and pharmacotherapy as indicated with the understanding that the specific role of immunity (eg, IgA, IgM, IgG, and IgG subclasses) in these forms of food allergy has not been demonstrated. [Strength of recommendation: Strong; B Evidence]

Summary Statement 10: Determine whether the reported history of food allergy, which often proves inaccurate, and laboratory data are sufficient to diagnose food allergy or whether an oral food challenge (OFC) is necessary. [Strength of recommendation: Strong; A Evidence]

Summary Statement 11: Consider the natural course of allergies to specific foods when deciding on the frequency of food allergy follow-up evaluations, recognizing that allergies to certain foods (milk, egg, wheat, and soy) generally resolve more quickly in childhood than others (peanut, tree nuts, fish, and shellfish). These observations could support individualized follow-up (ie, roughly yearly re-evaluations of these allergies in childhood) with less frequent retesting if results remain particularly high (eg, >20-50 kU_A/L). [Strength of recommendation: Moderate; C Evidence]

Summary Statement 12: Encourage exclusive breast-feeding for the first 4 to 6 months of life. [Strength of recommendation: Weak; C Evidence]

Summary Statement 13: For infants with a family history of atopy, consider a partially or extensively hydrolyzed infant formula for possible prevention of atopic dermatitis and infant cow's milk allergy if exclusive breast-feeding is not possible. [Strength of recommendation: Moderate; B Evidence]

Summary Statement 14: Do not recommend maternal allergen avoidance or avoidance of specific complementary foods at weaning because these approaches have not proved effective for primary prevention of atopic disease. [Strength of recommendation: Weak; C Evidence]

Summary Statement 15: Do not routinely recommend supplementation of the maternal or infant diet with probiotics or prebiotics as a means to prevent food allergy because there is insufficient evidence to support a beneficial effect. [Strength of recommendation: Weak; C Evidence]

Summary Statement 16: Do not routinely recommend that patients with chronic idiopathic urticaria (CIU) avoid foods containing additives. [Strength of recommendation: Strong; B Evidence]

Summary Statement 17: Do not routinely instruct asthmatic patients to avoid sulfites or other food additives unless they have a prior reaction to sulfites. Sulfites are the only food additive proved to trigger asthma. Although these reactions can be severe, even life-threatening in sensitive subjects, they are rare. [Strength of recommendation: Strong; B Evidence]

Summary Statement 18: Consider natural food additives in the evaluation of patients with a history of unexplained ingestant-related anaphylaxis. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 19: Patients who experience an adverse reaction to food additives should be evaluated for sensitivity to annatto and carmine. [Strength of recommendation: Strong; A Evidence]

Summary Statement 20: Clinicians should be aware that avoidance measures are appropriate for patients with histories compatible with adverse reactions to an additive until diagnostic evaluation can be performed. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 21: Clinicians should not recommend food additive avoidance in their patients with hyperactivity/attention deficit disorder. [Strength of recommendation: Strong; A Evidence]

Summary Statement 22: The clinician should obtain a detailed medical history and physical examination to aid in the diagnosis of food allergy. [Strength of recommendation: Strong; D Evidence]

Summary Statement 23: The clinician should use specific IgE tests (skin prick tests, serum tests, or both) to foods as diagnostic tools; however, testing should be focused on foods suspected of provoking the reaction, and test results alone should not be considered diagnostic of food allergy. [Strength of recommendation: Strong; B Evidence]

Summary Statement 24: Component-resolved diagnostic testing to food allergens can be considered, as in the case of peanut sensitivity, but it is not routinely recommended even with peanut sensitivity because the clinical utility of component testing has not been fully elucidated. [Strength of recommendation: Weak; C Evidence]

Summary Statement 25: The clinician should consider OFCs to aid in the diagnosis of IgE-mediated food allergy. [Strength of recommendation: Strong; A Evidence]

Summary Statement 26: If clinical history is not consistent with anaphylaxis, perform a graded OFC to rule out food allergy. Open food challenge is both cost- and time-efficient. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 27: If the diagnosis is still unclear after open food challenge, then recommend a blind food challenge. [Strength of recommendation: Moderate; B Evidence]

Summary Statement 28: Elimination diets and diet diaries can be used as an adjunctive means to diagnose food allergies but are not to be depended on solely for confirming a diagnosis. [Strength of recommendation: Weak; D Evidence]

Summary Statement 29: A diagnosis of food-dependent, exercise-induced anaphylaxis should be considered when ingestion of causal food or foods and temporally related exercise result in symptoms of anaphylaxis. The clinician should recognize that symptoms only occur with ingestion of the causal food or foods proximate to exercise and that ingestion of the food in the absence of exercise will not result in anaphylaxis. [Strength of recommendation: Strong; B Evidence]

Summary Statement 30: The clinician should consider the diagnosis of oral allergy syndrome (pollen-food allergy) and obtain specific IgE testing to pollens in patients who experience limited oropharyngeal symptoms after ingestion of food antigens that cross-react with pollen antigens. [Strength of recommendation: Strong; B Evidence]

Summary Statement 31: A diagnosis of IgE-mediated contact urticaria should be considered in patients with a history of immediate urticarial rash at the site of contact with a food allergen. [Strength of recommendation: Weak; D Evidence]

Summary Statement 32: Do not routinely obtain total serum IgE levels for the diagnosis of food allergy. [Strength of recommendation: Strong; C Evidence]

Summary Statement 33: Do not perform intracutaneous testing for the diagnosis of food allergy (see discussion). [Strength of recommendation: Strong; B Evidence]

Summary Statement 34: Unproved tests, including allergen-specific IgG measurement, cytotoxicity assays, applied kinesiology, provocation neutralization, and hair analysis, should not be used for the evaluation of food allergy. [Strength of recommendation: Strong; C Evidence]

Summary Statement 35: Although routine use of atopy patch tests for diagnosis of food allergy is not recommended, the use of food atopy patch tests in patients with pediatric eosinophilic esophagitis (EoE) have been demonstrated to be valuable in assessing potential food triggers. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 36: The physician should use the patient's medical history, response to a trial of elimination of the suspected food, and OFC to establish a diagnosis of food protein–induced enterocolitis syndrome (FPIES). However, when the history indicates that infants or children have experienced hypotensive episodes or multiple reactions to the same food, a diagnosis can be based on a convincing history and absence of symptoms when the causative food is eliminated from the diet. [Strength of recommendation: Strong; B Evidence]

Summary Statement 37: The clinician should be aware that a gastrointestinal evaluation with endoscopy and biopsy is usually not required for the diagnosis of FPIES and allergic proctocolitis with symptoms that respond to elimination of the offending food and recur when the food is reintroduced into the diet. [Strength of recommendation: Weak; C Evidence]

Summary Statement 38: Measurement of food-specific IgG and IgG_4 antibodies in serum are not recommended for the diagnosis of non–IgE-mediated food-related allergic disorders. [Strength of recommendation: Strong; B Evidence]

Summary Statement 39: A trial of twice daily protein pump inhibitor (PPI) therapy for 8 weeks before diagnostic testing for EoE is recommended to exclude gastroesophageal reflux disease (GERD) and PPI-responsive esophageal infiltration of eosinophils. [Strength of recommendation: Strong; C Evidence]

Summary Statement 40: The diagnosis of EoE should be based on the presence of characteristic symptoms and endoscopic features and the presence of 15 or more eosinophils per high-power field quantified by a pathologist using hematoxylin and eosin staining of esophageal biopsy specimens at $\times 400$ light microscopy. [Strength of recommendation: Strong; B Evidence]

Summary Statement 41: Eosinophilic gastroenteritis (EGE) should be considered a constellation of clinical symptoms in combination with gastric, small intestine, and/or large intestine infiltration of eosinophils at greater than the reported normal numbers of gastric and intestinal eosinophils. [Strength of recommendation: Weak; D Evidence]

Summary Statement 42: Prescribe a targeted allergen elimination diet as the treatment for known or strongly suspected food allergy. Education about proper food preparation and the risks of occult exposure is essential. [Strength of recommendation: Strong; C Evidence]

Summary Statement 43: Recommend consultation with a nutritionist for growing children in whom elimination diets might affect growth, as well as those patients with multiple food allergies, poor growth parameters, or both. Clinicians must be aware of the nutritional consequences of elimination diets and certain medications, such as esomeprazole, especially in growing children. Specifically, identifying alternative dietary sources of calcium and vitamin D is critical for patients with milk allergy. [Strength of recommendation: Strong; B Evidence]

Summary Statement 44: Review recognition and treatment of IgE-mediated food-related allergic reactions with each patient and caregivers, as appropriate. Emphasis should be placed on prompt awareness of anaphylaxis and swift intervention. [Strength of recommendation: Strong; C Evidence]

Summary Statement 45: Discuss self-care management techniques, especially with high-risk patients, (eg, adolescents, young adults, and asthmatic patients), focusing on risk reduction and recognition and treatment of anaphylaxis. [Strength of recommendation: Strong; C Evidence]

Summary Statement 46: Use epinephrine as first-line management for the treatment of anaphylaxis. [Strength of recommendation: Strong; C Evidence]

Summary Statement 47: Ensure that self-injectable epinephrine is readily available to the patient and instruct the patient, caregiver, or both on the importance of its use and self-administration, as relevant. [Strength of recommendation: Strong; C Evidence]

Summary Statement 48: Evaluate children with food allergies at regular intervals (1-2 years), according to the patient's age and the food allergen, to determine whether he or she is still allergic. If food allergy is unlikely to change over time, as in adults, periodic re-evaluation (2-5 years) is recommended, depending on the food allergy. [Strength of recommendation: Strong; C Evidence]

Summary Statement 49: For patients with food-dependent, exercise-induced anaphylaxis, avoid food ingestion within 2 to 4 hours of exercise for prevention of symptoms, and provide prompt treatment with onset of symptoms. [Strength of recommendation: Strong; C Evidence]

Summary Statement 50: Manage pollen-food allergy syndrome or oral allergy syndrome by dietary avoidance of raw fruits, vegetables, or both based on the patient's symptom profile severity. The extent of food avoidance depends on the severity of oropharyngeal symptoms. [Strength of recommendation: Strong; C Evidence]

Summary Statement 51: The clinician should understand the various clinical presentations of these conditions (ie, FPIES/proctocolitis/enteropathy), educate patients and care providers about common food triggers, and recommend strict food avoidance of allergenic foods for symptom management. [Strength of recommendation: Strong; C Evidence]

Summary Statement 52: Use volume replacement therapy for the acute care management of patients with FPIES. [Strength of recommendation: Strong; B Evidence]

Summary Statement 53: See patients with FPIES and allergic gastrointestinal disorders at regular intervals and consider rechallenge in an appropriate medical facility based on the natural history of the specific disorder. [Strength of recommendation: Strong; C Evidence]

Summary Statement 54: Consider serial tissue biopsies as part of disease management in patients with EoE. Symptoms alone or endoscopy without biopsy cannot be used as an accurate gauge of EoE disease activity. [Strength of recommendation: Strong; C Evidence]

Summary Statement 55: Consider assessment for aeroallergen sensitization because EoE can be triggered by aeroallergens in human subjects and animal models and there might be a seasonality to EoE diagnoses. [Strength of recommendation: Moderate; D Evidence]

Summary Statement 56: Consider food allergy evaluation with both skin prick and patch testing for EoE to rule out possible food triggers. Remember that positive serum specific IgE levels, food skin prick test responses, and food patch test results are not sufficient to diagnose food triggers for EoE. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 57: Consider the use of targeted or empiric food-elimination diets or amino acid–based diets for successful EoE therapy. [Strength of recommendation: Strong; B Evidence]

Summary Statement 58: Consider the use of swallowed topical esophageal corticosteroids for successful EoE therapy. [Strength of recommendation: Strong; A Evidence]

Summary Statement 59: Referral to a gastroenterologist for esophageal dilation is recommended for high-grade stenosis but does not provide inflammatory control. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 60: Administer oral corticosteroids for EGE as the preferred therapy. [Strength of recommendation: Weak; C Evidence]

Summary Statement 61: Although immunotherapeutic approaches, such as oral immunotherapy, in clinical trials show promise in treating food allergy, they are not ready for implementation in clinical practice at the present time because of inadequate evidence for therapeutic benefit over risks of therapy. [Strength of recommendation: Strong; A Evidence]

Summary Statement 62: Develop a written action plan for treatment of allergic reactions to food for adults and children. [Strength of recommendation: Moderate; D Evidence]

Summary Statement 63: Inquire about and address behavioral changes because of bullying in patients with food allergy. This inquiry should include adults and children. [Strength of recommendation: Strong; D Evidence]

Summary Statement 64: Teach patients that ingestion, rather than casual exposure through the skin or close proximity to an allergen, is almost the only route for triggering severe allergic/anaphylactic reactions. [Strength of recommendation: Strong; C Evidence]

PREFACE

As defined by the NIAID expert panel, *food allergy* is defined here "as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food."[2] Here, the term *allergy* is not limited to IgE-mediated immunologic reactions and is used to connote the induction of clinical signs and symptoms, as opposed to *sensitivity*, which indicates the presence of IgE antibodies to a food, often in the absence of clinical symptomatology. Although the prevalence of food allergy overall and of allergy to specific foods is uncertain because studies vary in methodological approaches,[3,4] allergists who have been in practice for at least a decade have been confronted with an ever-growing number of patients with food allergy. On the basis of a recent extensive review of the literature, food allergy is estimated to affect more than 1% to 2% and less than 10% of the population.[3] There are limited data to suggest that food allergy prevalence has increased, but national surveys suggest that peanut allergy has tripled since the late 1990s.[5,6] In considering a number of published studies,[4,7,8] it is apparent that estimates of food allergy prevalence are highest when based on self-report (approximately 12% to 13%) compared with estimates based on studies using tests, such as OFCs (approximately 3%). This observation regarding a discordance of suspected and proved food allergy underscores the importance of using proved diagnostic methods to evaluate individual patients suspected of a having food allergy.

The physician should apply information regarding epidemiologic features of food allergy when approaching diagnosis and management, recognizing that self-reported food allergy is more common than proved food allergy, that food allergy is more common in children, that a limited number of foods account for most significant food allergies, and that food allergy occurs more commonly in persons with other atopic diseases. There are a number of epidemiologic features regarding food allergy that might be helpful in constructing *a priori* assessment of risk and consideration of potential triggers when evaluating individual patients. Although more than 170 foods have been identified as triggers of food allergy, those causing most of the significant allergic reactions include peanut, tree nuts, fish, shellfish, milk, egg, wheat, soy, and seeds.[2,5,9-11] Food allergy (to foods other than shellfish and fruits/vegetables) is more common in children than in adults.[4,7,8,10-12] As described elsewhere in this parameter, milk, egg, wheat, and soy allergies are more common in children than in adults.

There is a high co-occurrence of food allergy with other atopic diseases, including atopic dermatitis, asthma, and allergic rhinitis.[2,6,13,14] In particular, children with moderate-to-severe atopic dermatitis appear to have a significant risk (approximately 35%) of food allergy.[13-15] There are no similar studies in adults, and therefore the prevalence of co-occurring food allergy in adults with atopic dermatitis is unknown.

Cutaneous reactions to foods are some of the most common presentations of food allergy and include IgE-mediated (urticaria,

angioedema, flushing, and pruritus), cell-mediated (contact dermatitis and dermatitis herpetiformis), and mixed IgE- and cell-mediated (atopic dermatitis) reactions. These are defined as follows:

- Acute urticaria is a common manifestation of IgE-mediated food allergy, although food allergy is not the most common cause of acute urticaria and is rarely a cause of chronic urticaria.[16] Urticaria is the most common symptom in patients experiencing food-induced anaphylaxis.[17-19]
- Angioedema most often occurs in combination with urticaria and, if food induced, is typically IgE mediated.[20] Angioedema is also a common symptom in patients with anaphylaxis.[17-19]
- Atopic dermatitis/atopic eczema is linked to a complex interaction between skin barrier dysfunction and environmental factors, such as irritants, microbes, and allergens.[21-23] In some sensitized patients food allergens might be significant triggers for atopic dermatitis/atopic eczema, especially in infants and young children, in whom food allergens are estimated to be a significant trigger in 30% to 40% of patients.[21]
- Allergic contact dermatitis is a form of eczema caused by cell-mediated allergic reactions to chemical haptens present in some foods, either naturally (eg, mango) or as additives.[24] Clinical features include marked pruritus, erythema, papules, vesicles, and edema.
- Contact urticaria caused by food allergy is an IgE-mediated reaction caused by direct skin contact in a sensitized subjects. Although common, reactions are typically not severe and confined only to the site of contact.

Gastrointestinal reactions are also a frequent manifestation of food allergy. However, the frequency and unpredictability of anaphylaxis cause the most anxiety in patients and their families. The incidence of food-induced anaphylaxis is unclear. The 5 US studies that have been conducted to estimate the prevalence of food-induced anaphylaxis have found wide differences in the rates of hospitalization or emergency department visits for anaphylaxis, as assessed by International Classification of Diseases codes or medical record review, from 1/100,000 population to as high as 70/100,000 population.[25-29] The proportion of anaphylaxis cases thought to be due to foods in these studies also varied widely, ranging from 13% to 65%, with the lowest percentages found in those studies with more stringent diagnostic criteria for anaphylaxis. One study reported that the number of hospitalizations for anaphylaxis increased with increasing age, whereas another study reported total cases of anaphylaxis were almost twice as high in children as in adults. These variations might be due to differences in study methods or differences in populations studied. Although it is estimated that greater than 12 million Americans have food allergies, data from the US Food and Drug Administration's National Electronic Injury Surveillance System of emergency department encounters suggest about 125,000 visits per year for food-induced allergic reactions, 14,000 visits per year for food-induced anaphylaxis, and approximately 3,100 hospitalizations per year related to food allergy.[26] Fatalities are rare and estimated to be less than 100 per year, with the majority occurring during the second through fourth decades of life.[30]

To read the Practice Parameter in its entirety, please download the online version of this article from www.jacionline.org, www.jcaai.org, or www.allergyparameters.org. Please note that all references cited in the Executive Summary can be found in the online document. The reader is referred to the online portion of the document for more detailed discussion of the comments made in the printed version.

Food allergy: A practice parameter update—2014

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This parameter was developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI). The AAAAI and the ACAAI have jointly accepted responsibility for establishing "Food Allergy: A practice parameter update—2014." This is a complete and comprehensive document at the current time. The medical environment is a changing one, 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. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

Key words: *Food allergy, food allergen, cross-reactivity, adverse food reactions, IgE-mediated food allergy, eosinophilic esophagitis*

Previously published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology are available at http://www.JCAAI.org or http://www.allergyparameters.org.

CONTRIBUTORS

The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

Disclosure of potential conflict of interest: H. A. Sampson has received research support from the National Institute of Allergy and Infectious Disease (NIAID; AI44236 and AI66738), the National Institutes of Health (NIH; RR026134), and Food Allergy Research and Education (FARE); has received travel support as the chair of PhARF Award review committee; has consultant arrangements with Allertein Therapeutics, Regeneron, and the Danone Research Institute; and has received payment for lectures from Thermo Fisher Scientific, UCB, and Pfizer. S. Aceves is a member of the medical advisory panel for the American Partnership for Eosinophilic Disorders; has received research support from the NIH (NIAID AI092135), the Department of Defense, and the American Academy of Allergy, Asthma & Immunology (AAAAI)/American Partnership for Eosinophilic Disorders; has a patent held by University of California–San Diego for OVB licensed to Meritage Pharma; and has received travel support from the NIH and the Falk Foundation. S. A. Bock is on the medical advisory board for FARE. S. Jones has received research support from the NIH (COFAR), the NIH/NIAID Immune Tolerance Network (A1-15416), and FARE. D. Lang is a speaker for Genentech/Novartis, GlaxoSmithKline, and Merck; has consultant arrangements with GlaxoSmithKline, Merck, Aerocrine; and has received research support from Genentech/Novartis and Merck. A. Nowak-Wegrzyn is a speaker for Thermo Fisher Scientific, is on the advisory board for Nutricia, is on the Data Safety Monitoring Board for Merck, and has received research support from Nestlé (grant 0955), Nutricia, and the NIH. J. Oppenheimer has received research support from AstraZeneca, GlaxoSmithKline, Merck, Boehringer Ingelheim, Novartis, and MedImmune; has provided legal consultation/expert witness testimony in malpractice defense cases; is chairman of the American Board of Allergy and Immunology; and has consultant arrangements with GlaxoSmithKline, Mylan, Novartis, and Sunovion. C. Randolph is a member of the Board of Regents for the American College of Allergy, Asthma & Immunology (ACAAI); has consultant arrangements with AstraZeneca and Genentech; has received payment for lectures from GlaxoSmithKline, AstraZeneca, Genentech, and TEVA; and has received travel support from TEVA. S. H. Sicherer has received research support from the NIAID, is a member of the American Board of Allergy and Immunology, has consultant arrangements with Novartis and FARE; and receives royalties from UpToDate. R. A. Simon has provided expert testimony for various law firms; has received payment for lectures from Merck, Novartis, and CSL-Behring; holds patents for the use of surfactants in chronic rhinosinusitis and asthma; has received royalties from Wiley Blackwell and UpToDate; and has stock options in URXmobile. B. P. Vickery has received research support from the NIH/NIAID (AI099083) and the Foundation of the ACAAI. R. Wood has consultant arrangements with the Asthma and Allergy Foundation of America, is employed by Johns Hopkins University, has received research support from the NIH, and receives royalties from UpToDate. The rest of the authors declare that they have no relevant conflicts of interest.

We thank Anne Munoz-Furlong for review and helpful comments to "Section IX: Management in special settings."

Received for publication February 7, 2014; revised May 2, 2014; accepted for publication May 6, 2014.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.05.013

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Recommendation rating scale

Statement	Definition	Implication
Strong recommendation (StrRec)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B).* In some clearly identified circumstances, strong recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate (Mod)	A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C).* In some clearly identified circumstances, recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Weak (Weak)	An option means that either the quality of evidence that exists is suspect (grade D)* or that well-done studies (grade A, B, or C)* show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they might set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is both a lack of pertinent evidence (grade D)* and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

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 quasiexperimental study
- III Evidence from nonexperimental descriptive studies, such as comparative studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation*

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated recommendation from category I evidence
- C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
- LB Laboratory based
- NR Not rated

SUMMARY OF CONFLICT OF INTEREST DISCLOSURES

The following is a summary of interests disclosed on work-group members' conflict of interest disclosure statements (not including information concerning family member interests). Completed conflict of interest disclosure statements are available on request.

Work group member	Disclosures
Hugh A. Sampson, MD	Allertein Therapeutics – Consultant Food Allergy Research and Education (FARE) – Medical Advisory Board, unpaid Novartis – Consultant, unpaid DBV Scientific Advisory Board, unpaid Thermo Fisher Scientific – EAACI travel expenses and honorarium UCB – XX National Congress of the Mexican Pediatric Specialists in Clinical Immunology and Allergy – Travel expenses and honorarium National Institute of Allergy and Infectious Diseases (NIAID) – Research grant FARE – Research grant University of Nebraska (FARRP) – Consultant Allergy and Asthma Foundation of America – Consultant

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Resolution of nondisqualifying interests

The Joint Task Force recognizes that experts in a field are likely to have interests that could come into conflict with development of a completely unbiased and objective practice parameter. A process has been developed to prevent potential conflicts from influencing the final document in a negative way to take advantage of that expertise.

At the workgroup level, members who have a potential conflict of interest either do not participate in discussions concerning topics related to the potential conflict, or if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is reviewed by the Joint Task Force, and any apparent bias is removed at that level. Finally, the practice parameter is sent for review both by invited reviewers and by anyone with an interest in the topic by posting the document on the Web sites of the ACAAI and AAAAI.

The practice parameter on food allergy was last updated in 2006[1] and focused primarily on IgE-mediated food allergy. In the ensuing years, there have been considerable advances in the field in many areas, including our basic understanding of food allergens, diagnostic testing, non–IgE-mediated disorders, and management of various food-induced allergic reactions. In 2010, the NIAID "Guidelines on the diagnosis and management of food allergy" were published, providing a comprehensive review of the scientific literature and expert opinion on food allergy.[2] Given the many advances in the field, the Joint Task Force on Practice Parameters appointed a working group to review and update the standing practice parameters. The working group relied heavily on the NIAID Guidelines and focused on advances since the publication of that landmark document.

THE JOINT TASK FORCE ON PRACTICE PARAMETERS

The Joint Task Force on Practice Parameters (JTF) is a 13-member task force consisting of 6 representatives assigned by the AAAAI, 6 by the ACAAI, and 1 by the Joint Council of Allergy and Immunology. This task force oversees the development of practice parameters, selects the workgroup chair or chairs, and reviews drafts of the parameters for accuracy, practicality, clarity, and broad utility of the recommendations for clinical practice.

FOOD ALLERGY: A PRACTICE PARAMETER UPDATE—2014 WORKGROUP

The Food Allergy: A Practice Parameter Update 2014 Workgroup was commissioned by the JTF to develop a practice parameter that addresses recent advances in the field of food allergy and the optimal methods of diagnosis and management based on an assessment of the most current literature. The Chair (Hugh A. Sampson, MD) invited workgroup members to participate in the parameter development who are considered to be experts in the field of food allergy. Workgroup members have been vetted for financial conflict of interest by the JTF, and their conflicts of interest have been listed in this document and are posted on the JTF Web site at http://www.allergyparameters.org.

The charge to the workgroup was to use a systematic literature review in conjunction with consensus expert opinion and workgroup-identified supplementary documents to develop a practice parameter that evaluates the current state of the science regarding food allergy.

PROTOCOL FOR FINDING EVIDENCE

The NIAID guidelines were used to identify previously identified impactful studies on these topics. Additional Clinical reports were reviewed to ensure parity of expert opinion (AAP and ICON). Additional PubMed searches were performed primarily to identify items in the literature after September 2009 that were pertinent to update these topics. Meta-analyses were always selected when available. Grading of each reference was performed as applicable (see the reference list), and overall grades and strengths of recommendations were placed after the summary statements. Search terms include food allergy, food allergen, and each of the specific conditions reviewed in this parameter.

SUMMARY STATEMENTS

Summary Statement 1: Evaluate the patient for possible food allergy with the understanding that a relatively small number of allergens cause a high proportion of food allergy (eg, cow's milk, hen's egg, soy, wheat, peanut, tree nuts, fish, and shellfish). See Summary Statement 48 for management. [Strength of recommendation: Strong; B Evidence]

Summary Statement 2: Advise patients who are allergic to certain specific foods about the risk of ingestion of similar cross-reacting foods. Examples include ingestion of other tree nuts in patients with tree nut allergy (eg, walnut and pecan or

pistachio and cashew), Crustacea in patients with crustacean seafood allergy, vertebrate fish in patients with fish allergy, and other mammalian milks in patients with cow's milk allergy. [Strength of recommendation: Strong; C Evidence]

Summary Statement 3: Avoid other mammalian milks, such as goat's milk or sheep's milk, in patients with cow's milk allergy because of highly cross-reactive allergens. [Strength of recommendation: Strong; B Evidence]

Summary Statement 4: Advise patients with seafood allergy that they are not at increased risk of a reaction to radiocontrast media. There is no documented relationship between non–IgE-mediated anaphylactic reactions to radiocontrast media and allergy to fish, crustacean shellfish, or iodine. [Strength of recommendation: Strong; D Evidence]

Summary Statement 5: Test for IgE antibodies specific for the immunogenic oligosaccharide galactose-α-1,3-galactose (alpha-gal) in patients who report a delayed systemic reaction to red meat or unexplained anaphylaxis, particularly if they have a history of previous tick bites. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 6: Avoid all mammalian meats in patients with alpha-gal allergy because this oligosaccharide antigen is widely expressed in mammalian tissues. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 7: Evaluate patients with latex allergy for the possibility of cross-reactivity to banana, avocado, kiwi, chestnut, potato, green pepper, and other fruits and nuts. Individualized management is recommended because clinical reactions caused by this cross-reactivity can range from mild to severe. [Strength of recommendation: Strong; C Evidence]

Summary Statement 8: Advise patients not to be concerned about ingesting genetically modified foods given the current state of knowledge and the US Food and Drug Administration's screening requirements to rule out allergenicity of genetically modified foods. [Strength of recommendation: Weak; D Evidence]

Summary Statement 9: Manage non–IgE-mediated reactions to foods with appropriate avoidance and pharmacotherapy as indicated with the understanding that the specific role of immunity (eg, IgA, IgM, IgG, and IgG subclasses) in these forms of food allergy has not been demonstrated. [Strength of recommendation: Strong; B Evidence]

Summary Statement 10: Determine whether the reported history of food allergy, which often proves inaccurate, and laboratory data are sufficient to diagnose food allergy or whether an oral food challenge (OFC) is necessary. [Strength of recommendation: Strong; A Evidence]

Summary Statement 11: Consider the natural course of allergies to specific foods when deciding on the frequency of food allergy follow-up evaluations, recognizing that allergies to certain foods (milk, egg, wheat, and soy) generally resolve more quickly in childhood than others (peanut, tree nuts, fish, and shellfish). These observations could support individualized follow-up (ie, roughly yearly re-evaluations of these allergies in childhood) with less frequent retesting if results remain particularly high (eg, >20-50 kU_A/L). [Strength of recommendation: Moderate; C Evidence]

Summary Statement 12: Encourage exclusive breast-feeding for the first 4 to 6 months of life. [Strength of recommendation: Weak; C Evidence]

Summary Statement 13: For infants with a family history of atopy, consider a partially or extensively hydrolyzed infant formula for possible prevention of atopic dermatitis and infant cow's milk allergy if exclusive breast-feeding is not possible. [Strength of recommendation: Moderate; B Evidence]

Summary Statement 14: Do not recommend maternal allergen avoidance or avoidance of specific complementary foods at weaning because these approaches have not proved effective for primary prevention of atopic disease. [Strength of recommendation: Weak; C Evidence]

Summary Statement 15: Do not routinely recommend supplementation of the maternal or infant diet with probiotics or prebiotics as a means to prevent food allergy because there is insufficient evidence to support a beneficial effect. [Strength of recommendation: Weak; C Evidence]

Summary Statement 16: Do not routinely recommend that patients with chronic idiopathic urticaria (CIU) avoid foods containing additives. [Strength of recommendation: Strong; B Evidence]

Summary Statement 17: Do not routinely instruct asthmatic patients to avoid sulfites or other food additives unless they have a prior reaction to sulfites. Sulfites are the only food additive proved to trigger asthma. Although these reactions can be severe, even life-threatening in sensitive subjects, they are rare. [Strength of recommendation: Strong; B Evidence]

Summary Statement 18: Consider natural food additives in the evaluation of patients with a history of unexplained ingestant-related anaphylaxis. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 19: Patients who experience an adverse reaction to food additives should be evaluated for sensitivity to annatto and carmine. [Strength of recommendation: Strong; A Evidence]

Summary Statement 20: Clinicians should be aware that avoidance measures are appropriate for patients with histories compatible with adverse reactions to an additive until diagnostic evaluation can be performed. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 21: Clinicians should not recommend food additive avoidance in their patients with hyperactivity/attention deficit disorder. [Strength of recommendation: Strong; A Evidence]

Summary Statement 22: The clinician should obtain a detailed medical history and physical examination to aid in the diagnosis of food allergy. [Strength of recommendation: Strong; D Evidence]

Summary Statement 23: The clinician should use specific IgE tests (skin prick tests, serum tests, or both) to foods as diagnostic tools; however, testing should be focused on foods suspected of provoking the reaction, and test results alone should not be considered diagnostic of food allergy. [Strength of recommendation: Strong; B Evidence]

Summary Statement 24: Component-resolved diagnostic testing to food allergens can be considered, as in the case of peanut sensitivity, but it is not routinely recommended even with peanut sensitivity because the clinical utility of component testing has not been fully elucidated. [Strength of recommendation: Weak; C Evidence]

Summary Statement 25: The clinician should consider OFCs to aid in the diagnosis of IgE-mediated food allergy. [Strength of recommendation: Strong; A Evidence]

Summary Statement 26: If clinical history is not consistent with anaphylaxis, perform a graded OFC to rule out food allergy. Open

food challenge is both cost- and time-efficient. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 27: If the diagnosis is still unclear after open food challenge, then recommend a blind food challenge. [Strength of recommendation: Moderate; B Evidence]

Summary Statement 28: Elimination diets and diet diaries can be used as an adjunctive means to diagnose food allergies but are not to be depended on solely for confirming a diagnosis. [Strength of recommendation: Weak; D Evidence]

Summary Statement 29: A diagnosis of food-dependent, exercise-induced anaphylaxis should be considered when ingestion of causal food or foods and temporally related exercise result in symptoms of anaphylaxis. The clinician should recognize that symptoms only occur with ingestion of the causal food or foods proximate to exercise and that ingestion of the food in the absence of exercise will not result in anaphylaxis. [Strength of recommendation: Strong; B Evidence]

Summary Statement 30: The clinician should consider the diagnosis of oral allergy syndrome (pollen-food allergy) and obtain specific IgE testing to pollens in patients who experience limited oropharyngeal symptoms after ingestion of food antigens that cross-react with pollen antigens. [Strength of recommendation: Strong; B Evidence]

Summary Statement 31: A diagnosis of IgE-mediated contact urticaria should be considered in patients with a history of immediate urticarial rash at the site of contact with a food allergen. [Strength of recommendation: Weak; D Evidence]

Summary Statement 32: Do not routinely obtain total serum IgE levels for the diagnosis of food allergy. [Strength of recommendation: Strong; C Evidence]

Summary Statement 33: Do not perform intracutaneous testing for the diagnosis of food allergy (see discussion). [Strength of recommendation: Strong; B Evidence]

Summary Statement 34: Unproved tests, including allergen-specific IgG measurement, cytotoxicity assays, applied kinesiology, provocation neutralization, and hair analysis, should not be used for the evaluation of food allergy. [Strength of recommendation: Strong; C Evidence]

Summary Statement 35: Although routine use of atopy patch tests for diagnosis of food allergy is not recommended, the use of food atopy patch tests in patients with pediatric eosinophilic esophagitis (EoE) have been demonstrated to be valuable in assessing potential food triggers. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 36: The physician should use the patient's medical history, response to a trial of elimination of the suspected food, and OFC to establish a diagnosis of food protein–induced enterocolitis syndrome (FPIES). However, when the history indicates that infants or children have experienced hypotensive episodes or multiple reactions to the same food, a diagnosis can be based on a convincing history and absence of symptoms when the causative food is eliminated from the diet. [Strength of recommendation: Strong; B Evidence]

Summary Statement 37: The clinician should be aware that a gastrointestinal evaluation with endoscopy and biopsy is usually not required for the diagnosis of FPIES and allergic proctocolitis with symptoms that respond to elimination of the offending food and recur when the food is reintroduced into the diet. [Strength of recommendation: Weak; C Evidence]

Summary Statement 38: Measurement of food-specific IgG and IgG_4 antibodies in serum are not recommended for the diagnosis of non–IgE-mediated food-related allergic disorders. [Strength of recommendation: Strong; B Evidence]

Summary Statement 39: A trial of twice daily protein pump inhibitor (PPI) therapy for 8 weeks before diagnostic testing for EoE is recommended to exclude gastroesophageal reflux disease (GERD) and PPI-responsive esophageal infiltration of eosinophils. [Strength of recommendation: Strong; C Evidence]

Summary Statement 40: The diagnosis of EoE should be based on the presence of characteristic symptoms and endoscopic features and the presence of 15 or more eosinophils per high-power field quantified by a pathologist using hematoxylin and eosin staining of esophageal biopsy specimens at $\times$400 light microscopy. [Strength of recommendation: Strong; B Evidence]

Summary Statement 41: Eosinophilic gastroenteritis (EGE) should be considered a constellation of clinical symptoms in combination with gastric, small intestine, and/or large intestine infiltration of eosinophils at greater than the reported normal numbers of gastric and intestinal eosinophils. [Strength of recommendation: Weak; D Evidence]

Summary Statement 42: Prescribe a targeted allergen elimination diet as the treatment for known or strongly suspected food allergy. Education about proper food preparation and the risks of occult exposure is essential. [Strength of recommendation: Strong; C Evidence]

Summary Statement 43: Recommend consultation with a nutritionist for growing children in whom elimination diets might affect growth, as well as those patients with multiple food allergies, poor growth parameters, or both. Clinicians must be aware of the nutritional consequences of elimination diets and certain medications, such as esomeprazole, especially in growing children. Specifically, identifying alternative dietary sources of calcium and vitamin D is critical for patients with milk allergy. [Strength of recommendation: Strong; B Evidence]

Summary Statement 44: Review recognition and treatment of IgE-mediated food-related allergic reactions with each patient and caregivers, as appropriate. Emphasis should be placed on prompt awareness of anaphylaxis and swift intervention. [Strength of recommendation: Strong; C Evidence]

Summary Statement 45: Discuss self-care management techniques, especially with high-risk patients, (eg, adolescents, young adults, and asthmatic patients), focusing on risk reduction and recognition and treatment of anaphylaxis. [Strength of recommendation: Strong; C Evidence]

Summary Statement 46: Use epinephrine as first-line management for the treatment of anaphylaxis. [Strength of recommendation: Strong; C Evidence]

Summary Statement 47: Ensure that self-injectable epinephrine is readily available to the patient and instruct the patient, caregiver, or both on the importance of its use and self-administration, as relevant. [Strength of recommendation: Strong; C Evidence]

Summary Statement 48: Evaluate children with food allergies at regular intervals (1-2 years), according to the patient's age and the food allergen, to determine whether he or she is still allergic. If food allergy is unlikely to change over time, as in adults, periodic re-evaluation (2-5 years) is recommended, depending on the food allergy. [Strength of recommendation: Strong; C Evidence]

Summary Statement 49: For patients with food-dependent, exercise-induced anaphylaxis, avoid food ingestion within 2 to 4 hours of exercise for prevention of symptoms, and provide

prompt treatment with onset of symptoms. [Strength of recommendation: Strong; C Evidence]

Summary Statement 50: Manage pollen-food allergy syndrome or oral allergy syndrome by dietary avoidance of raw fruits, vegetables, or both based on the patient's symptom profile severity. The extent of food avoidance depends on the severity of oropharyngeal symptoms. [Strength of recommendation: Strong; C Evidence]

Summary Statement 51: The clinician should understand the various clinical presentations of these conditions (ie, FPIES/proctocolitis/enteropathy), educate patients and care providers about common food triggers, and recommend strict food avoidance of allergenic foods for symptom management. [Strength of recommendation: Strong; C Evidence]

Summary Statement 52: Use volume replacement therapy for the acute care management of patients with FPIES. [Strength of recommendation: Strong; B Evidence]

Summary Statement 53: See patients with FPIES and allergic gastrointestinal disorders at regular intervals and consider rechallenge in an appropriate medical facility based on the natural history of the specific disorder. [Strength of recommendation: Strong; C Evidence]

Summary Statement 54: Consider serial tissue biopsies as part of disease management in patients with EoE. Symptoms alone or endoscopy without biopsy cannot be used as an accurate gauge of EoE disease activity. [Strength of recommendation: Strong; C Evidence]

Summary Statement 55: Consider assessment for aeroallergen sensitization because EoE can be triggered by aeroallergens in human subjects and animal models and there might be a seasonality to EoE diagnoses. [Strength of recommendation: Moderate; D Evidence]

Summary Statement 56: Consider food allergy evaluation with both skin prick and patch testing for EoE to rule out possible food triggers. Remember that positive serum specific IgE levels, food skin prick test responses, and food patch test results are not sufficient to diagnose food triggers for EoE. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 57: Consider the use of targeted or empiric food-elimination diets or amino acid–based diets for successful EoE therapy. [Strength of recommendation: Strong; B Evidence]

Summary Statement 58: Consider the use of swallowed topical esophageal corticosteroids for successful EoE therapy. [Strength of recommendation: Strong; A Evidence]

Summary Statement 59: Referral to a gastroenterologist for esophageal dilation is recommended for high-grade stenosis but does not provide inflammatory control. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 60: Administer oral corticosteroids for EGE as the preferred therapy. [Strength of recommendation: Weak; C Evidence]

Summary Statement 61: Although immunotherapeutic approaches, such as oral immunotherapy, in clinical trials show promise in treating food allergy, they are not ready for implementation in clinical practice at the present time because of inadequate evidence for therapeutic benefit over risks of therapy. [Strength of recommendation: Strong; A Evidence]

Summary Statement 62: Develop a written action plan for treatment of allergic reactions to food for adults and children. [Strength of recommendation: Moderate; D Evidence]

Summary Statement 63: Inquire about and address behavioral changes because of bullying in patients with food allergy. This inquiry should include adults and children. [Strength of recommendation: Strong; D Evidence]

Summary Statement 64: Teach patients that ingestion, rather than casual exposure through the skin or close proximity to an allergen, is almost the only route for triggering severe allergic/anaphylactic reactions. [Strength of recommendation: Strong; C Evidence]

PREFACE

As defined by the National Institute of Allergy and Infectious Diseases (NIAID) expert panel, *food allergy* is defined here "as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food."[2] Here, the term *allergy* is not limited to IgE-mediated immunologic reactions and is used to connote the induction of clinical signs and symptoms, as opposed to *sensitivity*, which indicates the presence of IgE antibodies to a food, often in the absence of clinical symptomatology. Although the prevalence of food allergy overall and of allergy to specific foods is uncertain because studies vary in methodological approaches,[3,4] allergists who have been in practice for at least a decade have been confronted with an ever-growing number of patients with food allergy. On the basis of a recent extensive review of the literature, food allergy is estimated to affect more than 1% to 2% and less than 10% of the population.[3] There are limited data to suggest that food allergy prevalence has increased, but national surveys suggest that peanut allergy has tripled since the late 1990s.[5,6] In considering a number of published studies,[4,7,8] it is apparent that estimates of food allergy prevalence are highest when based on self-report (approximately 12% to 13%) compared with estimates based on studies using tests, such as oral food challenges (OFCs; approximately 3%). This observation regarding a discordance of suspected and proved food allergy underscores the importance of using proved diagnostic methods to evaluate individual patients suspected of a having food allergy.

The physician should apply information regarding epidemiologic features of food allergy when approaching diagnosis and management, recognizing that self-reported food allergy is more common than proved food allergy, that food allergy is more common in children, that a limited number of foods account for most significant food allergies, and that food allergy occurs more commonly in persons with other atopic diseases. There are a number of epidemiologic features regarding food allergy that might be helpful in constructing *a priori* assessment of risk and consideration of potential triggers when evaluating individual patients. Although more than 170 foods have been identified as triggers of food allergy, those causing most of the significant allergic reactions include peanut, tree nuts, fish, shellfish, milk, egg, wheat, soy, and seeds.[2,5,9-11] Food allergy (to foods other than shellfish and fruits/vegetables) is more common in children than in adults.[4,7,8,10-12] As described elsewhere in this parameter, milk, egg, wheat, and soy allergies are more common in children than in adults.

There is a high co-occurrence of food allergy with other atopic diseases, including atopic dermatitis, asthma, and allergic rhinitis.[2,6,13,14] In particular, children with moderate-to-severe atopic dermatitis appear to have a significant risk (approximately

35%) of food allergy.[13-15] There are no similar studies in adults, and therefore the prevalence of co-occurring food allergy in adults with atopic dermatitis is unknown.

Cutaneous reactions to foods are some of the most common presentations of food allergy and include IgE-mediated (urticaria, angioedema, flushing, and pruritus), cell-mediated (contact dermatitis and dermatitis herpetiformis), and mixed IgE- and cell-mediated (atopic dermatitis) reactions. These are defined as follows:

- Acute urticaria is a common manifestation of IgE-mediated food allergy, although food allergy is not the most common cause of acute urticaria and is rarely a cause of chronic urticaria.[16] Urticaria is the most common symptom in patients experiencing food-induced anaphylaxis.[17-19]
- Angioedema most often occurs in combination with urticaria and, if food induced, is typically IgE mediated.[20] Angioedema is also a common symptom in patients with anaphylaxis.[17-19]
- Atopic dermatitis/atopic eczema is linked to a complex interaction between skin barrier dysfunction and environmental factors, such as irritants, microbes, and allergens.[21-23] In some sensitized patients food allergens might be significant triggers for atopic dermatitis/atopic eczema, especially in infants and young children, in whom food allergens are estimated to be a significant trigger in 30% to 40% of patients.[21]
- Allergic contact dermatitis is a form of eczema caused by cell-mediated allergic reactions to chemical haptens present in some foods, either naturally (eg, mango) or as additives.[24] Clinical features include marked pruritus, erythema, papules, vesicles, and edema.
- Contact urticaria caused by food allergy is an IgE-mediated reaction caused by direct skin contact in a sensitized subjects. Although common, reactions are typically not severe and confined only to the site of contact.

Gastrointestinal reactions are also a frequent manifestation of food allergy. However, the frequency and unpredictability of anaphylaxis cause the most anxiety in patients and their families. The incidence of food-induced anaphylaxis is unclear. The 5 US studies that have been conducted to estimate the prevalence of food-induced anaphylaxis have found wide differences in the rates of hospitalization or emergency department visits for anaphylaxis, as assessed by International Classification of Diseases codes or medical record review, from 1/100,000 population to as high as 70/100,000 population.[25-29] The proportion of anaphylaxis cases thought to be due to foods in these studies also varied widely, ranging from 13% to 65%, with the lowest percentages found in those studies with more stringent diagnostic criteria for anaphylaxis. One study reported that the number of hospitalizations for anaphylaxis increased with increasing age, whereas another study reported total cases of anaphylaxis were almost twice as high in children as in adults. These variations might be due to differences in study methods or differences in populations studied. Although it is estimated that greater than 12 million Americans have food allergies, data from the US Food and Drug Administration's National Electronic Injury Surveillance System of emergency department encounters suggest about 125,000 visits per year for food-induced allergic reactions, 14,000 visits per year for food-induced anaphylaxis, and approximately 3,100 hospitalizations per year related to food allergy.[26] Fatalities are rare and estimated to be less than 100 per year, with the majority occurring during the second through fourth decades of life.[30]

SECTION I: CLASSIFICATION OF MAJOR FOOD ALLERGENS, CROSS-REACTIVITIES, GENETICALLY MODIFIED FOODS, AND CLINICAL IMPLICATIONS

Classification

Summary Statement 1: Evaluate the patient for possible food allergy with the understanding that a relatively small number of allergens cause a high proportion of food allergy (eg, cow's milk, hen's egg, soy, wheat, peanut, tree nuts, fish, and shellfish). See Summary Statement 48 for management. [Strength of recommendation: Strong; B Evidence]

It is generally believed that virtually any food can elicit an IgE-mediated allergic reaction in a predisposed subject, and more than 170 foods have been reported to be allergenic. However, it is now well recognized, based on many studies, that allergy to certain foods appears to be especially common. In order of prevalence, these most common food allergens are milk, egg, peanut, tree nuts, crustacean shellfish, fish, wheat, and soy.[2] This is consistent with the finding that allergens belong to a very restricted number of protein families. It is important to note that prevalence data are most often derived from studies of westernized populations that focus on a relatively limited number of foods[31] and that true food allergy prevalence is difficult to accurately ascertain because of a lack of large rigorously performed studies.[3] In addition, differing patterns of consumption and allergic sensitization might influence the relevance of specific foods to the public health of different countries.[32] For example, studies of European patients have identified, in addition to the common allergens named above, celery, mustard, sesame, lupine, stone fruits, and molluscan shellfish as prevalent allergens.[31]

Food allergens belong to a limited number of protein families thought to be allergenic in part because of shared physicochemical characteristics.

Allergenic proteins are increasingly being analyzed with detailed molecular, biochemical, and computational techniques and then classified, organized, and catalogued into public databases that are now available to scientists and practitioners; examples include allergenonline.org, allergen.org, allergome.org, immuneepitope.org, and fermi.utmb.edu/SDAP/. In addition, the immune responses to these allergens are being analyzed with molecular and immunologic techniques to link clinical outcomes to specific antibody-binding patterns. These scientific and technical advances are contributing to a new understanding of the taxonomy of all allergens, including food allergens. One key feature of this new understanding is the highly restricted distribution of allergens (2% to 5% of all known structural protein families), regardless of their source and route of exposure.[33-35] This suggests that certain properties of proteins can confer allergenicity, although this remains controversial.[36]

In particular, a putative food allergen must have physicochemical characteristics that will permit it to survive the harsh digestive process and elicit an immunologic response on exposure to the mucosal immune system of an atopic subject. Such characteristics are thought to include water solubility, glycosylation residues, relatively low molecular weight, resistance to digestion by heat and proteases, and abundance within the food source.[37] Most plant and animal food allergens belong to a limited number of

major protein families possessing these characteristics, and they can be significantly affected by food processing.[38] A brief summary of the major families follows. To obtain an up-to-date classification of food allergens, their protein family relationships, and "fact sheets" summarizing key points, please visit http://www.meduniwien.ac.at/allergens/allfam/search.php.

Food allergens of animal origin by family:

1. *Tropomyosins*: The invertebrate tropomyosins are a family of muscle proteins sharing homology across species (but not with vertebrate tropomyosins), and therefore they act as panallergens. These are the major allergens in crustaceans and mollusks and are generally heat stable and cross-reactive.[39]
2. *Parvalbumins/EF-hand proteins*: These muscle proteins are major allergens from vertebrate fish and frogs and possess a calcium-binding domain referred to as an EF-hand motif. The allergens in this second-largest family are considered to be highly cross-reactive panallergens.[40]
3. *Caseins*: Caseins bind calcium in mammalian milk and stabilize it in micellar form. These are the major allergens in cow's milk, and because of high sequence homology (approximately ≥90%), they are cross-reactive with other mammalian milks frequently consumed by human subjects (eg, goat's and sheep's milk). Other animal milks from horses, donkeys, camels, and human subjects have caseins with roughly 60% homology, possibly accounting for less allergenicity.[41]
4. *Minor families*: These include lipocalins, lysozymes, transferrins, serpins, oligosaccharides, and ovomucoids/Kazal inhibitors.

Food allergens of plant origin by family:

5. *Prolamin superfamily*: The prolamin superfamily contains the highest number of plant food allergens and is characterized by rich disulfide bonds and a core of 8 conserved cysteine residues, providing stability and resistance to digestion.[42] This superfamily contains the 2S albumin seed storage proteins of seeds, tree nuts, and legumes, including peanut; nonspecific lipid transfer proteins from fruits, nuts, seeds, vegetables, pollen, and latex; and the α-amylase/trypsin inhibitors found in wheat, barley, rye, corn, and rice.
6. *Cupin superfamily*: The cupins are a large and functionally diverse superfamily of proteins that share a β-barrel structural core domain. Cupin allergens are seed storage globulins representing major food allergens from legumes, nuts, and seeds.[43] Seed storage globulins can be grouped into 2 families: vicilins and legumins.
7. *Bet v 1 superfamily*: The major birch pollen allergen Bet v 1 is a member of the pathogenesis-related protein 10 family within this superfamily. Many patients sensitized to Bet v 1 also have oral allergy syndrome (OAS) after ingestion of certain fruits and vegetables, which is caused by IgE cross-reactivity between Bet v 1 and homologous allergens from plant foods.[44] Most Bet v 1–related food allergens were found in members of certain plant families: Rosaceae (apple, pear, and stone fruits), Apiaceae (celery and carrot), and Fabaceae (soybean and peanut).
8. *Minor families*: These include class I chitinases, profilins, protease inhibitors, lectins, and thaumatin-like proteins.

Cross-reactivity

Cross-reactivity is an immune-mediated phenomenon that can occur when a specific antibody reacts not only to the original allergen but also to a different homologous allergen. When a food allergen shares sufficient structural or sequence similarity with a different food allergen or aeroallergen, epitopes on the second allergen are bound by cross-reactive antibodies, triggering an adverse reaction similar to that elicited by the original food allergen (Table E1).[2] Immunologically, this is distinct from coallergy, in which patterns of reactivity to multiple foods might be prevalent but are not mediated by shared epitope-specific antibodies. Accurate epidemiologic data on the prevalence of clinical cross-reactivities are generally limited by the lack of large, controlled population-based studies incorporating OFCs.

Despite having high sequence homology in some cases, the ability of cross-reactive allergens to mediate clinical allergic reactions is highly variable and often depends on the specific foods involved.[2,31]

Legumes. In a patient clinically allergic to a legume, it is common to detect IgE to other legumes, given the high homology shared by this family of plants. Despite this observation, clinical cross-reactivity to other legumes is generally uncommon,[45,46] although this might be a regional observation influenced by pollen exposure and the prominence of legumes in the diet. For example, recent studies focused primarily on populations in Mediterranean Europe have demonstrated clinical allergies to multiple legumes, particularly in patients allergic to lupine,[47] lentil, and chickpea.[48,49]

Patients with peanut allergy. Because patients with peanut allergy generally tolerate other legumes, including soy, a recommendation to empirically avoid all legumes is generally unnecessary.[50,51] Possible legume allergy should be evaluated on a case-by-case basis in patients with peanut allergy.

Patients with soy allergy. The ability to evaluate cross-reactivity in patients allergic to soy has been hampered by a lack of understanding of the major soy allergens, although progress is being made in this area.[36,52] Although cross-reactivity between soybean and other legumes is extensive *in vitro* because of the high homology between proteins, clinical cross-reactivity of patients with soy allergy to other legumes is generally uncommon, and extensive elimination diets based only on positive test results are not recommended.

Grains. Patients with IgE-mediated wheat allergy alone show extensive *in vitro* cross-reactivity to other cereal grains and grass pollens. However, clinical cross-reactivity to multiple cereal grains occurs in a minority of patients sensitized to multiple grains.[53] Therefore elimination of all grains (eg, wheat, rye, barley, oats, rice, and corn) from the diet of a patient with grain allergy is not recommended and might be nutritionally harmful.[54]

Fruits and vegetables. Self-report of immediate reactions and sensitization to multiple fruits and vegetables are common, but very few studies have been performed that incorporate rigorous methods, including food challenges.[8] Thus it is unclear to what extent such reports reflect nonspecific factors (eg, contact or irritant dermatitis), OAS, or true gastrointestinal food allergen cross-reactivity. Although there are exceptions (eg, lipid transfer proteins acting as panallergens in Mediterranean patients),[55] it is uncommon for cross-reactivity among and between fruits and vegetables to result in severe reactions, and extensive elimination diets are not recommended.[56]

Summary Statement 2: Advise patients who are allergic to certain specific foods about the risk of ingestion of similar cross-reacting foods. Examples include ingestion of other tree nuts in patients with tree nut allergy (eg, walnut and pecan or pistachio and cashew), Crustacea in patients with crustacean seafood allergy, vertebrate fish in patients with fish allergy, and other mammalian milks in patients with cow's milk allergy. [Strength of recommendation: Strong; C Evidence]

Tree nuts. Cross-reactivity and coallergy among tree nuts is common,[57,58] and serologic studies demonstrate IgE binding to multiple tree nuts.[59] In particular, strong correlations between IgE levels to cashew and pistachio, as well as between walnut and pecan, have been observed[59] and confirmed with inhibition ELISA experiments.[60] These studies suggest shared allergens exist among tree nuts and between tree nuts and other plant-derived foods and pollen. Reactions to these shared allergens can be serious and can occur on initial exposure. Careful assessment is necessary before considering whether to introduce other nuts into the diet. This assessment might involve the use of supervised OFCs to multiple nuts because skin prick test (SPT) results might not be reliable in determining which nuts can be tolerated.[61]

Peanut and tree nuts. Between 25% and 50% of patients with peanut allergy are coallergic to tree nuts,[58,62] and there is significant cross-reactivity between homologous T- and B-cell epitopes within peanut allergens and certain tree nuts (eg, almond, walnut, pecan, hazelnut, and Brazil nut).[63-66] Management of patients with peanut allergy seeking guidance on tree nut ingestion should be individualized, but because of practical concerns about cross-contamination and the difficulty in reliably identifying specific tree nuts, avoidance of all tree nuts by young children with peanut allergy should be considered.[31]

Shellfish. The clinician should be aware of several important principles related to cross-reactivity that influence the care of patients allergic to crustacean shellfish. First, invertebrate tropomyosin acts as a major panallergen,[67,68] producing *in vitro* cross-reactivity between Crustacea and arthropods (eg, house dust mite and cockroach, which also express invertebrate tropomyosin),[69] as well as considerable risk of clinical cross-reactivity between crustaceans.[70] Cross-reactivity can result in severe reactions, and avoidance of all members of the crustacean family is generally recommended; less well defined is cross-reactivity between mollusks and crustaceans.[71] Second, tropomyosins do not cross-react with those in vertebrate fish (parvalbumins), and avoidance of both vertebrate fish and crustaceans is generally unnecessary on the basis of cross-reactivity.

Vertebrate fish. IgE cross-reactivity after *in vitro* or skin prick testing is common between different species of vertebrate fish because of the shared expression of parvalbumins across species.[72,73] The clinical relevance of this cross-reactivity varies widely.[40,70,74,75] Careful individualized evaluation, including the use of OFCs, as indicated, might be necessary to determine clinical tolerance to various vertebrate fish.

When evaluating and treating patients for potential allergy to multiple related foods, coallergy, cross-contamination, or both might need to be considered.[54]

Summary Statement 3: Avoid other mammalian milks, such as goat's milk or sheep's milk, in patients with cow's milk allergy because of highly cross-reactive allergens. [Strength of recommendation: Strong; B Evidence]

Because of high homology between proteins in milk from cows, goats, and sheep, patients with milk allergy should avoid all of them. Milk from mares or camels might be less cross-reactive. Generally speaking, plant-based alternatives are recommended.[76-78]

Summary Statement 4: Advise patients with seafood allergy that they are not at increased risk of a reaction to radiocontrast media. There is no documented relationship between non–IgE-mediated anaphylactic reactions to radiocontrast media and allergy to fish, crustacean shellfish, or iodine. [Strength of recommendation: Strong; D Evidence]

Systemic, non–IgE-mediated immediate hypersensitivity reactions occur in 1% to 3% of patients receiving ionic radiocontrast media and in less than 0.5% of those receiving nonionic agents. Established risk factors include prior non–IgE-mediated anaphylactic reactions from contrast infusion, female sex, β-blocker exposure, and asthma.[79] The evidence implicating atopy (including allergy to foods or drugs) as a risk factor is weak, and for this reason, risk reduction measures are not required in the absence of the other factors listed above. Although seafood can contain iodine, the allergenicity of these foods is related to specific muscle proteins (tropomyosin and parvalbumin, as previously described) that do not contain iodine. Therefore allergy to fish or shellfish does not indicate an allergy or sensitivity to iodine.[80] There is no convincing evidence that the inorganic iodine levels present in seafood or in topically applied iodine-containing solutions are related to adverse events from contrast media or that patients with seafood allergy are at particularly increased risk for systemic reactions to contrast media.[81]

In Version 8 of their *Manual on Contrast Media*, newly revised in 2012, the American College of Radiology Committee on Drugs and Contrast Media issued the following statement: "The predictive value of specific allergies, such as those to shellfish or dairy products, previously thought to be helpful, is now recognized to be unreliable. A significant number of health care providers continue to inquire specifically into a patient's history of 'allergy' to seafood, especially shellfish. There is no evidence to support the continuation of this practice" (American College of Radiology. Manual on Contrast Media, v8. http://www.acr.org/Quality-Safety/Resources/Contrast-Manual. Accessed October 5, 2012).

Summary Statement 5: Test for IgE antibodies specific for the immunogenic oligosaccharide alpha-gal in patients who report a delayed systemic reaction to red meat or unexplained anaphylaxis, particularly if they have a history of previous tick bites. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 6: Avoid all mammalian meats in patients with alpha-gal allergy because this oligosaccharide antigen is widely expressed in mammalian tissues. [Strength of recommendation: Moderate; C Evidence]

Recently, delayed allergy to mammalian meats has been linked to the production of IgE to alpha-gal in susceptible subjects,[82] the vast majority of whom report tick bites.[83,84] Urticaria, angioedema, and anaphylaxis can occur 3 to 6 hours after eating beef, pork, lamb, and venison, and the mechanisms for this delay remain poorly understood. Results of epicutaneous testing to the above foods might not be strongly positive, but *in vitro* assays for alpha-gal IgE are now commercially available. Alpha-gal–specific IgE (sIgE) will recognize epitopes present in all of these animals, and thus all of these meats should be eliminated from the diet.

Summary Statement 7: Evaluate patients with latex allergy for the possibility of cross-reactivity to banana, avocado, kiwi, chestnut, potato, green pepper, and other fruits and nuts. Individualized management is recommended because clinical reactions caused by this cross-reactivity can range from mild to severe. [Strength of recommendation: Strong; C Evidence]

Proteins in products derived from the natural rubber latex tree *Hevea brasiliensis* share homologous epitopes with many other plant foods.[85,86] Approximately 30% to 50% of patients allergic to latex might be clinically reactive to 1 or more foods, typically fresh fruits and nuts.[87] Although irrelevant sensitization is more common than true clinical cross-reactivity, reactions to fruit in patients with latex allergy can be severe.[88] Caution is warranted when evaluating such patients.

Genetically modified organisms in foods and the potential for allergenicity

Summary Statement 8: Advise patients not to be concerned about ingesting genetically modified foods given the current state of knowledge and the US Food and Drug Administration's screening requirements to rule out allergenicity of genetically modified foods. [Strength of recommendation: Weak; D Evidence]

Although the determinants of allergenicity are the subject of continued study, no single finding can predict whether a given food protein will cause allergy in human subjects. Therefore the Codex Alimentarius Commission of the World Health Organization has recommended a weight-of-evidence approach for allergenicity assessment of the novel food proteins produced through molecular biologic techniques.[89] These assessments are largely based on the current knowledge of food allergens and whether the genetically modified food in question might act as or cross-react to a known allergen. To determine whether this might be the case, the codex recommends investigating the history of human exposure and safety of the gene product or products and then analyzing and comparing the protein sequence and physicochemical properties with those of known allergens by using current bioinformatics tools. When these preliminary assessments suggest risk (≥35% shared identity over ≥80 amino acid span), sIgE-binding studies with well-characterized serum from patients allergic to the identified source or skin prick testing with relevant subjects are also conducted.[90]

Perhaps in part because of the safety and allergenicity assessments performed during product development, there is no published evidence to date of allergic reactions to any genetically modified protein or any adverse human health reactions associated with consumption of foods from approved genetically modified crops.[91] However, most of the safety and allergenicity assessments are based on existing knowledge of known allergenic structures (ie, cross-reactivity), and there is no way to predict whether novel proteins will become allergenic *de novo*[92]; similarly, there is no reliable way to assess the safety of engineered foods that have been modified with the intent of creating a "hypoallergenic" alternative.

SECTION II: MUCOSAL IMMUNE RESPONSES INDUCED BY FOODS

Summary Statement 9: Manage non–IgE-mediated reactions to foods with appropriate avoidance and pharmacotherapy as indicated with the understanding that the specific role of immunity (eg, IgA, IgM, IgG, and IgG subclasses) in these forms of food allergy has not been demonstrated. [Strength of recommendation: Strong; B Evidence]

Delayed gastrointestinal reactions include eosinophilic esophagitis (EoE), eosinophilic gastroenteritis, eosinophilic proctocolitis, and food protein–induced enterocolitis syndrome (FPIES).[93-98] Delayed-type hypersensitivity reactions can be triggered by many foods but most commonly cow's milk, soy, wheat, and egg.[93-95,99,100]

Autoimmune mucosal disease triggered by food antigens include celiac disease.[93-98] IgA anti-gliadin and anti-endomysial (transglutaminase) antibodies have been studied extensively in gluten-sensitive enteropathy. In part, the presence of anti-gliadin antibodies strongly suggests that gluten-sensitive enteropathy is due to a dietary element.[101]

Both serum and secretory specific IgA to dietary proteins can be produced in healthy subjects and allergic patients, and this does not predict allergy status. In some instances the levels of the local secretory IgA_2 subclass might be increased in the absence of measurable levels of serum IgA (primarily IgA_1).[102] Oral ingestion of microparticles that contain dietary proteins leads to enhanced synthesis of IgA_2 secretory antibodies compared with soluble proteins alone.[102]

The role of cellular *in vitro* correlates as diagnostic or prognostic indicators of food allergy is currently under investigation. Basophil and eosinophilic reactivity tests have been shown to be associated with food-induced allergic responses and have been shown in current research to be modified over time during immunotherapy.[94-98,103,104] Indexes of cell-mediated immunity, such as lymphocyte proliferation, have been implicated as possible correlates of food hypersensitivity, with relatively greater proliferation seen in patients with food allergy, but these assays are not specific.[94,98,105]

The role of specific cytokine profiles in serum or peripheral mononuclear cells of patients with food allergy remains under study and has not been well established to date. There is some evidence suggesting the interaction of IL-4 versus IL-5 in immediate versus delayed food-related allergic diseases.[106]

SECTION III: THE CLINICAL SPECTRUM OF FOOD ALLERGY

The clinician should be aware that adverse reactions to food can be best categorized as those involving immunologic or nonimmunologic mechanisms, as summarized in Fig E1. A food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. The term food allergy includes clinical conditions associated with altered immunologic reactivity that might be either IgE mediated or non-IgE mediated.

Although food allergy is most often caused by sIgE-mediated reactions, it can also be the result of reactions that are immunologic but through non–IgE-induced mechanisms (eg, food protein–induced enteropathy and some allergic gastrointestinal disorders, such as allergic colitis and proctocolitis).[2,31] Some disorders, such as atopic dermatitis and EoE, often have characteristics of both mechanisms and are therefore categorized as mixed IgE and non–IgE-mediated conditions. With non–IgE-mediated food allergy, food sensitization cannot be demonstrated based on the detection of food sIgE, and the diagnosis is therefore typically based on a combination of reproducible clinical signs and symptoms consistent with true food allergy occurring on

exposure to a food, resolution of those signs and symptoms with specific food avoidance, and, in some cases, histologic evidence of an immunologically mediated process, such as eosinophilic inflammation of the gastrointestinal tract that resolves with food avoidance.

Categories of adverse food reactions

Nonimmunologic reactions to food (food intolerances) can include metabolic, pharmacologic, toxic, and/or undefined mechanisms. Because food intolerances can sometimes mimic reactions typical of an immunologic response, it is important to keep these mechanisms in mind when evaluating patients reporting adverse food reactions.

An adverse reaction to milk, for example, might be due to an immunologic response to milk protein or an intolerance caused by an inability to digest lactose. Most adverse reactions to food additives, such as artificial colors and various preservatives, have no defined immunologic mechanisms and are most appropriately categorized as food intolerances if reproducible reactions do occur. Other common food intolerances include those related to pharmacologic (eg, caffeine) or toxic (eg, scromboid) effects of food, whereas for others, no clear mechanism or mechanisms have been defined (eg, sulfites; see "Section VI: Diagnosis of food allergy, differential diagnosis, and diagnostic algorithm).

Summary Statement 10: Determine whether the reported history of food allergy, which often proves inaccurate, and laboratory data are sufficient to diagnose food allergy or whether an oral food challenge (OFC) is necessary. [Strength of recommendation: Strong; A Evidence]

Sensitization alone is not sufficient to diagnose food allergy because subjects can have immunologic sensitization (as evidenced by the presence of allergen sIgE) to food allergens without having clinical symptoms after exposure to those foods.

As detailed in Section VI, testing for the presence of food allergen sIgE in the form of skin or *in vitro* laboratory testing is highly sensitive (ie, low rate of false-negative results) but only moderately specific (higher rate of false-positive results) and must always be selected and interpreted in the context of the patient's specific clinical history.[2,31,107,108] The details of the history are used to generate an estimate of the patient's likelihood of having true food allergy. The general sensitivity and specificity of skin prick or *in vitro* testing for the diagnosis of food allergy are estimated to be greater than 90% and approximately 50%, respectively. Given the low predictive value of both the history and test results, it is important that all suspected food allergy be confirmed by using appropriate evaluation.

Definitions of specific food-induced allergic conditions

The clinician should be aware that gastrointestinal food allergies include a spectrum of disorders that result from adverse immunologic responses to dietary antigens. Although there might be significant overlap between these conditions, several specific syndromes have been described.

These are defined as follows:

- *Immediate gastrointestinal hypersensitivity* refers to an IgE-mediated food allergy in which upper gastrointestinal symptoms can occur within minutes and lower gastrointestinal symptoms can occur either immediately or with a delay of up to several hours.[109,110] This is commonly seen as a manifestation of anaphylaxis.[17-19] Among the gastrointestinal conditions, acute immediate vomiting is the most common reaction and the one best documented as IgE mediated.
- *EoE* is a clinicopathologic diagnosis that requires symptoms related to esophageal dysfunction and isolated eosinophilic inflammation of the esophagus.[100,111-113] Although EoE is commonly associated with the presence of food sIgE, the precise mechanistic role of food allergy in its cause is not well defined, and both IgE-mediated and non–IgE-mediated mechanisms can be involved in the pathogenesis of this disease. In younger children EoE presents with feeding disorders, vomiting, reflux symptoms, and abdominal pain, whereas in adolescents and adults EoE most often presents with dysphagia and esophageal food impactions.
- *Eosinophilic gastroenteritis (EGE)* is less common than EoE, which is also believed to be both IgE-mediated and non–IgE-mediated and occasionally linked to food allergies.[109,110] EGE describes a constellation of symptoms that vary depending on the portion of the gastrointestinal tract involved and a pathologic infiltration of the gastrointestinal tract by eosinophils that might be quite localized or very widespread. Common symptoms include vomiting, abdominal pain, diarrhea, and failure to thrive/weight loss. Multiple food allergens are often implicated in this condition.
- *Dietary protein-induced proctitis/proctocolitis* typically presents in infants who seem generally healthy but have visible specks or streaks of blood mixed with mucus in the stool. IgE to specific foods is generally absent.[100,101] Milk protein is most commonly implicated, although multiple food allergens can be involved. Symptoms will resolve with dietary avoidance, which might include maternal dietary restriction in breast-fed infants. This condition typically resolves during infancy.
- *FPIES* is another non–IgE-mediated disorder that usually occurs in young infants and manifests as chronic emesis, diarrhea, and failure to thrive.[16,114] On re-exposure to the offending food after a period of elimination, a subacute syndrome can present with repetitive projectile emesis and dehydration that typically occurs 2 to 4 hours after ingestion of the offending food protein.
- *Pollen-food allergy syndrome*, also referred to as pollen-associated food allergy syndrome, is a form of localized IgE-mediated allergy, usually to raw fruits or vegetables, and confined to the lips, mouth, and throat.[88,115] OAS most commonly affects patients who are allergic to (specific) pollens (eg, ragweed and birch). Symptoms include pruritus and/or tingling of the lips, tongue, roof of the mouth, and throat with or without swelling. Systemic clinical reactions are rare.
- It has been suggested that colic, gastroesophageal reflux, and constipation might be caused by food allergy in small subsets of patients. Additional evidence is required to support a causal relationship for food allergy in patients with these disorders.

The clinician should be aware that respiratory manifestations of IgE-mediated food allergy occur frequently during systemic

allergic reactions and are an important indicator of severe anaphylaxis.

Food allergy is an uncommon cause of chronic respiratory symptoms of the upper (rhinitis) and/or lower (asthma) airways.[116] However, acute respiratory tract reactions are a common and potentially fatal manifestation of food allergy. In patients with anaphylaxis and other acute food-induced allergic reactions, respiratory manifestations might include nasal congestion, rhinorrhea, stridor, tachypnea, labored breathing, cough, and wheeze. Severe airway compromise can occur as a result of laryngeal edema and/or bronchospasm, edema, and mucous plugging in the lower airways, which can lead to hypoxia and airway collapse. Asthmatic patients appear to be at significantly increased risk of severe airway compromise that might result in fatal and near-fatal food-induced reactions.[117]

SECTION IV: PREVALENCE, NATURAL HISTORY, AND PREVENTION

Natural history

Summary Statement 11: Consider the natural course of allergies to specific foods when deciding on the frequency of food allergy follow-up evaluations, recognizing that allergies to certain foods (milk, egg, wheat, and soy) generally resolve more quickly in childhood than others (peanut, tree nuts, fish, and shellfish). These observations could support individualized follow-up (ie, roughly yearly re-evaluations of these allergies in childhood) with less frequent retesting if results remain particularly high (eg, >20-50 kU_A/L). [Strength of recommendation: Moderate; C Evidence]

The rate of allergy resolution (natural tolerance) varies according to the food, the patient's age, pathophysiology of the allergy, and other factors and is not well characterized for most foods.[2,31] The physician should be familiar with the natural course of food allergy resolution to provide patients with prognostic information and to determine the frequency of periodic longitudinal re-evaluations. Typically, allergy tests, such as skin and serum food sIgE tests, are monitored to determine whether immune indexes are improving (eg, lower food sIgE levels and smaller skin test results), as described elsewhere in this parameter. On the basis of studies of childhood allergies, risk factors for persistence include high initial levels of IgE antibodies and comorbid atopic diseases.[31,118-121] Non–IgE-mediated disorders, such as allergic proctocolitis and FPIES, typically resolve more quickly than IgE-mediated disorders.[122,123]

Most children with food allergy eventually tolerate milk, egg, wheat, and soy.[31] Regarding milk, early studies suggested resolution rates of approximately 80% by age 5 years,[2] but a more recent study from a referral center[118] suggested a slower resolution rate: 19% at age 4 years, 64% at age 12 years, and 79% by age 16 years. Roughly similar observations have been made for egg allergy,[121] but slightly more rapid resolution rates were observed for wheat (29% by age 4 years and 65% by age 12 years) and soy (25% by age 4 years and 69% by age 10 years).[120,124] These observations could support roughly yearly re-evaluations of these allergies in childhood, with less frequent retesting if results remain particularly high (eg, >20-50 kU_A/L).

Allergies to peanut, tree nuts, fish, and shellfish persist more often, but re-evaluations are warranted because long-term studies are lacking and studies of children suggest about 20% become tolerant to peanut[125] and 10% resolve tree nut allergy.[119] The rate of resolution is probably slightly lower for fish and shellfish allergy.[70] Recurrence of a resolved peanut allergy is uncommon and appears more likely among those not incorporating it into the diet after resolution proved by OFC (approximately 4%).[126,127]

On the basis of these data, periodic re-evaluation of peanut, tree nut, fish, and shellfish allergies initially by laboratory testing can be considered approximately yearly for young children with favorable test results and every few years or longer for older children and adults, depending on the patient's history and test results, with more frequent testing if values are becoming more favorable for tolerance.

Prevention of food allergy

Summary Statement 12: Encourage exclusive breast-feeding for the first 4 to 6 months of life. [Strength of recommendation: Weak; C Evidence]

Summary Statement 13: For infants with a family history of atopy, consider a partially or extensively hydrolyzed infant formula for possible prevention of atopic dermatitis and infant cow's milk allergy if exclusive breast-feeding is not possible. [Strength of recommendation: Moderate; B Evidence]

Summary Statement 14: Do not recommend maternal allergen avoidance or avoidance of specific complementary foods at weaning because these approaches have not proved effective for primary prevention of atopic disease. [Strength of recommendation: Weak; C Evidence]

Summary Statement 15: Do not routinely recommend supplementation of the maternal or infant diet with probiotics or prebiotics as a means to prevent food allergy because there is insufficient evidence to support a beneficial effect. [Strength of recommendation: Weak; C Evidence]

Recent guidelines have suggested exclusive breast-feeding for all infants regardless of allergy risks for general health reasons.[2,128] There are conflicting data on whether breast-feeding is protective against atopic disease, but a recent meta-analysis and a recent large study suggested no significant protection compared with formula feeding.[129,130] Should breast-feeding not be possible, guidelines[2,128,131] have suggested that soy or cow's milk formula do not have a protective effect on atopic disease, particularly atopic dermatitis, or food allergy but that substitution with a hydrolyzed infant formula can be considered as a strategy for the prevention of food allergy (milk allergy specifically) or atopic dermatitis for infants at risk, who are typically defined by having a parent or sibling with an atopic disease. The data supporting these recommendations are limited and sometimes conflicting[2,131-137] and include the possibility that an extensively hydrolyzed formula might be more effective,[134,135] but cost and taste factors are additional considerations.

Regarding maternal avoidance diets during pregnancy or lactation, there are some conflicting data,[138-143] but in general, there is insufficient evidence that maternal diet during pregnancy or lactation affects the development of food allergy.[2,31,128]

Experts recommend that introduction of solid foods, including potentially allergenic foods, should not be delayed beyond 4 to 6 months of age.[2,128,144,145] This recommendation is based in part on multiple recent studies that appear to support delayed introduction of allergens, such as egg, milk, wheat, and peanut, as possible risk factors for allergy to the foods or atopic disease.[146-150] However, these recommendations are made in the context of primary prevention, and the timing of adding additional allergens to the

diet of an infant/child with a known food allergy has not been specifically studied. Infants or children with 1 food allergy might be at higher risk for other food allergies, and some caution is needed when advancing the diet.[151,152] Thus feeding recommendations for infants/children regarding primary prevention of food allergy might be different from those suggested for children with an established food allergy, and this remains unexplored.

Although expert recommendations address prevention strategies regarding breast-feeding, maternal diet during pregnancy/lactation, timing/selection of introduction of complementary foods, and use of selected supplemental infant formulas, the relative effect of these strategies, individually or in combination, has not been fully established in controlled trials.

The use of prebiotics, probiotics, or synbiotics as an active means to prevent food allergy or atopic disease requires additional study. Many studies, primarily on probiotics, have been published, but comparability is limited by the selection of probiotic, dose, length of therapy, outcome measures, target population, and other differences in methodology. Two meta-analyses on probiotics concluded that they might reduce the risk of eczema, but there was no effect on other atopic conditions,[153,154] and inconsistency among studies was noted.[153] Studies have generally not shown a preventive effect on food sensitization or allergy, although power to do so is generally lacking.[155-158] There are few prevention studies on prebiotics and synbiotics that also support a possible but inconsistent prevention effect on atopic dermatitis without addressing or not showing effects on food allergy/sensitization.[159-163] Physicians should be aware that probiotics can contain milk proteins.[164]

SECTION V: ADVERSE REACTIONS TO FOOD ADDITIVES

Food additives are defined as substances added to foods during processing to improve color, texture, flavor, or keeping qualities; examples include antioxidants, emulsifiers, thickeners, preservatives, and colorants.[165] Most food additives are identified on the ingredient label; however, there are a number of food additives that are "generally regarded as safe" by the US Food and Drug Administration, and these are not required to be listed on labels, although food manufacturers might list them.

Food additives can be chemicals or natural factors (derived from plant or animals). The materials added to food include preservatives, emulsifiers, stabilizers, acids, nonstick agents, humectants, firming agents, antifoaming agents, colorings and flavorings, solvents, antioxidants, flavor enhancers, and even nutritive materials, such as minerals and vitamins.

Summary Statement 16: Do not routinely recommend that patients with chronic idiopathic urticaria (CIU) avoid foods containing additives. [Strength of recommendation: Strong; B Evidence]

Although the cause of CIU is unknown, there is an underlying autoimmune pathogenesis (ie, an IgG antibody directed against the high-affinity IgE receptor, anti-FcεRIα, or the Fc region of IgE anti-IgE) in a significant number of subjects.[166,167] Although the cause remains truly idiopathic in many cases, there are no convincing data that demonstrate that CIU can result from an allergic reaction or sensitivity to food or food additives. Although earlier studies reported that oral challenges with a number of commonly used food additives provoked urticaria in patients with chronic urticaria, these studies had a number of design flaws. Their designs included complete lack of or poor controls and/or used subjective nonurticarial reactions or simply the presence/increase of hives as end points for a positive challenge outcome. Time points for a positive reaction could be as long as 24 hours or more. When one also considers that antihistamines were withheld before challenge, it makes interpretation of positive results dubious. A recent oral double-blind, placebo-controlled food challenge (DBPCFC) study with common food additives in patients with CIU using semiquantitative skin scores as the end point produced positive reactions at rates little different than those seen with placebo.[168] The most recent study, using semi-quantitative skin scores as the end point, concluded the prevalence of food additive sensitivity in CIU patients occurs rarely if at all.[169] These include challenges with monosodium glutamate (MSG), benzoates, parabens, sulfites, butylated hydroxyanisole/butylated hydroxytoluene (BHA/BHT), tartrazine (FD&C Yellow #5, E102), Sunset yellow (FD&C Yellow #6, E110), and aspartame (Nutrasweet).

Clinicians should not recommend their patients with CIU avoid foods containing additives.[168,169]

Summary Statement 17: Do not routinely instruct asthmatic patients to avoid sulfites or other food additives unless they have a prior reaction to sulfites. Sulfites are the only food additive proved to trigger asthma. Although these reactions can be severe, even life-threatening in sensitive subjects, they are rare. [Strength of recommendation: Strong; B Evidence]

Sulfite-sensitive asthma is a well-recognized but rare condition affecting less than 5% of asthmatic patients.[170] These patients usually have severe steroid-dependent asthma.[170,171] Such asthmatic patients generally have a history of reactions to sulfited foods, such as dried fruit or wine.[171] The reactions can be severe and even life-threatening. If clinically indicated, testing would be by means of oral challenge. These reactions are not IgE mediated, and therefore skin testing is not indicated. However, other food additives have not been shown to provoke asthmatic reactions in DBPCFCs, and thus neither oral challenges nor avoidance is recommended (including tartrazine [FD&C Yellow #5, E102], MSG, benzoates, parabens, BHA/BHT, Sunset yellow [FD&C Yellow #6, E110], and aspartame [Nutrasweet]).[172,173]

Summary Statement 18: Consider natural food additives in the evaluation of patients with a history of unexplained ingestant-related anaphylaxis. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 19: Patients who experience an adverse reaction to food additives should be evaluated for sensitivity to annatto and carmine. [Strength of recommendation: Strong; A Evidence]

Clinicians need to recognize that the natural food additives annatto (yellow) and carmine (red) have been associated with anaphylaxis.[174-177] They must also be cognizant that the following additives have been reported to cause anaphylaxis: erythritol, guar gum, psyllium, carrageenan, lupine, pectin, gelatin, mycoprotein, and certain spices.[178-186] Thus natural food additives and spices should be included in the work-up of patients with a history of unexplained anaphylaxis.

Summary Statement 20: Clinicians should be aware that avoidance measures are appropriate for patients with histories compatible with adverse reactions to an additive until diagnostic evaluation can be performed. [Strength of recommendation: Moderate; C Evidence]

Despite the many studies that demonstrate a lack of association between food additives and allergic reactions, there have been isolated case reports confirmed by well-designed DBPCFCs of reactions to some food additives. These include, but are not

limited to, urticaria and anaphylaxis from sulfites,[187-190] 2 studies with positive SPT responses but no oral challenges,[189,190] delayed angioedema from MSG,[191] and urticaria from BHA/BHT[192] and aspartame.[193] Therefore if an otherwise healthy patient or a patient with CIU or asthma, for example, presents with a good history of a reaction to a food additive, one should still consider avoidance until diagnostic testing (skin or oral challenge) can be performed.[194]

Summary Statement 21: Clinicians should not recommend food additive avoidance in their patients with hyperactivity/attention deficit disorder. [Strength of recommendation: Strong; A Evidence]

Anecdotal reports and noncontrolled or poorly controlled elimination diet or challenge studies have suggested a link between food additives and attention deficit hyperactivity disorder (ADHD). However, in a very recently published meta-analysis of well-controlled double-blind elimination diets and/or challenge studies of additives in patients with ADHD, although there was a small change in parental reports of symptoms, no significant changes in teacher-reported symptoms were found.[195] Additionally, neither the American Academy of Pediatrics nor the United Kingdom's National Institute for Health and Clinical Excellence guidelines recommend routine elimination diets for the treatment of ADHD.[196,197]

SECTION VI: DIAGNOSIS OF FOOD ALLERGY, DIFFERENTIAL DIAGNOSIS, AND DIAGNOSTIC ALGORITHM

Diagnosis of IgE-mediated food allergy

Summary Statement 22: The clinician should obtain a detailed medical history and physical examination to aid in the diagnosis of food allergy. [Strength of recommendation: Strong; D Evidence]

The evaluation of the patient with suspected food allergy should include a detailed medical history that considers the symptoms indicative of various types of adverse reactions to foods, including other immunologic and nonimmunologic food reactions (Fig E1), the epidemiologic characteristics of potential triggers (see "Section I: Classification of major food allergens, cross-reactivities, genetically modified foods, and clinical implications"), and evaluation of the temporal relationship between food ingestion and onset of symptoms.[4,37] Because IgE-mediated food allergy most often presents with immediate symptoms (within 2 hours) after ingestion of the culprit food, the medical history can provide important clues that will aid in the identification of suspected food allergens and focus the diagnostic evaluation on the allergen or allergens most likely related to reported symptoms.

Although the medical history lacks sufficient sensitivity and specificity to make the diagnosis of IgE-mediated food allergy,[7] historical aspects of food reactions can certainly aid in identification of suspected allergens and help determine whether other factors play a role in the presentation of symptoms. The clinician should consider foods that consistently elicit symptoms of food allergy to improve the accuracy of diagnosing IgE-mediated disease.[2] The clinician should also ascertain historical aspects, such as the quantity ingested, preparation of the suspected food, and frequency of symptoms associated with ingestion. Foods that have been eaten on multiple occasions and historically tolerated are less likely to be causal foods; however, the ingestion of subthreshold doses or certain preparations (eg, extensively baked or fermented) might result in ingestion of a food allergen without reaction.[198,199] Review of the history should take into consideration hidden or unidentified food allergens in processed foods, and review of food labels might be needed to identify possible food allergens ingested at the time of the reaction. The medical history might also reveal other special circumstances that result in symptoms after ingestion, such as temporally related alcohol consumption, medication dosing, exercise, or other activities.

In addition to aiding in the identification of suspected food allergens, a detailed description of symptoms is another important aspect of the medical history that can assist the clinician in determining whether symptoms are elicited by IgE-mediated or other mechanisms. There are no pathognomonic symptoms for food allergy, and there is considerable overlap between food-related allergic disorders (see "Section III: The clinical spectrum of food allergy"); however, certain historical aspects make the diagnosis of IgE-mediated disease more likely, such as the immediate onset of oropharyngeal symptoms or skin abnormalities (eg, pruritus, flushing, or urticaria) after ingestion of a suspected food allergen. Also, foods have been implicated as the most common trigger of anaphylaxis, particularly among children[200]; therefore a history consistent with anaphylaxis or immediate multisystem symptoms after food ingestion is highly suggestive of a diagnosis of IgE-mediated disease.[81,200,201]

The physical examination of the patient with suspected IgE-mediated food allergy might reveal signs of an acute allergic reaction (Table E2) or chronic findings consistent with allergic diatheses; however, the physical examination alone cannot be considered diagnostic of food allergy,[202] and physical examination findings should be considered within the context of the patient's individual medical history. Findings on examination in conjunction with the medical history are important in determining the most useful diagnostic test or tests. Evidence of atopy, such as asthma, allergic rhinitis, or atopic dermatitis, might indicate an increased risk of IgE-mediated food allergy. Conversely, physical findings related to other disorders, such as failure to thrive or dermatitis herpetiformis, might indicate other non–IgE-mediated, autoimmune, or nonimmunologic disease.

When considering the medical history and physical findings, the clinician should be aware of several adverse food reactions or other allergic disorders that are often misclassified as IgE-mediated food reactions.[203] It is important to rule out other clinical entities and accurately diagnose IgE-mediated food allergy because the natural history, severity of clinical reactivity, and disease management vary for each disorder. Clinical syndromes that are often misclassified as IgE-mediated food allergy include the following:

A. allergic reactions caused by medications or insect stings that coincidentally occur at the time of food ingestion/meal;
B. metabolic disorders (eg, lactose intolerance);
C. toxic reactions (eg, food poisoning caused by scromboid fish toxin[204] or bacteria, such as *Salmonella* species, *Shigella* species, or *Escherichia coli*;
D. chemical effects (eg, gustatory rhinitis caused by hot/spicy foods[205];
E. auriculotemporal (Frey) syndrome or gustatory flushing syndrome caused by foods[206,207];
F. pharmacologic reactions (eg, caffeine, tryptamine, or alcohol);

G. irritant reactions, particularly in patients with atopic dermatitis;
H. infectious syndromes (eg, *Staphylococcus aureus* toxin or urticaria during concurrent viral infection); or
I. other/idiosyncratic reactions (eg, sulfites, nitrites, or MSG).

The clinician should suspect IgE-mediated food allergy in patients with anaphylaxis or allergic symptoms within minutes to hours after ingestion of a specific food or delayed reactions in selected persons given a diagnosis of mixed IgE/non–IgE-mediated disorders, such as atopic dermatitis or EoE.

IgE-mediated allergic reactions have varied presentations and can involve 1, 2, or multiple organ systems (Table E2). IgE-mediated symptoms typically occur immediately to a few minutes to hours after ingestion of the causative food.[208] The majority of IgE-mediated food reactions involve skin manifestations, such as urticaria, angioedema, or erythema (flushing).[2,209] However, the clinical presentation and severity of IgE-mediated reactions can depend on several factors, including individual patient characteristics, such as underlying comorbid conditions (eg, asthma), current health status (eg, concurrent upper respiratory tract infection or uncontrolled atopic dermatitis), activities proximate to the ingestion of the causative food (eg, exercise or alcohol consumption), dose and/or preparation of the causative food, and use of various medications (eg, antihistamines). Fatal and near-fatal reactions have been reported to be caused by food allergy, and these reactions have been related to a number of factors, including adolescent age, underlying respiratory disease (eg, asthma), concomitant use of β-blocker medications, reactions that do not involve the skin, and delayed treatment or failure to treat with epinephrine.[117,210-214]

Mixed reactions involving both IgE-mediated and non–IgE-mediated (cellular) mechanisms can be delayed by several hours or result in chronic symptoms (eg, EoE or atopic dermatitis) caused by ingestion of the causative food or foods.[2,31,37] Because the history often lacks direct temporal correlation between food ingestion and symptom onset, the diagnostic evaluation of patients experiencing mixed reactions might require extensive dietary documentation and dietary manipulations to accurately identify the culprit food or foods. Dietary elimination and reintroduction of suspected food allergens can be useful diagnostic tools in patients with mixed IgE/non–IgE-mediated food reactions. The clinician should observe a reduction in symptoms with dietary elimination of culprit foods and subsequent recurrence of symptoms with reintroduction.[2,31]

Summary Statement 23: The clinician should use specific IgE tests (SPTs, serum tests, or both) to foods as diagnostic tools; however, testing should be focused on foods suspected of provoking the reaction, and test results alone should not be considered diagnostic of food allergy. [Strength of recommendation: Strong; B Evidence]

Because of the low PPV of self-reported symptoms[7] and lack of pathognomonic signs on physical examination, the accurate diagnosis of IgE-mediated food allergy should be aided by laboratory allergy testing, including skin prick and/or serum IgE testing.[208] The clinician should be aware that a relatively small number of foods are responsible for the majority of IgE-mediated food reactions, and therefore panel testing to a large number of allergens should not be conducted. The selection of allergens for testing should be guided by the patient's history of clinical reactivity to specific food allergens that have either been temporally related to acute symptoms in IgE-mediated disease or foods that are suspected to exacerbate chronic symptoms in mixed IgE-mediated/non–IgE-mediated disease. The clinician should also consider epidemiologic factors related to common food allergens.[4] For example, reactions to shellfish and peanuts are almost always IgE mediated, whereas other foods, such as milk and soy, are commonly associated with IgE-mediated, non–IgE-mediated, and mixed reactions.

For children at high risk, such as children with early development of severe atopic disease or children with a sibling/parent with peanut allergy, sIgE testing can be considered before introduction of certain foods. For these high-risk patients, the clinician should consider sIgE testing for highly allergenic foods, such as milk, egg, and peanut. Peanut allergy has been found to be more prevalent among children with a primary relative with peanut allergy,[215] and in a cohort of young infants with early development of milk and egg allergy, investigators found a 69% sensitization rate to peanut.[151] Therefore testing might provide the clinician with important data to aid in decision making regarding the need for OFCs or food introductions. There is insufficient evidence to support the widespread use of sIgE testing in children who are not at high risk because such testing can lead to unnecessary dietary restrictions.[2]

SPTs can be performed in the office setting and represent a safe and effective method of detecting sIgE antibodies. Although standardized commercial extracts are not available and international standards for administering and interpreting results have not been established,[216] SPTs are commonly used to aid in the diagnosis of IgE-mediated food allergy. In evaluating fruits and vegetables, or in cases in which extracts for foods are not available, physicians might use a prick-prick method with the fresh food or a slurry made with the food and sterile saline. Results are interpreted by comparing the skin response with negative (eg, saline) and/or positive (eg, histamine) controls. A positive SPT response will produce a wheal-and-flare reaction within 10 to 20 minutes after allergen introduction, and generally, an SPT response is considered positive if the wheal has a mean diameter 3 mm or larger than that elicited by the negative control.[216]

Because a positive SPT response only reflects the presence of sIgE bound to the surfaces of cutaneous mast cells, skin test reactivity should not be considered diagnostic of clinical reactivity. SPTs for foods have low specificity,[217] and previous studies have reported PPVs at variable wheal sizes depending on the population and food being studied.[218] SPTs should be conducted only for suspected food allergens, and interpretation of results should be considered in light of the patient's history of clinical reactivity in an effort to reduce the risks of overdiagnosis and unnecessary dietary eliminations.

The clinician should realize that although wheal size has not been correlated with disease severity, wheal size can be used to aid in medical decision making. The larger the wheal, the more likely the allergen is to be clinically relevant. Mean diameter wheal size can be used as a predictor for oral tolerance development for selected foods.[219-222] In a study examining the predictive value of SPT-induced wheal size in children with a diagnosis of peanut allergy, investigators found that a mean wheal size of 8 mm or greater was highly predictive of having a positive food challenge result to peanut (95% PPV).[223] Other investigations have established SPT mean wheal size cutoffs and PPVs for a limited number of common food allergens (Table E3).[219,224-226] These cutoffs can be used to help the clinician

establish the probability of clinical reactivity versus oral tolerance and determine the need for further testing (eg, OFC) or dietary manipulations. The clinician should be aware that PPVs of wheal sizes can vary with age[224] or other factors, such as skin test location (eg, volar surface of forearm vs back), SPT device, or reagents (which are not standardized) used for testing.[31]

SPTs have a relatively high NPV and are particularly useful in ruling out IgE-mediated food allergy to a specific food during the initial diagnostic workup of patients with suspected IgE-mediated food allergy.[208] However, a negative SPT response does not rule out clinical reactivity. When evaluating patients with a high degree of clinical suspicion, the clinician should use further diagnostic tests if the SPT response is negative. Other diagnostic tests, such as serum sIgE measurement and/or OFCs, should be used to aid in the diagnosis before allowing the patient to reintroduce a highly suspect food into the diet. Immediate hypersensitivity skin testing for foods is associated with an estimated sensitivity and specificity of 85% and 74%,[227] respectively, and a calculated positive likelihood ratio of 3.3. This implies that a positive skin test result would entail a relatively small effect on a pretest probability for food allergy determined by a detailed history. For instance, in the case of a patient whose pretest probability is 30%, a positive skin test response would lead to a posttest probability of only 50%. In using a diagnostic test with a positive likelihood ratio in this range, it is important for the clinician to be aware that when a pretest probability for allergy to a specific food is not high and certainly when there is no history suggestive for food allergy, a positive skin test response to that food cannot reliably establish a diagnosis of food allergy.

Serum sIgE testing is another important diagnostic tool that can aid in accurate identification of causal food allergens.[229-234] Fluorescence-labeled antibody assays are used to detect the presence of circulating IgE antibodies to suspected foods. Although useful in determining allergic sensitization, detection of sIgE alone cannot be considered diagnostic of food allergy. Foods selected for testing should be based on the medical history and epidemiologic factors related to food allergens. Testing to large panels or multiple allergens without consideration of the patient's history should be avoided because false-positive test results can result in unnecessary dietary elimination of safe foods.[108,228]

Investigators have established predictive thresholds for peanut, egg, milk, fish, soy, and wheat (Table E3),[229-233] and these cutoffs are useful in determining whether an OFC is warranted or when advising patients about the likelihood of clinical reactivity to the suspected food allergen. Generally, higher sIgE levels are more likely to be associated with clinical reactivity, but the predictive value of sIgE levels varies across patient populations and might be related to the patient's age, time since last ingestion of the suspected food allergen, and other underlying disorders.[230,233-236] sIgE testing can be useful in the clinical setting when there is a high degree of clinical suspicion but negative SPT responses, and sIgE testing is particularly useful when SPTs are precluded by ongoing antihistamine therapy, moderate-to-severe skin disease, or dermatographism.[2]

The clinician should be aware that negative sIgE results do not rule out clinical allergy. If there is a high degree of clinical suspicion, other tests, such as SPTs, an OFC to the suspected food, or both, might be warranted. Advice regarding reintroduction of a potential food allergen cannot rely solely on sIgE testing because of the risk of a serious or life-threatening allergic reaction. The history of clinical reactivity along with results of other diagnostic tests are useful adjunctive tools when sIgE test results are negative or less than the established PPV thresholds.[31]

Summary Statement 24: Component-resolved diagnostic testing to food allergens can be considered, as in the case of peanut sensitivity, but it is not routinely recommended even with peanut sensitivity because the clinical utility of component testing has not been fully elucidated. [Strength of recommendation: Weak; C Evidence]

Component-resolved diagnosis (CRD) uses allergenic proteins derived from rDNA technology or purification from natural sources to identify the patient's sIgE reactivity to recombinant allergenic proteins rather than whole allergen.[237] CRD is a promising new diagnostic tool in the field of allergy; however, further investigation is warranted. CRD is not routinely recommended for the diagnosis of food allergy, but CRD might be useful in certain clinical scenarios.[2,31,238]

Studies of the clinical utility of CRD for specific allergens have shown promising results for a relatively small number of foods. Recent studies propose sIgE antibodies to Ara h 2 as the most common peanut allergen associated with clinical reactivity,[239-241] and sensitization to Ara h 1, 2, or 3 has been associated with increased severity of reactions in certain subjects, especially compared with those sensitized to Ara h 8 (Bet v 1 related), who experience predominantly oral allergy symptoms.[242] Similarly, sensitization to Cor a 9 and Cor a 14 has been associated with both symptom severity and objective findings during DBPCFCs to hazel nut.[243] These findings suggest that CRD could potentially enhance diagnostic accuracy and provide insight regarding the natural history or severity risks for patients. However, studies have been limited, and inconsistencies exist. Although Ara h 1, 2, and 3 peanut components have been implicated as the predominant allergens related to peanut allergy in certain geographic regions, Ara h 9 has been implicated as the major allergen in other geographic regions (ie, the Mediterranean area).[244] In a pediatric investigation CRD did not improve diagnostic accuracy in predicting egg or milk OFC outcome,[245] and a number of studies have suggested that CRD testing is inconsistent across geographic regions for other foods.[246,247] Additional studies are needed to define the clinical utility of CRD testing.

Summary Statement 25: The clinician should consider OFCs to aid in the diagnosis of IgE-mediated food allergy. [Strength of recommendation: Strong; A Evidence]

There are various types of OFCs, and the type of challenge chosen for assessment of clinical reactivity depends on the potential for bias in interpretation of results. The types of food challenges include open (unmasked), single-blind with or without placebo, and double-blind, placebo-controlled challenges.[228] The DBPCFC is the gold standard and the most rigorous type of challenge.[248] Although DBPCFCs reliably predict clinical reactivity, they are labor- and time-intensive procedures. Single-blind and open OFCs are frequently used for clinical use. For diagnosis of IgE-mediated food allergy, graded dosing during OFCs is recommended, regardless of the type of challenge conducted.[228] Graded dosing minimizes the risks of a severe allergic reaction and identifies the lowest provoking dose (dose threshold). Additional practical details regarding selection of OFC formats, food preparation, dosing, and interpretation of results are beyond the scope of this practice parameter but are reviewed in detail in a workgroup report and PRACTALL consensus report.[228,248]

Interpretation of OFC outcome can be affected by patient bias, observer bias, or both. Blinding or masking the challenge food

can be used to reduce or eliminate bias. The challenge food can be blinded by mixing with another food vehicle or placing the food in a capsule, although the latter approach might affect outcomes by eliminating oral symptoms. In the single-blind OFC the observer knows when the challenge food is being tested, but the patient does not. In the double-blind challenge the challenge food is prepared by a third party, and neither the observer nor patient is aware of when the challenge food is given. Placebo-controlled OFCs can be conducted in a single-blind or double-blind fashion. If a placebo is used, the challenge food should be administered in a form that makes it indistinguishable from the placebo.[249,250]

In a single-blind OFC the patient is told that foods will be ingested over 1 or more sessions, but the patient is not told when the challenge food will be given. Consecutive sessions can be conducted on the same day (separated by 2 hours) or on different days. Because the observer is aware of when the challenge food is administered, it is important for the observer to remain consistent throughout all sessions to avoid disclosing when the challenge food is being served to the patient. This challenge format can be used in cases that are considered at risk for patient-related bias, such as anxiety or fear of the challenge food.

In double-blind OFCs a third party prepares and codes 2 foods for testing. The 2 prepared foods consist of 1 challenge food and 1 placebo food that should be indistinguishable from each other (eg, pudding vehicle with and without egg protein powder). The coded foods are served to the patient in consecutive sessions separated by at least 2 hours, and the code is not broken until both foods have been ingested. If the patient experiences allergic symptoms requiring definitive treatment, such as antihistamines or epinephrine during ingestion of the first challenge food, testing to the second food should be deferred until a later date. A DBPCFC can be considered for research purposes or for clinical purposes when an open or single-blind challenge result was ambiguous, when past symptoms were primarily subjective, or if patient anxiety is suspected to influence the challenge.

An open OFC is an unmasked unblinded feeding of the food in its natural form. Open OFCs are the most cost- and time-efficient type of OFC, but they have the highest risk for bias. Although a negative open OFC result can definitively determine oral tolerance to the challenge food, a positive open OFC resulting in subjective symptoms only (eg, pruritus or throat tightness without rash or abdominal pain) might need to be verified with a blinded challenge because of potential patient bias.

Summary Statement 26: If clinical history is not consistent with anaphylaxis, perform a graded OFC to rule out food allergy. Open food challenge is both cost- and time-efficient. [Strength of recommendation: Moderate; C Evidence]

Summary Statement 27: If the diagnosis is still unclear after open food challenge, then recommend a blind food challenge. [Strength of recommendation: Moderate; B Evidence]

In deciding on undertaking an OFC for diagnostic purposes, the clinician should consider the probability of tolerating the food (based on history and testing), dosing regimen, form of food, masking/use of placebos, location of challenge, risk of severe reactions, nutritional status, and other patient-related characteristics.

At the time of initial diagnostic evaluation, the decision to conduct an OFC should be determined by both the patient's history of clinical reactivity and sIgE testing.[228,248,251] In many cases OFC is not prudent or necessary to make the diagnosis of IgE- mediated food allergy if the patient has an unequivocal and convincing history of clinical reactivity to a known food allergen and positive sIgE test results (SPT or sIgE measurement). Furthermore, the patient's history can take priority over laboratory findings because results of sIgE testing should not be interpreted as absolute indications or contraindications for conducting an OFC when making the diagnosis of food allergy. OFCs can be used to determine clinical reactivity when the history is uncertain and results of sIgE testing (SPT or sIgE measurement) are negative or when sIgE test results are positive but less than established positive predictive cutoffs for the suspected food (Table E3). OFCs can also be effective in determining the development of oral tolerance during the follow-up of patients with established food allergy (see "Section VII: Management of food allergy and food-dependent, exercise-induced anaphylaxis").

Patients undergoing OFCs should be counseled on the risks/benefits of the food challenge, and informed consent should be obtained before conducting OFCs.[228] The benefits of conducting OFCs include the possibility of expanding the patient's diet if the OFC result is negative. A negative OFC result also has potential benefits of decreasing anxiety related to fear of allergic reaction and improving the patient's quality of life. These important factors should be considered when determining whether an OFC is warranted.

The clinician should consider the benefits of adding foods that are high in nutritional value or ubiquitous in the patient's dietary culture when deciding on the timing of OFCs. Foods with little nutritional value or foods that are not of interest to the patient can be given lower priority when planning to conduct multiple OFCs. For example, the clinician should consider conducting an OFC to milk before shellfish in a young child who is considered a candidate for OFCs to both milk and shellfish because of increased nutritional benefits of adding dairy products in the diet of a young child.

In addition to potential benefits, the patient should be made aware of the risk of anaphylaxis during OFC if oral tolerance has not been achieved. Because of the risk of life-threatening symptoms or anaphylaxis, OFCs should always be conducted under the supervision of trained medical staff in a health care facility equipped to treat anaphylaxis.[2,228,248,249] The decision to conduct OFCs in the clinical versus hospital setting should be determined based on the severity of the patient's prior reaction to the food, epidemiologic risks associated with the food being challenged,[117,210,211] availability of necessary tools in the event of a severe reaction, and expertise of the supervising clinician.[228]

The clinician should be aware of certain patient characteristics that increase the risks associated with OFCs, including having a history of a previous severe reaction or history of reaction after ingestion of trace amounts of the causal food. Concomitant medical conditions, such as asthma or respiratory tract infection, should be considered before performing OFCs. OFCs should be delayed or deferred in patients with conditions that might obscure interpretation of OFC outcomes, such as uncontrolled urticaria or atopic dermatitis, or factors that might increase risk in the event of a failed challenge, such as underlying cardiovascular disease, difficult vascular access, or concomitant treatment with β-blockers or angiotensin-converting enzyme inhibitors.[2,228,251] Patients with food allergy might be at increased risk for a severe reaction during OFCs if they have asthma (regardless of severity) or if they are being challenged with a food that is frequently associated with fatal/near-fatal reactions. All food allergens have the

potential for resulting in anaphylaxis; however, the foods most often implicated in fatal or near-fatal reactions are peanuts, tree nuts, milk, fish, and shellfish.[117,210,211]

When deciding on the type of challenge, patient characteristics and potential for bias should be considered.[228] If the patient is highly anxious about ingestion of the challenge food or there is a history of subjective or difficult to interpret symptoms, a blinded challenge is warranted in an effort to reduce bias. If the patient is a young child, blinding might be necessary because of refusal to eat the food in its natural form. Ideally, blinded OFCs should be followed by an age-appropriate full serving (open feeding) of the challenge food in its natural form to ensure that the food will be tolerated. The ability to conduct an open feeding immediately after an OFC might be limited in young children because of volume or refusal to eat the food in its natural form.

Summary Statement 28: Elimination diets and diet diaries can be used as an adjunctive means to diagnose food allergies but are not to be depended on solely for confirming a diagnosis. [Strength of recommendation: Weak; D Evidence]

Dietary elimination and diet diaries can be used when the patient has an uncertain or unclear history of clinical reactivity to food or when symptoms are suspected to be due to non–IgE- or mixed IgE/non–IgE-mediated food allergy (see Summary Statement 42). In these clinical entities onset of symptoms often lack temporal correlation with food ingestion, making the accurate identification of causal foods more difficult. Dietary elimination and reintroduction of the suspected food or foods should be used to determine whether symptoms are responsive to dietary elimination of specific food allergens and thus will assist the clinician in identifying the causal food or foods.[2,31] Dietary eliminations should be limited to 1 or a few foods during the initial diagnostic evaluation, and noncausal foods should be promptly reintroduced in an effort to avoid nutritional risks associated with prolonged and multiple dietary eliminations.[252,253]

The clinician should consider the effect and address the relationship of comorbid atopic diseases, such as atopic dermatitis and asthma, in patients with food allergies. These comorbid diseases might be risk factors for severe reactions (asthma) or exacerbated by food-induced allergic reactions (atopic dermatitis).

Food allergy often coexists in patients with other atopic disorders, including asthma and atopic dermatitis, and the clinician should be aware of the risks associated with these comorbid conditions in the patient with food allergy. Atopic dermatitis is a common skin disorder, and concomitant food allergy is present in approximately one third of children with moderate-to-severe atopic dermatitis.[13] In patients with food allergy, atopic dermatitis can be exacerbated by and responsive to dietary elimination of culprit foods.[13,203,254,255] To accurately diagnose causal foods, the evaluation of patients with atopic dermatitis might require a combination of diagnostic tests, including sIgE testing, elimination diets, and OFCs, because symptoms are caused by mixed IgE/non–IgE-mediated mechanisms, and food allergen ingestion might be related to both immediate and chronic symptoms.

SPTs cannot be performed in patients with uncontrolled atopic dermatitis or patients who cannot discontinue antihistamine therapy because of underlying allergic conditions.[228] OFCs should not be conducted if symptoms of uncontrolled atopic dermatitis, asthma, or allergic rhinitis are present because these uncontrolled conditions will obscure interpretation of OFC outcomes. Food allergy is uncommonly implicated as the cause of uncontrolled asthma; however, underlying asthma, regardless of severity, has been associated with increased risk of severe allergic reactions and death caused by food-induced allergic reactions.[117,210,211] Patients with concomitant asthma and food allergy should be advised regarding these risks, and the clinician should consider uncontrolled asthma as an absolute contraindication for conducting OFCs.[228] When conducting OFCs for diagnostic purposes, it is imperative to have readily available rescue asthma medications (short-acting β-agonist) in the event of an allergic reaction involving the lower respiratory tract in addition to epinephrine.

Summary Statement 29: A diagnosis of food-dependent, exercise-induced anaphylaxis should be considered when ingestion of causal food or foods and temporally related exercise result in symptoms of anaphylaxis. The clinician should recognize that symptoms only occur with ingestion of the causal food or foods proximate to exercise and that ingestion of the food in the absence of exercise will not result in anaphylaxis. [Strength of recommendation: Strong; B Evidence]

Food-dependent, exercise-induced anaphylaxis occurs when a specific food allergen triggers anaphylaxis after or during temporally related exercise. Accurate diagnosis might be obscured based on the fact that ingestion of the culprit food does not result in symptoms unless the patient engages in temporally related exercise. Consequently, the clinician should be aware of this relationship and ascertain a detailed dietary history in patients presenting with exercise-associated anaphylaxis. Symptoms are IgE mediated, and specific allergen testing (SPT or sIgE measurement) should be used to aid in accurate diagnosis.[256,257] Diagnostic OFCs can be carried out to further elucidate the culprit food or foods, and these challenges should be conducted in a facility that has appropriate equipment and allows for exercise after ingestion of the suspected food.[228,248]

Summary Statement 30: The clinician should consider the diagnosis of oral allergy syndrome (pollen-food allergy) and obtain specific IgE testing to pollens in patients who experience limited oropharyngeal symptoms after ingestion of food antigens that cross-react with pollen antigens. [Strength of recommendation: Strong; B Evidence]

Pollen-food allergy syndrome refers to a form of localized IgE-mediated allergy resulting from oral contact or ingestion of foods that cross-react with homologous pollen antigens (see the "Cross-reactivity" subsection).[258,259] It is estimated that up to 76% of persons with pollen allergy also have pollen-associated food allergy syndrome to at least 1 food.[88,258] The food allergens involved are typically raw fruits and vegetables (Table E4), and symptoms are generally confined to the oropharynx, resulting in pruritus and angioedema of the lips, soft palate, and oral mucosa.

Diagnosis of pollen-associated food allergy can be aided by confirming a history of pollen allergy with sIgE testing and concomitant history of having localized symptoms after ingestion of cross-reactive raw foods (fruits and vegetables). Because the cross-reactive proteins are heat labile, patients might provide a history of being able to tolerate the food without symptoms in its cooked form (eg, canned peaches).[88] Additionally, patients might report experiencing more prominent symptoms after the associated pollen season (priming).[1] Diagnostic SPTs with the suspected fresh fruit (prick-prick method) can be used to further aid in diagnosis. SPTs with commercially available fruit and vegetable extracts are generally less useful because the allergens

are heat labile and often lose potency, thus leading to false-negative results. OFCs can be considered if the diagnosis is uncertain; however, results can be affected by growth conditions and ripening of the fruit or processing that might decrease or destroy the allergenicity of the fruit or vegetable. Investigations of the predictive value of sIgE to the cross-reactive food allergens have revealed variable results and are generally poor predictors of clinical reactivity.[258]

Summary Statement 31: A diagnosis of IgE-mediated contact urticaria should be considered in patients with a history of immediate urticarial rash at the site of contact with a food allergen. [Strength of recommendation: Weak; D Evidence]

IgE-mediated contact urticaria results from contact with substances in foods that interact with sIgE bound to cutaneous mast cells. Contact with the food substance leads to release of histamine and other inflammatory mediators, and urticarial lesions develop only on the area of skin that is in direct contact with the food.[2,260] Occupational exposure to raw meats, seafood, raw vegetables, and fruits are among the most common foods implicated in contact urticaria. A detailed medical history confirming the absence of symptoms when the suspected food is avoided, and positive specific (serum or skin) IgE test results to the food should aid in the diagnosis.

Summary Statement 32: Do not routinely obtain total serum IgE levels for the diagnosis of food allergy. [Strength of recommendation: Strong; C Evidence]

Although increased in many patients with food allergy or other atopic conditions, total serum IgE lacks both sensitivity and specificity regarding specific food allergy diagnosis.[2,261] There is insufficient evidence to support the use of total serum IgE in the diagnosis of food allergy, and an investigation of the predictive value of sIgE to total IgE ratio found no correlation between the ratio and OFC outcome.[261]

Summary Statement 33: Do not perform intracutaneous testing for the diagnosis of food allergy (see discussion). [Strength of recommendation: Strong; B Evidence]

Intradermal skin testing for food allergy is not recommended to aid in the diagnosis of acute IgE-mediated food allergy caused by increased risk of systemic reactions.[1,2,216] Intradermal skin testing with food extracts has also been shown to have significantly higher false-positive rates compared with SPTs.[262] Therefore if relied on, intradermal testing would not only increase systemic reaction risks but also increase risks associated with inappropriate diagnosis and unnecessary dietary elimination of foods. One possible exception to the use of intradermal testing in IgE-mediated food allergy includes the use of intradermal testing in delayed anaphylaxis associated with hypersensitivity to the carbohydrate moiety alpha-gal found in mammalian red meats. This syndrome is characterized by delayed onset of anaphylactic symptoms, and SPTs do not reliably identify the culprit food or foods.[82]

Summary Statement 34: Unproved tests, including allergen-specific IgG measurement, cytotoxicity assays, applied kinesiology, provocation neutralization, and hair analysis, should not be used for the evaluation of food allergy. [Strength of recommendation: Strong; C Evidence]

Insufficient evidence exists to support the use of a number of unproved or nonstandardized procedures and tests. Examples of unproved methods include allergen-specific IgG measurement, cytotoxicity assays, applied kinesiology, provocation neutralization, hair analysis, lymphocyte stimulation, gastric juice analysis, measures of specific IgA levels, HLA screening, type III immune complex levels, and others. These tests should not be used because results can lead to misdiagnosis or missed diagnosis of IgE-mediated food allergy, thus leading to inappropriate or unnecessary dietary elimination of foods. Such testing can also result in delay of appropriate diagnostic evaluation and management of IgE-mediated food allergy.[1,31,263] Food patch testing can be valuable in assessing food triggers in pediatric patients with EoE.[264,265]

Summary Statement 35: Although routine use of atopy patch tests (APTs) for diagnosis of food allergy is not recommended, the use of food APTs in patients with pediatric EoE have been demonstrated to be valuable in assessing potential food triggers. [Strength of recommendation: Moderate; C Evidence]

There is insufficient evidence to support the routine use of APTs in the diagnosis of food allergy. APTs for food allergy lack standardization, and results of previous studies show wide variability in the sensitivity and specificity of results. There is no consensus among experts regarding the appropriate reagents, methodology, or interpretation of results of APTs in the diagnosis of IgE-mediated food allergy.[1,31] Food patch testing can be valuable in assessing food triggers in patients with pediatric EoE.[264]

Non–IgE mediated: FPIES, allergic proctocolitis, and enteropathy

The physician should use a careful and detailed history (including diet records), physical examination, response to the trial elimination diets, and OFCs to diagnose non–IgE-mediated adverse reactions to foods. FPIES, allergic proctocolitis, and enteropathy usually affect young infants and manifest with delayed symptoms, starting within hours (FPIES) to days and weeks (proctocolitis and enteropathy) after ingestion of the offending food.[2] When the food is ingested on a regular basis, chronic symptoms develop. In patients with acute FPIES, when food is ingested intermittently, symptoms start with repetitive projectile emesis in 1 to 3 hours of food ingestion, followed by lethargy, ashen appearance, and hypothermia in more protracted cases, with increased white blood cell and platelet counts and methemoglobinemia in severe cases. In patients with chronic FPIES, which is uncommon, recurrent severe emesis, bloody diarrhea, anemia hypoproteinemia, increased white blood cell counts with eosinophilia, and failure to thrive can be seen. Allergic proctocolitis usually manifests with blood and mucus in the stool in an otherwise healthy thriving infant; 60% of these patients have proctocolitis while being exclusively breast-fed. Laboratory findings can include anemia, mild hypoalbuminemia, and hypoproteinemia.

Food protein–induced enteropathy is an uncommon syndrome of small-bowel injury with resulting malabsorption similar to that seen in celiac disease, although less severe. Food protein–induced enteropathy presents with protracted diarrhea in the first 9 months of life, typically the first 1 to 2 months, and typically within weeks after introduction of cow's milk formula. Food proteins, such as soybean, wheat, and egg, can also cause enteropathy. More than 50% of the affected infants have vomiting and failure to thrive, and some present with abdominal distension, early satiety, and malabsorption. Moderate anemia (typically caused by iron deficiency) is present in 20% to 69% of infants with cow's milk protein–induced enteropathy. Bloody stools are usually absent, but occult blood can be found in 5% of patients. Malabsorption is

common; hypoproteinemia, steatorrhea, sugar malabsorption, and deficiency of vitamin K–dependent factors can be seen.

The laboratory abnormalities reported in patients with FPIES, allergic proctocolitis, and enteropathy are nondiagnostic but provide supportive evidence for the clinical manifestations.

A trial elimination diet is suggested to determine whether chronic gastrointestinal symptoms are responsive to dietary manipulation. Dietary elimination of the offending food results in significant improvement in emesis and diarrhea within a few days in patients with FPIES and resolution of visible blood in the stool within a few days in patients with allergic proctocolitis. In patients with enteropathy, resolution of symptoms occurs usually within 1 to 4 weeks, although villous atrophy on biopsy might persist for several months, up to 1.5 years after symptom resolution.[266-270]

Summary Statement 36: The physician should use the patient's medical history, response to a trial of elimination of the suspected food, and OFC to establish a diagnosis of FPIES. However, when the history indicates that infants or children have experienced hypotensive episodes or multiple reactions to the same food, a diagnosis can be based on a convincing history and absence of symptoms when the causative food is eliminated from the diet. [Strength of recommendation: Strong; B Evidence]

In the absence of noninvasive laboratory biomarkers, it is recommended that a physician-supervised OFC be performed for a conclusive initial diagnosis of FPIES and for follow-up evaluations to determine whether FPIES resolved.[2]

A physician-supervised OFC in patients with FPIES is considered a high-risk procedure, with up to 50% of reactions requiring treatment with intravenous fluids.[271] Foods suspected of provoking FPIES should not be challenged at home because of risks of severe adverse reactions and should be challenged in a medical facility.[2,228] Although the recent population-based study reported successful management of reactions during OFCs with oral rehydration, it is advisable to have intravenous hydration readily available in case of severe reactions.[272]

Challenge results are considered positive if typical symptoms and laboratory findings are present. Symptoms include emesis (onset of 1-3 hours), lethargy (onset of 1-3 hours), and, less often, diarrhea (onset of 2-10 hours; mean, 5 hours). Laboratory values include increased neutrophil (>3500 cells/mL) and fecal leukocyte counts, frank or occult blood, and/or eosinophil counts. A CBC with differential should be sent before and about 6 hours after challenge if there are symptoms. If diarrhea is present, stool guaiac tests can be performed, and stool samples can be sent for fecal leukocyte, red blood cell, and eosinophil evaluation.[267,273-275]

OFCs might not be necessary for the initial diagnosis if the child presents with recurrent symptoms of typical FPIES (≥2 reactions with classic symptoms in a 6-month period) and is well when the offending food is eliminated from the diet. However, subsequent OFCs are warranted to determine whether FPIES has resolved and the food elimination diet can be stopped.

The physician should be aware that supervised OFCs are not usually necessary for the diagnosis of allergic proctocolitis and enteropathy. Considering the delayed onset and chronic nature of symptoms, the reintroduction of the suspected food after an elimination diet trial can be usually performed at home and documented with a symptom diary and stool tests for occult blood or reducing substances. However, if food sIgE is detected by using SPTs or serum tests, indicating the potential for an immediate allergic reaction, or the history suggests associated vomiting, physician-supervised OFCs might be necessary to safely reintroduce the suspected food.

Infants and children with non–IgE-mediated gastrointestinal food allergy can have food-sIgE antibodies to the food that historically induced only gastrointestinal reactions and transition to an immediate-type food allergy.

Summary Statement 37: The clinician should be aware that a gastrointestinal evaluation with endoscopy and biopsy is usually not required for the diagnosis of FPIES and allergic proctocolitis with symptoms that respond to elimination of the offending food and recur when the food is reintroduced into the diet. [Strength of recommendation: Weak; C Evidence]

Given the description of the typical constellation of clinical symptoms and strict criteria for a positive OFC result, endoscopic examination is not generally performed in patients with suspected FPIES.[276] However, before establishment of diagnostic criteria, endoscopic evaluations were done in severely ill infants with cow's milk and/or soy FPIES and rectal bleeding. They reported rectal ulceration and bleeding with friability of the mucosa in most patients. Diffuse colitis with a variable degree of ileal involvement was reported; in the most severe cases prominent eosinophilia, lymphocytic infiltration, and villous atrophy was seen. Colon mucosa can be mildly friable to severe spontaneous hemorrhage, and minute ulcers similar to those seen in patients with ulcerative colitis can be found. Crypt abscesses have been identified in some patients.

In patients with allergic proctocolitis, there are no standard accepted criteria for diagnosis.[277] Eosinophilic infiltration throughout the mucosal layers, particularly in the lamina propria, is characteristic. The presence of greater than 60 eosinophils per 10 high-power fields in the lamina propria is strongly suggestive of allergic proctocolitis.[278] Eosinophils in crypts or interspersed in the muscularis mucosae are also highly associated with allergic proctocolitis. The mucosal architecture is usually intact.

Food protein–induced enteropathy is diagnosed by the confirmation of villous injury, crypt hyperplasia, and inflammation on small-bowel biopsy specimens obtained from a symptomatic patient who is being fed a diet containing the offending food allergen.[279-281]

Gastrointestinal evaluation with endoscopy and biopsy is necessary for the conclusive diagnosis of enteropathy and might be required for persistent severe chronic FPIES and allergic proctocolitis unresponsive to dietary manipulation.

Summary Statement 38: Measurement of food-specific IgG and IgG_4 antibodies in serum are not recommended for the diagnosis of non–IgE-mediated food-related allergic disorders. [Strength of recommendation: Strong; B Evidence]

Measurement of food-specific IgG and IgG_4 antibodies for the diagnosis of gastrointestinal food allergy disorders is not recommended.

Eosinophilic esophagitis

Summary Statement 39: A trial of twice daily protein pump inhibitor (PPI) therapy for 8 weeks before diagnostic testing for EoE is recommended to exclude gastroesophageal reflux disease (GERD) and PPI-responsive esophageal infiltration of eosinophils. [Strength of recommendation: Strong; C Evidence]

Summary Statement 40: The diagnosis of EoE should be based on the presence of characteristic symptoms and endoscopic

features and the presence of 15 or more eosinophils per high-power field quantified by a pathologist using hematoxylin and eosin staining of esophageal biopsy specimens at ×400 light microscopy. [Strength of recommendation: Strong; B Evidence]

EoE is a chronic, antigen-driven, predominantly eosinophilic inflammation that is isolated to the esophagus. The diagnosis and management of EoE requires esophageal endoscopy with biopsy to evaluate the numbers of eosinophils, as well as other characteristic histologic features, including basal zone hyperplasia, eosinophil degranulation, and dilated intercellular spaces.[100] Multiple esophageal biopsy specimens from at least 2 levels of the esophagus (proximal, middle, and distal) should be evaluated when diagnosing EoE.[100,282] Other causes of esophageal infiltration of eosinophils, including gastroesophageal reflux disease, PPI-responsive esophageal infiltration of eosinophils, eosinophilic gastroenteritis with esophageal involvement, inflammatory bowel disease, esophageal infiltration of eosinophils associated with celiac disease, post-Barrett ablation, and tracheoesophageal fistula repair, should be excluded before diagnosing primary isolated EoE.[100,283-285] Typical EoE symptoms include dysphagia, abdominal and/or chest pain, poor appetite, and regurgitation. No symptom is pathognomonic for EoE, and symptoms cannot be used in isolation to diagnose EoE because validated symptom metrics are still under development.[100,286-289] Typical endoscopic features include pallor, furrows, rings, exudates, narrowing, and strictures, but endoscopic features in the absence of biopsy should not be used to diagnose EoE.[100,290]

Subjects with suspected EoE should be treated with high-dose PPIs to rule out acid-induced esophageal infiltration of eosinophils. Symptomatic and histologic response suggests GERD or PPI-responsive esophageal infiltration of eosinophils.[100] The clinician should follow subjects with PPI-responsive esophageal infiltration of eosinophils clinically because repeat esophagogastroduodenoscopy with biopsy might be warranted to ensure that the PPI response is not a transient phenomenon.[291] The clinician should remember that PPIs can have anti-inflammatory effects in addition to acid-blocking effects.[292]

Eosinophilic gastroenteritis

Summary Statement 41: Eosinophilic gastroenteritis (EGE) should be considered a constellation of clinical symptoms in combination with gastric, small intestine, and/or large intestine infiltration of eosinophils at greater than the reported normal numbers of gastric and intestinal eosinophils. [Strength of recommendation: Weak; D Evidence]

There are no agreed upon histologic or diagnostic criteria for eosinophilic gastritis, enteritis, or eosinophilic colitis, but clinicians should consider using the Klein classification of mucosal, serosal, or muscularis to describe the location of the eosinophilic infiltrate in patients with EGE.[293] It is recommended that the clinician follow patients with EGE because it can be transient, persistent, or chronic intermittent. EGE symptoms can include abdominal pain, diarrhea, eosinophilic ascites, and/or nausea/vomiting.

The clinician should recognize that EoE and EGE are 2 distinct clinical diseases that likely have different causes and are managed differently. There is no evidence that isolated EoE progresses to EGE, but EGE can have esophageal involvement.[294,295]

SECTION VII: MANAGEMENT OF FOOD ALLERGY AND FOOD-DEPENDENT, EXERCISE-INDUCED ANAPHYLAXIS

The primary therapy for food allergy is strict avoidance of the causal food or foods.[2] This is true for all types of food allergy, including IgE-mediated and non–IgE-mediated food allergy. This section will address specific management issues related to each category of food allergy.

IgE-mediated food allergy is common and often associated with life-threatening reactions. Current treatment approaches focus on education about dietary avoidance of culprit allergens and prompt treatment of allergic reactions. New treatment strategies are under investigation, including allergen-specific and nonspecific therapies that might change the approach to treating food allergies in the future.

Summary Statement 42: Prescribe a targeted allergen elimination diet as the treatment for known or strongly suspected food allergy. Education about proper food preparation and the risks of occult exposure is essential. [Strength of recommendation: Strong; C Evidence]

Allergen avoidance diets should be specific and limited to the relevant foods based on a confirmed diagnosis to minimize the risk of an allergic reaction.[2,31] The primary exposure to a food allergen for most patients is through ingestion, although some patients can exhibit symptoms after skin contact or inhalation of aerosolized protein. Patients, care providers, and all persons responsible for preparing or obtaining foods should be educated on how to read ingredient labels to avoid specific food allergens. Educational materials related to the 8 most common food allergens and general approaches to avoidance in different settings are available through resources, such as the Food Allergy & Research and Education Network (www.foodallergy.org) and the Consortium of Food Allergy Research (www.cofargroup.org).[296]

In the United States, Canada, Europe, and Australia food labeling laws exist to improve safety for consumers[297] and require food manufacturers to declare in plain language the presence of common allergens (including egg, milk, wheat, soy, fish, crustacean, peanut, and tree nuts) or a product derived from that allergen when used as an ingredient.[297,298] In the United States the Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004 (http://www.fda.gov/Food/FoodSafety/FoodAllergens) requires labeling of foods related to the "major allergens," with the common names listed within the ingredient list or in a separate "contains" label. FALCPA applies to foods manufactured in or imported into the United States but not to agricultural products or alcoholic beverages. FALCPA does not regulate the use of advisory labeling, such as "may contain" or "manufactured on equipment with" that are often used to describe possible cross-contamination.[299,300] Avoidance of products with the advisory labels is most prudent for patients with food allergy.

Cross-contact or cross-contamination of an allergen in a food product is a concern for food preparation at home, school, or restaurants and in other settings.[2] Examples of cross-contact include poor hand washing, shared grills or pans, utensils or equipment that are poorly washed between uses, use of a fryer for multiple foods, and contaminated or poorly cleaned work spaces. These examples result in contamination of a safe food by a food allergen that can be avoided. Additionally, hidden food ingredients, such as peanut butter used as a flavor enhancer

in chili or nuts in Asian food, are examples that can also place a patient with food allergy at risk. Lastly, patients with known inhalational exposure and those with occupational allergy caused by foods might need to further avoid aerosolized food exposure or wear gloves and masks if alternate employment is not possible. Young children might need to be supervised around food allergens to avoid hand to mouth or eye contact. Standard cleaning procedures (wiping or washing with soapy water) suffice to remove allergens from surfaces and hands. Patients and caregivers must be educated about appropriate label reading, cross-contact, hidden foods, and environmental exposures when obtaining or preparing meals.[2]

When prescribing an elimination diet, the clinician must understand the differences in potential risk among cross-reactive foods and make appropriate recommendations.

Dietary avoidance of foods that are related and have potentially cross-reactive proteins should be individualized according to the risk of clinical cross-reactivity (see "Section I: Classification of major food allergens, cross-reactivities, genetically modified foods, and clinical implication").[2] Particular foods, such as milk protein sources (eg, cow and goat), tree nuts (eg, cashew and pistachio/walnut and pecan), fish species, and shellfish species, often have shared protein cross-reactivity, and patients with food allergy should avoid the food class. In contrast, the majority of patients with peanut allergy can safely consume other legumes (eg, soy and beans), despite being in the same food family. Similarly, patients with wheat or other grain allergy can often consume other grains without adverse symptoms. As noted below, some patients with pollen allergy are not able to consume raw fruits or vegetables, but once cooked, these foods can usually be safely consumed without causing symptoms. Patients with latex allergy often have to avoid foods, such as bananas, avocados, or chestnuts, because of cross-reactive proteins. Lastly, mammalian red meats (eg, beef, pork, lamb, and venison) have a cross-reactive carbohydrate determinant, alpha-gal, in common with alpha-gal found in tick saliva.[301,302] Patients with prior tick exposure can produce IgE to alpha-gal that results in delayed anaphylaxis after consumption of red meat. Even though shared clinical allergy across meats is generally uncommon, when alpha-gal hypersensitivity is present, all mammalian red meat should be avoided.

The appropriate elimination diet must be tailored to each patient. The clinician should recognize that a proper diet can vary from regular exposure to some modified proteins (eg, a baked egg– or baked milk–tolerant patient) to strict avoidance of allergen.

Although a strict avoidance diet of all allergic foods is typically recommended,[2,31] recent studies indicate that regular exposure of heat-modified egg and milk protein in allergic patients is not only well tolerated in up to 70% of allergic patients but might be clinically beneficial.[198,303-305] Extensive heating (baking) of egg and milk proteins results in conformational modification and reduced allergenicity. Recent data suggest that introduction of these foods also accelerates development of tolerance. Patients who can safely consume baked egg and milk should continue regular ingestion of these foods. For known allergic patients who are not consuming baked egg or milk proteins, an observed food challenge with a serving portion of a muffin or other appropriate food is warranted to ensure safe consumption.[198,303-305]

Several recent studies have demonstrated that trace egg exposures in most injectable influenza vaccines are generally well tolerated by patients with egg allergy. On the basis of these results, current guidelines, including a focused practice parameter, have been recently updated to encourage routine immunization of such patients without testing or special accommodation (ie, split dosing or desensitization).

Summary Statement 43: Recommend consultation with a nutritionist for growing children in whom elimination diets might affect growth, as well as those patients with multiple food allergies, poor growth parameters, or both. Clinicians must be aware of the nutritional consequences of elimination diets and certain medications, such as esomeprazole, especially in growing children. Specifically, identifying alternative dietary sources of calcium and vitamin D is critical for patients with milk allergy. [Strength of recommendation: Strong; B Evidence]

When the history and/or test results do not clearly identify an IgE-mediated food allergy as the likely cause of the patient's symptoms, further workup to confirm the appropriate diagnosis is the most critical next step.[2,31] Elimination diets in such a scenario might be unnecessarily restrictive and nutritionally harmful and are not recommended. Allergen avoidance diets can result in failure to thrive and/or vitamin, mineral, or nutrient deficiencies when not carefully managed or when overly aggressive.[306,307] Addressing nutritional concerns, such as calcium and vitamin D intake for a patient with milk allergy or poor protein and fat consumption in a child with multiple food allergies, requires close attention to dietary intake with patients often benefitting from consultation with a registered dietitian. Nutritional counseling and regular growth monitoring is recommended for children with food allergies. The US Department of Agriculture regularly updates information regarding dietary recommendations through www.usda.gov or www.choosemyplate.gov.

Summary Statement 44: Review recognition and treatment of IgE-mediated food-related allergic reactions with each patient and caregivers, as appropriate. Emphasis should be placed on prompt awareness of anaphylaxis and swift intervention. [Strength of recommendation: Strong; C Evidence]

Food-induced anaphylaxis is a serious allergic reaction that is rapid in onset and can cause death. Prompt recognition of signs or symptoms of an allergic reaction is essential for appropriate management. Symptoms can be uniphasic, biphasic, or protracted and can involve all organ symptoms.[2,201,308] Delays in symptom recognition and appropriate treatment can result in poor outcomes after allergenic food ingestion.[309] Patients, parents, and all care providers should be educated about the signs and symptoms of anaphylaxis, the importance of early recognition and prompt treatment, and the steps of action to prevent and treat allergic reactions.[2]

Summary Statement 45: Discuss self-care management techniques, especially with high-risk patients, (eg, adolescents, young adults, and asthmatic patients), focusing on risk reduction and recognition and treatment of anaphylaxis. [Strength of recommendation: Strong; C Evidence]

IgE-mediated food allergy is associated with an increased risk of death after accidental ingestion.[30,210,211,310,311] Food-induced fatalities are most commonly reported from exposure to peanuts and tree nuts, but severe and fatal reactions can occur with any culprit food allergen. Fatalities are often associated with a lack of or delayed treatment with epinephrine. The risk factors associated with heightened mortality include teen and young adult age, pre-existing/poorly controlled asthma, and previously diagnosed food allergy. Other factors include an absence of skin symptoms,

patient denial of symptoms, concomitant alcohol consumption, or reliance on oral antihistamines to manage symptoms in place of epinephrine.[2,309]

Summary Statement 46: Use epinephrine as first-line management for the treatment of anaphylaxis. [Strength of recommendation: Strong; C Evidence]

Summary Statement 47: Ensure that self-injectable epinephrine is readily available to the patient and instruct the patient, caregiver, or both on the importance of its use and self-administration, as relevant. [Strength of recommendation: Strong; C Evidence]

Intramuscular epinephrine is the first-line treatment in all cases of anaphylaxis. All other drugs have a delayed onset of action. Repeat epinephrine dosing should be used when symptoms progress or response is suboptimal.[2,81,201,308]

Summary Statement 48: Evaluate children with food allergies at regular intervals (1-2 years), according to the patient's age and the food allergen, to determine whether he or she is still allergic. If food allergy is unlikely to change over time, as in adults, periodic re-evaluation (2-5 years) is recommended, depending on the food allergy. [Strength of recommendation: Strong; C Evidence]

The management of food allergy should include ongoing clinical assessment to re-evaluate the patient's allergic status; monitoring of dietary allergen avoidance, including label reading/cross-contact/special settings, nutritional status, accidental ingestions, and associated reactions; and overall consequences involving quality of life and effect on the patient and his or her family.[2,31] The clinician must also assess for comorbidities, such as asthma, atopic dermatitis, and allergic rhinitis. Yearly education is needed to reinforce the importance of early recognition and emergency treatment of acute allergic reactions, use of an updated emergency action plan, and repeat training with the epinephrine autoinjector, if applicable.

Because the natural history of food allergy varies with the allergen and the patient, long-term management should include monitoring for evidence of tolerance or for development of new food allergies. This includes obtaining interim clinical data regarding reactions to foods and, if indicated, performing SPTs or allergen sIgE tests. The optimal interval for follow-up testing is not known. Allergy to some foods, such as milk and egg,[118,121] can be outgrown relatively quickly, whereas allergy to other foods, such as peanut, tree nuts, fish, and shellfish, are typically lifelong.[4,119,312] Testing every 12 to 18 months is recommended in the first 5 years of life to assess for evidence of tolerance development. This testing interval can be extended to every 2 to 3 years thereafter if levels remain high. For allergies to tree nuts, fish, and crustacean shellfish, testing can be performed less frequently (every 2-4 years). This interval could be extended in adults with little change over time in sIgE levels.[4,119] If a patient has had a recent food-induced allergic reaction, then there is little reason to retest during the 1- to 2-year time interval after the reaction, depending on the allergen and the severity of the reaction. For example, an adolescent allergic to peanuts with an increased specific peanut level of 25 kU_A/L and a history of generalized hives and laryngeal edema with ingestion in the last year would not require testing for at least 2 to 3 years or longer because of the low possibility of becoming tolerant during that interval. However, for a younger child (eg, <5 years of age) with the same peanut sIgE level and clinical reaction, testing every 1 to 2 years for several years to determine the decrease in sIgE level can assist in assessing for natural tolerance development. If a patient has had a known food allergen ingestion without symptoms or has sufficiently reduced food sIgE test and/or SPT results, further assessment of tolerance with a medically supervised OFC might be warranted to ensure safe addition to the diet.[2,228]

Summary Statement 49: For patients with food-dependent, exercise-induced anaphylaxis, avoid food ingestion within 2 to 4 hours of exercise for prevention of symptoms, and provide prompt treatment with onset of symptoms. [Strength of recommendation: Strong; C Evidence]

Food-dependent, exercise-induced anaphylaxis can occur during or soon after exercise that is preceded by ingestion of a causal food allergen.[313] Whether a reaction occurs depends on the amount of time between food consumption and exercise, usually within 2 and 4 hours. Wheat and crustaceans are the most common food culprits, but other foods have been implicated.[314,315] Management involves separation of food ingestion and exercise, with avoidance of exercise for 2 to 4 hours after allergenic food ingestion, as well as prescription of epinephrine for treatment of acute symptoms.[2,313,314] When exercising, patients should be accompanied by a "buddy" who is aware of their condition, carries a cell phone, and is able to manage anaphylaxis, should it occur.

Summary Statement 50: Manage pollen-food allergy syndrome or oral allergy syndrome by dietary avoidance of raw fruits, vegetables, or both based on the patient's symptom profile severity. The extent of food avoidance depends on the severity of oropharyngeal symptoms. [Strength of recommendation: Strong; C Evidence]

Most patients with OAS benefit from cooking raw fruits and vegetables to denature proteins before ingestion. Patients with mild-to-moderate oral symptoms, such as lip/mouth tingling or swelling or throat pruritus, are advised to cook foods before ingestion[2,115,316] and to continue ingesting cooked or baked forms of plant foods, as tolerated. However, if symptoms are more severe, progress in severity, or are associated with systemic symptoms, full dietary restriction of the causal food or foods is warranted.[115] Patients with a history of laryngeal swelling or respiratory compromise should avoid raw foods strictly and be prescribed an epinephrine autoinjector. A subset of patients with pollen-food allergy syndrome treated with high-dose pollen subcutaneous immunotherapy might experience complete resolution or significant improvement in symptoms, but the utility of immunotherapy OAS is an area that merits further study.[115]

Summary Statement 51: The clinician should understand the various clinical presentations of these conditions (ie, FPIES/proctocolitis/enteropathy), educate patients and care providers about common food triggers, and recommend strict food avoidance of allergenic foods for symptom management. [Strength of recommendation: Strong; C Evidence]

The management of non–IgE-mediated food allergy relies on strict avoidance of dietary food protein and attention to adequate nutrition. Pharmacologic agents are not recommended for treatment of chronic symptoms. The most common food allergens in FPIES/proctocolitis/enteropathy are cow's milk and soy proteins.[2] The reactivity to both foods can coexist in up to 50% of affected subjects.[266,273,317] In patients with FPIES, solid foods, including cereal proteins, such as rice and oat, egg, fish, and poultry, have been reported in children, whereas shellfish and mollusks have been reported in adults.[318-320] Nutritional consultation might be necessary to establish principles of avoidance, as well as to ensure a nutritionally complete diet. Infants with

FPIES to multiple foods are at risk of feeding disorders, likely because of both traumatic experiences associated with acute reactions and reluctance of parents to introduce new foods, and might benefit from feeding therapy. Hypoallergenic casein-based formula is tolerated by the majority of patients; however, 10% to 15% might require an amino acid–based formula.[321,322] Children with milk/soy FPIES are usually asymptomatic while being breast-fed, although if symptoms are noted during breastfeeding, strict maternal dietary avoidance of the causal allergen should be implemented. In contrast, up to 60% of infants with allergic proctocolitis have symptoms while being breast-fed.[323] When appropriate food allergen is eliminated from the maternal diet, the resolution of fresh blood is observed within a few days and the disappearance of occult blood is observed usually within 5 to 7 days. It is unknown whether children with non–IgE-mediated food allergy tolerate extensively heated (baked) milk and egg.

Summary Statement 52: Use volume replacement therapy for the acute care management of patients with FPIES. [Strength of recommendation: Strong; B Evidence]

The physician should recognize that acute FPIES is a medical emergency with up to a 15% risk of hypovolemic shock.[266,317,324] The acute onset of severe repetitive emesis within 1 to 3 hours after food ingestion, lethargy, and dusky appearance, together with lack of cutaneous and respiratory symptoms, is consistent with FPIES. Diarrhea might follow within 4 to 6 hours.[325] The first line of treatment is vigorous intravenous hydration with rapid normal saline boluses. Epinephrine can be used in case of severe hypotension but is not helpful as a first-line treatment, unlike in anaphylaxis.[271] A single dose of 1 to 2 mg/kg intravenous methylprednisolone can be used in some patients with protracted symptoms, although efficacy has not been established. A recent small case series of children with FPIES successfully treated with ondansetron during a supervised OFC suggested that ondansetron might be useful for managing acute FPIES reactions.[326] In patients with milder reactions, oral rehydration might be possible.[272] Because FPIES is underrecognized by primary care and emergency department providers and is therefore frequently mismanaged, a letter describing manifestations of FPIES and management of acute reactions should be provided to patients. A template of such an FPIES emergency letter can be found in an article by Sicherer[271] and online (http://www.iaffpe.org/er_letter). In patients with proctocolitis and enteropathy, symptoms are usually chronic, and there is low risk for acute reactions. Management includes dietary avoidance of culprit foods.[323,327]

Summary Statement 53: See patients with FPIES and allergic gastrointestinal disorders at regular intervals and consider rechallenge in an appropriate medical facility based on the natural history of the specific disorder. [Strength of recommendation: Strong; C Evidence]

Foods inducing FPIES should not be challenged at home because of the risk of hypotension and should be challenged in a medical facility.[2,228] Although a recent population-based study reported successful management of reactions during OFCs with oral rehydration, it is advisable to have intravenous hydration readily available in case of severe reactions.[272] There are no biomarkers predictive of the natural history or the risks of life-threatening reactions in patients with FPIES. Timing of the follow-up challenges is based on the natural history, usually about 12 to 18 months after the most recent acute reaction. However, more frequent rechallenge attempts might be appropriate in young children with milk and soy allergy and no history of severe/life-threatening FPIES.[16,272,328] APTs are not helpful for timing food reintroduction attempts.[331] Introduction of foods avoided on a precautionary basis and without prior reactions can be attempted carefully at home. It is prudent to start from foods that belong to the same group as already tolerated foods, such as soy for legumes or rice for cereal grains.[271] If no food-sIgE is detected, reintroduction of the offending food in patients with proctocolitis and enteropathy is usually performed at home. If food sIgE is detected, physician-supervised challenge might be necessary because of the potential progression of the delayed gastrointestinal symptoms to immediate anaphylactic symptoms.[323]

Summary Statement 54: Consider serial tissue biopsies as part of disease management in patients with EoE. Symptoms alone or endoscopy without biopsy cannot be used as an accurate gauge of EoE disease activity. [Strength of recommendation: Strong; C Evidence]

Current prospective clinical EoE trials have used histology as one primary end point variable.[100] Studies show that symptoms, as currently evaluated, do not provide an adequate surrogate marker of esophageal disease activity and do not serve as an adequate sole determinant for clinical decisions.[286,287,330] Symptoms are an important component of EoE management, but there are no validated EoE symptom or activity indexes available.[286-288,331] There can be discordance between histology and symptoms in patients with EoE because of the intermittency of symptoms and behavioral changes that can compensate for symptoms of dysphagia.[333,334] Although a validated endoscopy tool has been developed with good interobserver agreement for endoscopic findings of furrows, edema, rings, and exudates,[334] endoscopy without biopsy does not provide an adequate disease activity marker.[290] There is controversy regarding the best treatment end point variable for EoE resolution, but histologic evaluation is recommended.[100]

Summary Statement 55: Consider assessment for aeroallergen sensitization because EoE can be triggered by aeroallergens in human subjects and animal models and there might be a seasonality to EoE diagnoses. [Strength of recommendation: Moderate; D Evidence]

Control of other concurrent allergic diatheses, including allergic rhinitis, asthma, eczema, and immediate hypersensitivity to foods, is recommended in patients with EoE.[100,335,336] Animal models clearly demonstrate that murine EoE can be triggered by *Aspergillus* species, house dust mite, and cockroach extracts.[335,336] Pollens can also drive human esophageal infiltration of eosinophils, EoE can remit and recur during the pollen season, and aeroallergen immunotherapy can induce EoE remission.[337-340] Although there can be seasonality to EoE diagnosis, more studies are required to provide direct evidence that patients with EoE given a diagnosis in a given season have a predicted aeroallergen sensitization pattern. Cross-reactivity to pollens might be important in EoE pathogenesis.[341] It is possible that in some patients there will be spontaneous EoE remission and recrudescence in and out of the pollen season. As such, aeroallergen avoidance measures should be recommended, and treating physicians might want to consider seasonality in the context of aeroallergen sensitization when assessing esophageal biopsy specimens.[100]

Summary Statement 56: Consider food allergy evaluation with both skin prick and patch testing for EoE to rule out possible food triggers. Remember that positive serum specific IgE levels, food

SPT responses, and food patch test results are not sufficient to diagnose food triggers for EoE. [Strength of recommendation: Moderate; C Evidence]

Although EoE clearly can be a food-triggered process in both human subjects and animal models,[342,343] current testing modalities are not sufficient to reliably predict EoE food triggers. High rates of positive IgE test results to foods occur in patients with EoE, but skin prick testing predicted 13% of causative foods in adults and children,[99] and combination prick and patch testing predicted 44% of causative foods in children.[264] Food patch testing has not been standardized or validated in patients with EoE. However, positive food patch test results occur in 30% to 95% of children and adults with EoE. In one study the NPVs of combined prick and patch testing vary by the food tested (42% for milk and up to 92% for other foods).[264] This has not been uniformly reproducible. As such, food testing might be useful during food reintroduction after eliminations in patients with EoE. In addition, IgE testing to foods should be used in patients with EoE to assess those patients who might require a medically supervised food challenge to exclude IgE-mediated clinical reactions on food reintroduction. The currently reported rates of food-induced anaphylaxis are higher in patients with EoE than in the general population.[100,264,265,344] Additional research is required to assess whether CRD or serum specific food IgE is valuable in guiding dietary elimination in patients with EoE.

Summary Statement 57: Consider the use of targeted or empiric food-elimination diets or amino acid–based diets for successful EoE therapy. [Strength of recommendation: Strong; B Evidence]

Although amino acid–based formulas have the highest success rates (often in the 90% range) and the largest effects on inflammatory control, elemental diets can be difficult to administer without nasogastric or gastrostomy tube placement.[100,264,265,345] Amino acid–based formulas are also effective in adults, but adherence is difficult.[346] Empiric elimination of common food antigens, specifically milk, wheat, egg, soy, peanuts, tree nuts, fish, and shellfish, is a recommended EoE therapy with reported histologic response rates of 53% to 82% in adults and children.[99,264,265,347]

The most common food allergens in adult and pediatric patients with EoE are milk, wheat, and egg,[99,348] and the addition of milk elimination in combination with a prick/patch-based elimination diet has been reported to have 77% histologic success.[264]

Summary Statement 58: Consider the use of swallowed topical esophageal corticosteroids for successful EoE therapy. [Strength of recommendation: Strong; A Evidence]

A number of prospective trials in adult and pediatric patients with EoE demonstrate histologic efficacy of topical esophageal corticosteroids at rates of 50% to greater than 80%.[100,332,348-352] Used therapies include puffed fluticasone or ciclesonide to the back of the throat followed by forceful swallow[353] through metered-dose inhalers. Swallowed viscous suspension of budesonide is also successful EoE therapy and might be more effective than nebulized/swallowed budesonide.[349,350] The optimal duration of therapy requires additional studies, but EoE is a chronic disease in most adults and children. When the topical corticosteroid dose is decreased in adults with EoE, inflammation and fibrosis return, although to a lesser extent than after placebo.[354] Oral and/or esophageal candidiasis is a potential side effect of topical corticosteroids and occurs in up to 15% of subjects. In addition, the long-term safety data on esophageal corticosteroids require clarification. *(The use of leukotriene antagonists and oral cromolyn [Gastrocrom] are not recommended.)*

Summary Statement 59: Referral to a gastroenterologist for esophageal dilation is recommended for high-grade stenosis but does not provide inflammatory control. [Strength of recommendation: Moderate; C Evidence]

Significant symptom control is achieved after dilation. Complications include chest pain (5%), perforation (0.8%), and bleeding requiring blood transfusion (reported in only 1 patient).[355,356]

Summary Statement 60: Administer oral corticosteroids for EGE as the preferred therapy. [Strength of recommendation: Weak; C Evidence]

The most successful documented treatment for EGE is oral corticosteroid therapy, and this is recommended, but use of corticosteroids should be judicious and as short term as possible. There are a number of case reports that document EGE clearance with milk elimination, and a limited trial of amino acid–based or elimination diets can be considered.[358,359] Results of immediate hypersensitivity skin testing are usually negative. There is no clear utility of montelukast in disease management. Current data show that EGE can have a single flare, recurring or continuous courses with the subserosal form having single and recurring flares, whereas mucosal and muscular variants can present with any of the 3 courses.

SECTION VIII: EMERGING THERAPIES FOR FOOD ALLERGY

Summary Statement 61: Although immunotherapeutic approaches, such as oral immunotherapy (OIT), in clinical trials show promise in treating food allergy, they are not ready for implementation in clinical practice at the present time because of inadequate evidence for therapeutic benefit over risks of therapy. [Strength of recommendation: Strong; A Evidence]

Several new therapeutic approaches are being tested in clinical trials, with the major focus on IgE-mediated food allergy.[360] None of these therapies are ready for clinical care because of the uncontrolled nature of most trials, small number of subjects studies, selection bias, and uncertain safety profiles.[361-363] OIT has been studied most extensively and shown to be effective for several food allergens (eg, milk, egg, and peanut) for providing protection against life-threatening reactions during therapy (desensitization) and for the potential of developing tolerance when therapy is discontinued.[364-374] Although promising, OIT is also associated with frequent adverse allergic reactions, and thus it is not ready for widespread clinical use. Diets containing extensively heated (baked) milk and egg might be an alternative approach to OIT in approximately 70% of affected patients if findings of efficacy are maintained with improved safety profiles.[198,302,303] Sublingual immunotherapy has shown early promising results to decrease sensitization with low side effect profiles during treatment for peanut allergy, but protective desensitization is significantly less than with OIT.[375,376] In limited studies therapies using modified antigens,[360] epicutaneously administered allergen immunotherapy,[377] or Chinese herbal therapy[340] could also represent safe and efficient alternatives or adjunctive therapies in the future. Additionally, treatment with anti-IgE mAbs used alone or in combination with other forms of immunotherapy might increase threshold doses needed to stimulate an allergic reaction and provide enhanced safety profiles for patients.[378-380] Biologic

therapies with anti–IL-5, anti-TNF, and anti-IgE have had varying success and are not recommended for routine use in patients with EoE.[100,345,381-386] Other therapies, such as azathioprine, methotrexate, oral cromolyn, leukotriene antagonists, and other nonspecific immunomodulators, have not demonstrated a beneficial effect on disease manifestations of EoE.[100]

SECTION IX: MANAGEMENT IN SPECIAL SETTINGS

To optimally manage patients with food allergy, the clinician and the rest of the health care team must be educators, discussing avoidance of the allergen and the effect of locations at which the allergic reaction might occur, such as schools, homes of friends or relatives, restaurants, and other public places with regard to implementation of the treatment plan. In some communities there are teams that include caregivers and health educators, as well as physicians and families.

Education is an ongoing process that requires review during each visit for both children and adults. As noted above, teams of educators might include nurses, disease-specific educators, and persons to help with feeding/nutrition issues. Specific recommendations depend on the physical and developmental age of the patient at the time of the initial diagnosis and changes over time. Young children must be supervised and taught to share toys but never food, whereas older children must learn to ask before they eat anything not supplied by parents or other regular caregivers (and sometimes supplied by family members including parents and grandparents). School-aged children should be taught to read labels themselves and ask about ingredients with parental help and supervision. During adolescence, the transition to self-care becomes crucial, so that teens can protect themselves when they leave home. This transition is critical because there might be trips in high school and certainly college when they are far from home. Even adult patients need ongoing reinforcement, so that they do not become careless regarding ingredients in foods eaten away from home and careless about carrying self-injectable epinephrine. This is particularly important for adult-onset food allergy to foods previously eaten, such as shrimp.

Most caregivers will recognize the importance of educating patients about avoidance issues in the home, at school, and in restaurants.[296,387-389] Schools and childcare centers should have policies and programs for facilitating avoidance of food allergens.[390-394] Staff education should include label reading and information about cross-contact/contamination during food preparation, proper cleaning of utensils, and potential allergens in class projects.[395-401]

Education of restaurant management and personnel is a significant problem and has begun to respond to concerns voiced by multiple medical and industry groups.[402-406]

In addition, there are a number of other sites that must be considered and discussed. These include (but are not limited to) religious school settings, sports practices, or afterschool clubs, where snacks are often made available without the ability to check the ingredients. Even hospitalized patients must make their food allergies known to their physicians and nurses and the dietary/kitchen staff. Hospital personnel should ask about food allergy, but patients must ensure their own safety by reporting these allergies and carefully inspecting their meals.[407] Camps might not have adequate systems for inquiring about food allergies (and they might not have adequate action plans, see below).[408] Transportation by various means also presents a risk of accidental exposure. Air travel has received the most attention, but long rail trips (especially in foreign countries) and cruise ships present their own set of risks that must be anticipated.[409,410]

In the last few years, there has been an increase in the number of organ transplant recipients who have had reactions to foods to which the donor was allergic. Because donors' nearest of kin are usually involved in permission to donate organs, queries about the donor's food allergies should be part of the information gathered. This information should be relayed to the recipient and the recipient's family so that proper precautions can be undertaken.[411-418]

Clinicians must educate their patients with food allergy about optimal treatment of accidental ingestions and reinforce the fact that only self-injectable epinephrine is life-saving for IgE-mediated disease.

There is only 1 life-saving treatment for allergic reaction to foods: injectable epinephrine.[210,211,308] In the vast majority of situations, this involves self-injectable epinephrine with an autoinjector. Although it is impossible to undertake a controlled trial of treatment choices for anaphylactic reactions, there is no evidence that antihistamines can be life-saving, and there are reports from clinical series of patients dying despite the administration of an antihistamine, thus reinforcing the sentinel place of self-injectable epinephrine. Clinicians should continue to educate parents or patients about the proper use of epinephrine autoinjectors when they come to the clinic for a visit to ensure their ability to use these devices correctly.

A major issue in the education of patients and families is recognition of an allergic reaction. As noted previously, there are a number of situations/circumstances in which accidental ingestions can occur. Recognition that a reaction is occurring requires vigilance and a willingness not to deny the symptoms that have begun or assume that the patient will be able to "tough it out." Patients should be taught that a severe reaction is a distinct possibility. In cases in which a previous life-threatening reaction has occurred, self-injectable epinephrine must be given promptly, and the patient should immediately seek emergency medical treatment.[419-428] Identification jewelry for patients who might have a food-induced reaction and might need injected epinephrine is recommended because this reminds the patient and alerts others of their reactivity.

Adolescents and young adults should be taught never to be alone or go home alone (eg, including dormitories and apartments) if they think they are having a reaction. They should always stay with someone or go to the hospital. They should always check to ensure that someone is available and, if not, find someone to be with them until it is clear that any possible danger has passed, such as about 4 hours after symptoms clear. They should never drive alone if symptoms are present.

Summary Statement 62: Develop a written action plan for treatment of allergic reactions to food for adults and children. [Strength of recommendation: Moderate; D Evidence]

Patients with food allergy should have written avoidance and treatment plans that change as they age. The treatment plan should be separate from the avoidance plan, so that in the event of a reaction, the treatment protocol can be identified quickly and accurately and action can be taken promptly.[296,387,419,423] There are numerous handouts available from various sources that detail the manner in which avoidance is accomplished (see the Web site list below). These should be made freely

available to patients with food allergy. There should be a provision for substitution of safe foods in all settings. Ingredient labels should be easily available and regularly reviewed. Care should be taken to prevent cross-contamination/cross-contact, and this includes instructions for avoidance during craft, cooking, and science projects.

Treatment protocols should be designed to prevent delays in recognition and treatment of symptoms. These plans should be simple so that symptoms can be recognized quickly, and they should be readily available in the event of a reaction. In day care centers and schools the plans should be reviewed periodically for each patient. There should be a physician-prescribed protocol, and the medication should be readily available and not locked in a cabinet.

Several states have standard protocols that are to be used in their schools. There is also a commonly used protocol available at http://www.foodallergy.org or http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Libraries/Anaphylaxis-Emergency-Action-Plan.pdf.

Many adults do not have a written protocol for treatment of their food-induced allergic reactions; however, it should be clear to all adults with food allergy and their family members how to respond to the onset of symptoms and when self-injectable epinephrine should be administered.

Summary Statement 63: Inquire about and address behavioral changes because of bullying in patients with food allergy. This inquiry should include adults and children. [Strength of recommendation: Strong; D Evidence]

An important and often neglected aspect of food allergy education involves bullying of the child with food allergy. This is a consequential problem that can lead to ongoing emotional problems, school avoidance, and actual harm. Bullying should not be tolerated. It should be promptly recognized and reported, and the consequences should be significant. Often the issue is lack of education of the perpetrator and his or her family.[429-431]

Summary Statement 64: Teach patients that ingestion, rather than casual exposure through the skin or close proximity to an allergen, is almost the only route for triggering severe allergic/anaphylactic reactions. [Strength of recommendation: Strong; C Evidence]

Intimate relationships begin to present risk in adolescence and thereafter. Precautions for intimate kissing should be discussed thoroughly with adolescents and adults and should be reinforced by parents of teens and directly by physicians to adult patients at regular intervals. Exposure during incidental environmental contact can occur, but the circumstances would determine whether a reaction would occur.[432,433] Casual skin contact is unlikely to cause anaphylaxis, as has been demonstrated in studies in which patients with peanut allergy have been directly exposed to peanut in controlled settings, although it might play a role in maintaining sensitization. This study exposed patients with high-level peanut allergy through both contact and inhalation. Although it cannot be directly extrapolated to other populations, the results are reassuring.[396]

Although there are families and patients that are very concerned about casual contact triggering severe allergic reactions, there are few, if any, well-documented cases of this exposure causing mortality. The most important point for caregivers to make with patients/parents is that patients with food allergy must learn to "live in the world." This issue must be discussed in an ongoing process that entails multiple meetings with families and, on occasion, might even involve in-office casual exposure (as was undertaken in the study by Simonte et al[396]). Having such meetings to address these issues is strongly encouraged because there is likely no good substitute for making families more comfortable.

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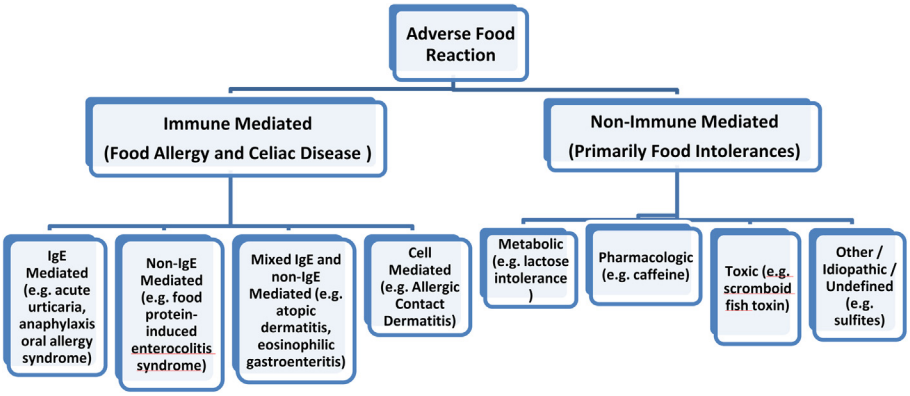

FIG E1. Categories of food reactions.

TABLE E1. Food allergen cross-reactivity

Reference(s)	Food group	Major allergens	Sensitization (%)	Clinical reactivity (%)	Comments
305-308	Avian and mammalian proteins	Milk: cow vs other	20-100	4-92	• High cross-reactivity with goat's, sheep's, and buffalo's milk • Low cross-reactivity with mare's, donkey's, and camel's milk
309-311		Milk vs beef/meat		10-20	• Sensitization to BSA is a predictor. • Seventy-three percent to 79% of children with beef allergy are reactive to cow's milk.
312		Egg: hen vs other	Common	—	• Cross-reactivity varies among species but is common.
313		Egg vs chicken/meat		22-32	• Bird-egg syndrome: sensitization to α-livetin
33, 314-316	Shellfish	Shrimp vs other crustacean Crustacea vs Mollusca Mollusca vs Mollusca	47	38* 14* 49*	• Tropomyosins are panallergens that also are responsible for cross-reactions to crustaceans in those with dust mite and cockroach allergy.
33, 317-320	Fish	Codfish vs other fish	5-100	30-75	• Gad c 1 (codfish parvalbumin) is a panallergen.
61, 321-323	Tree nuts	Tree nut vs other tree nut	92	12-37*	• Higher serum IgE correlations between cashew and pistachio and between pecan and walnut
321, 322		Tree nuts vs peanut (legume)	59-86	33-34*	• Higher sIgE correlations with almond and hazelnut
57, 324-327	Legumes	Peanut vs soy (other)	19-79	3-5 (28-30)†	• Sensitization to lentils and chickpeas might be associated with increased chance for multiple legume allergy.
328, 329	Cereals	Wheat vs other	47-88	21	• Most available data are from patients with atopic dermatitis.

*Percentage based on reported clinical reactions and not systematically evaluated by using DBPCFCs.
†DBPCFC data for lupine challenge in peanut-sensitized patients.

TABLE E2. Systems and examples of symptoms involved in acute IgE-mediated reactions to foods

Cutaneous
Pruritus
Erythema/flushing
Urticaria
Angioedema
Contact urticaria
Ocular
Pruritus
Tearing
Conjunctival injection
Periorbital edema
Respiratory tract
Upper
Pruritus
Nasal congestion
Rhinorrhea
Sneezing
Hoarseness
Laryngeal edema
Lower
Cough
Wheezing
Dyspnea
Chest tightness/pain
Gastrointestinal
Oral pruritus
Oral angioedema (lips, tongue, or palate)
Colicky abdominal pain
Nausea
Emesis
Diarrhea
Cardiovascular
Tachycardia
Dizziness
Hypotension
Loss of consciousness/fainting
Miscellaneous
Sense of impending doom
Uterine cramping/contractions

TABLE E3. Predictive value of IgE testing in positive or negative OFC results[219-222,224-226,228]

	>95% Positive		~50% Negative	
Food	**sIgE**	**SPT**	**sIgE**	**SPT wheal (mm)**
Egg white	≥7 ≥2 if age <2 y	≥7	≤2	≤3
Cow's milk	≥15 ≥5 if age <1 y	≥8	≤2	
Peanut	≥14	≥8	≤2 = history of prior reaction ≤5 = no history of prior reaction	≤3
Fish	≥20			

TABLE E4. Pollens and cross-reactive foods in patients with OAS[85-88,258,259]

Pollen/plant	Fruit/vegetable
Birch	Apple, cherry, apricot, carrot, potato, kiwi, hazelnut, celery, pear, peanut, soybean
Ragweed	Melon (eg, cantaloupe or honeydew), banana
Grass	Kiwi, tomato, watermelon, potato
Mugwort	Celery, fennel, carrot, parsley
Latex	Banana, avocado, chestnut, kiwi, fig, apple, cherry