

Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report

Primary Authors: Joshua A. Boyce, MD,^a Amal Assa'ad, MD,^d A. Wesley Burks, MD,^e Stacie M. Jones, MD,^g Hugh A. Sampson, MD,^h Robert A. Wood, MD,ⁱ Marshall Plaut, MD,^j Susan F. Cooper, MSc,ⁱ and Matthew J. Fenton, PhDⁱ

NIAID-Sponsored Expert Panel Authors: S. Hasan Arshad, MBBS, MRCP, DM, FRCP,^{k,l,m} Sami L. Bahna, MD, DrPH,ⁿ Lisa A. Beck, MD,^o Carol Byrd-Bredbenner, PhD, RD, FADA,^p Carlos A. Camargo, Jr, MD, DrPH,^b Lawrence Eichenfield, MD,^{q,r} Glenn T. Furuta, MD,^{s,t,u} Jon M. Hanifin, MD,^v Carol Jones, RN, AE-C,^w Monica Kraft, MD,^f Bruce D. Levy, MD,^c Phil Lieberman, MD,^x Stefano Luccioli, MD,^y Kathleen M. McCall, BSN, RN,^z Lynda C. Schneider, MD,^{aa} Ronald A. Simon, MD,^{bb} F. Estelle R. Simons, MD,^{cc} Stephen J. Teach, MD, MPH,^{dd} and Barbara P. Yawn, MD, MPH, MSc^{ee,ff}

Contributing Author: Julie M. Schwaninger, MSc^j

Boston, Mass, Cincinnati, Ohio, Durham, NC, Little Rock, Ark, New York and Rochester, NY, Baltimore, Bethesda, and College Park, Md, Southampton and Newport, Isle of Wight, United Kingdom, Shreveport, La, New Brunswick, NJ, San Diego and Orange, Calif, Aurora and Denver, Colo, Portland, Ore, McLean, Va, Memphis, Tenn, Winnipeg, Manitoba, Canada, Washington, DC, and Rochester and Minneapolis, Minn

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From ^athe Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Department of Medicine, and ^bthe Department of Emergency Medicine, Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, and ^cthe Partners Asthma Center, Pulmonary and Critical Care Medicine Division, Brigham and Women's Hospital and Harvard Medical School, Boston; ^dthe Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, University of Cincinnati; ^ethe Division of Allergy and Immunology, Department of Pediatrics, and ^fthe Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Duke University Medical Center, Durham; ^gthe Division of Allergy and Immunology, Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital; ^hthe Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York; ⁱthe Division of Allergy and Immunology, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore; ^jthe Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda; ^kthe School of Medicine, University of Southampton; ^lThe David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport; ^mthe Southampton University Hospital NHS Trust; ⁿthe Department of Pediatrics, Allergy and Immunology Section, Louisiana State University Health Sciences Center; ^othe Department of Dermatology, University of Rochester Medical Center, Rochester, NY; ^pthe Department of Nutritional Sciences, Rutgers University, New Brunswick; ^qthe Division of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego;

^rthe Departments of Pediatrics and Medicine, University of California, San Diego; ^sthe Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Digestive Health Institute, Children's Hospital Denver, Aurora; ^tthe Department of Pediatrics, National Jewish Health, Denver; ^uthe Department of Pediatrics, University of Colorado Denver School of Medicine, Aurora; ^vthe Department of Dermatology, Oregon Health and Science University; ^wthe Allergy and Asthma Network Mothers of Asthmatics, McLean; ^xthe Division of Allergy and Immunology, Department of Medicine, University of Tennessee College of Medicine; ^ythe Office of Food Additive Safety, US Food and Drug Administration, College Park; ^zthe Children's Hospital of Orange County, Orange; ^{aa}the Division of Immunology, Children's Hospital Boston; ^{bb}the Division of Allergy, Asthma and Immunology, Scripps Clinic, San Diego; ^{cc}the Departments of Pediatrics and Child Health and Immunology, Faculty of Medicine, University of Manitoba; ^{dd}the Division of Emergency Medicine, Children's National Medical Center, Washington, DC; ^{ee}the Department of Research, Olmsted Medical Center, Rochester, Minn; and ^{ff}the Department of Family and Community Health, University of Minnesota School of Medicine, Minneapolis.

Received for publication October 12, 2010; accepted for publication October 13, 2010. Corresponding author: Matthew J. Fenton, PhD, Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 6610 Rockledge Drive, Room 3105, Bethesda, MD 20892. E-mail: fentonm@niaid.nih.gov.

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J. A. Boyce has served on the Advisory Board of GlaxoSmithKline. He has served as a consultant and/or speaker for Altana, GlaxoSmithKline, and Merck. He has received funding/grant support from the National Institutes of Health.

A. Assa'ad holds, or is listed as an inventor on, US patent application #10/566903, entitled "Genetic markers of food allergy." She has served as a consultant for GlaxoSmithKline and as a speaker for the American College of Allergy, Asthma, and Immunology, the North East Allergy Society, the Virginia Allergy Society, the New England Allergy Society, and the American Academy of Pediatrics. Dr Assa'ad has received funding/grant support from GlaxoSmithKline.

A. W. Burks holds, or is listed as an inventor on, multiple US patents related to food allergy. He owns stock in Allertein and MastCell, Inc, and is a minority stockholder in Dannon Co Probiotics. He has served as a consultant for ActoGeniX NV, McNeil Nutritionals, Mead Johnson, and Novartis. He has served on the speaker's bureau for EpiPen/Dey, LP, and has served on the data monitoring committee for Genentech. He has served on an expert panel for Nutricia. Dr Burks has received funding/grant support from the Food Allergy and Anaphylaxis Network, Gerber, Mead Johnson, and the National Institutes of Health.

S. M. Jones has served as a speaker and grant reviewer and has served on the medical advisory committee for the Food Allergy and Anaphylaxis Network. She has received funding/grant support from Dyax Corp, the Food Allergy and Anaphylaxis Network, Mead Johnson, the National Peanut Board, and the National Institutes of Health.

H. A. Sampson holds, or is listed as an inventor on, multiple US patents related to food allergy. He owns stock in Allertein Therapeutics. He is the immediate past president of the American Academy of Allergy, Asthma, and Immunology. He has served as a consultant for Allertein Therapeutics, the American Academy of Allergy, Asthma, and Immunology, the Food Allergy Initiative, and Schering Plough. He has received funding/grant support for research projects from the Food Allergy Initiative, the National Institutes of Health (Division of Receipt and Referral, National Institute of Allergy and Infectious Diseases, National Center for Complementary and Alternative Medicine), and Phadia AB. He is a co-owner of Herbal Spring, LLC.

R. A. Wood has served as a speaker/advisory board member for GlaxoSmithKline, Merck, and Dey. He has received funding/grant support from Genentech and the National Institutes of Health (National Institute of Allergy and Infectious Diseases).

S. H. Arshad has received funding/grant support from the National Institutes of Health and the National Institute of Health Research, UK.

S. L. Bahna has received funding/grant support from Genentech.

L. A. Beck has received funding/grant support from the American Academy of Allergy, Asthma, and Immunology, the National Eczema Association, and the National Institutes of Health.

C. Byrd-Bredbenner owns stock in Johnson & Johnson. She has received funding/grant support from the US Department of Agriculture, the Canned Food Alliance, and the New Jersey Department of Health and Senior Services.

C. A. Camargo Jr has consulted for Dey and Novartis. He has received funding/grant support from a variety of government agencies and not-for-profit research foundations, as well as Dey and Novartis.

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G. T. Furuta has served as a consultant and/or speaker to Ception Therapeutics and TAP. He has received funding/grant support from the American Gastrointestinal Association and the National Institutes of Health.

J. M. Hanifin has served as served as a consultant for ALZA, Anesiva, Inc, Barrier Therapeutics, Inc, Milliken & Company, Nordic Biotech, Novartis Pharmaceuticals Corporation, Shionogi USA, Taisho Pharmaceutical R&D, Inc, Teikoku Pharma USA, Inc, UCB, York Pharma, ZARS, Inc, and ZymoGenetics. He has served as an investigator or received research funding from ALZA, Astellas Pharma US, Inc, Asubio Pharmaceuticals, Inc, Centocor, Inc, Corgentech, Novartis, Nucryst Pharmaceuticals, Seattle Genetics, and Shionogi USA.

M. Kraft has served as a consultant and/or speaker for Astra-Zeneca, Genentech, GlaxoSmithKline, Merck, Novartis, and Sepracor. She has received funding/grant support from Genentech, GlaxoSmithKline, the National Institutes of Health and Novartis.

B. D. Levy holds, or is listed as an inventor on, US patent applications #20080064746 entitled "Lipoxins and aspirin-triggered lipoxins and their stable analogs in the treatment of asthma and inflammatory airway diseases" and #20080096961 entitled "Use of docosatrienes, resolvins and their stable analogs in the treatment of airway diseases and asthma." He owns stock in Resolvix Pharmaceuticals. He has served as a consultant for Bayer Healthcare and Resolvix Pharmaceuticals. Dr Levy has received funding/grant support from the National Institutes of Health.

P. Lieberman has served as a consultant and/or speaker to Dey Laboratories, Novartis, Schering-Plough, AstraZeneca, Merck, TEVA, Pfizer, MEDA, Alcon, Genentech, Intelliject, and the Food Allergy and Anaphylaxis Network. He is past president of the American Academy of Allergy, Asthma, and Immunology.

L. C. Schneider has served as a consultant/clinical advisor for the Food Allergy Initiative. She has received funding/grant support from a variety of not-for-profit research foundations, as well as Novartis and the National Institutes of Health.

R. A. Simon has served as a speaker for Dey Laboratories, Genentech, GlaxoSmithKline, Merck, Novartis, and the US Food and Drug Administration.

F. E. R. Simons holds a patent on "Fast-disintegrating epinephrine tablets for sublingual administration." She is a past-president of the American Academy of Allergy, Asthma, and Immunology and of the Canadian Society of Allergy and Clinical Immunology. She is a member of the advisory boards of Dey, Intelliject, and ALK-Abello. She has received funding/grant support from AllerGen, the Canadian Allergy, Asthma and Immunology Foundation/Anaphylaxis Canada, and the Canadian Institutes of Health Research.

S. J. Teach has served as a speaker for AstraZeneca. He has received funding/grant support from the AstraZeneca Foundation, Aventis, the Child Health Center Board, the CNMC Research Advisory Council, the National Association of Chain Drug Stores Foundation, the National Institutes of Health (National Institute of Allergy and Infectious Diseases; National Heart, Lung, and Blood Institute), Novartis/Genentech, the Robert Wood Johnson Foundation, the US Centers for Disease Control and Prevention, the US Public Health Service, and the Washington, DC, Department of Health. The other authors have declared that they have no conflict of interest.

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*Some numbered sections found in the Guidelines are not included in this Summary because they do not include a guideline recommendation or an "In summary" statement, or because the detailed information in the section was not suitable for a concise Summary.

SECTION 1. INTRODUCTION

1.1. Overview

Food allergy (FA) is an important public health problem that affects adults and children and may be increasing in prevalence. Despite the risk of severe allergic reactions and even death, there is no current treatment for FA: the disease can only be managed by allergen avoidance or treatment of symptoms. Moreover, the diagnosis of FA may be problematic, given that nonallergic food reactions, such as food intolerance, are frequently confused with FAs. Additional concerns relate to the differences in the diagnosis and management of FA in different clinical practice settings.

Due to these concerns, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, working with more than 30 professional organizations, federal agencies, and patient advocacy groups, led the development of "best practice" clinical guidelines for the diagnosis and management of FA (henceforth referred to as the Guidelines).¹ Based on a comprehensive review and objective evaluation of the recent scientific and clinical literature on FA, the Guidelines were developed by and designed for allergists/immunologists, clinical researchers, and practitioners in the areas of pediatrics, family medicine, internal medicine, dermatology, gastroenterology, emergency medicine, pulmonary and critical care medicine, and others.

The Guidelines focus on diseases that are defined as FA (see section 2.1) and include both IgE-mediated reactions to food and some non-IgE-mediated reactions to food. The Guidelines do not discuss celiac disease, which is an immunologic non-IgE-mediated reaction to certain foods. Although this is an immune-based disease involving food, existing clinical guidelines for celiac disease will not be restated here.

Finally, these Guidelines do not address the management of patients with FA outside of clinical care settings (for example, schools and restaurants) or the related public health policy issues. These issues are beyond the scope of this document.

1.2. Relationship of the US Guidelines to other guidelines

(Not summarized here; refer to Guidelines.)

1.3. How the Guidelines were developed

1.3.1. The Coordinating Committee. NIAID established a Coordinating Committee (CC), whose members are listed in Appendix A of the Guidelines, to oversee the development of the Guidelines; review drafts of the Guidelines for accuracy, practicality, clarity, and broad utility of the recommendations in clinical practice; review the final Guidelines; and disseminate the Guidelines. The CC members were from 34 professional organizations, advocacy groups, and federal agencies, and each member was vetted for financial conflict of interest (COI) by NIAID staff.

1.3.2. The Expert Panel. The CC convened an Expert Panel (EP) in March 2009 that was chaired by Joshua Boyce, MD (Brigham and Women's Hospital, Boston, Mass). Panel members were specialists from a variety of relevant clinical, scientific, and public health areas (see Acknowledgments). Each member was vetted for financial COI by NIAID staff and approved by the CC. The charge to the EP was to use an independent, systematic literature review, in conjunction with consensus expert opinion and EP-identified supplementary documents, to develop Guidelines that provide a comprehensive approach for diagnosing and managing FA based on the current state of the science.

1.3.3. The independent, systematic literature review and report. RAND Corporation prepared an independent, systematic literature review and evidence report on the state of the science in FA. This work was supported by an NIAID contract awarded in September 2008. The contract's principal investigator was Paul G. Shekelle, MD, PhD, an internationally recognized expert in the fields of practice guidelines and meta-analysis. RAND screened more than 12,300 titles, reviewed more than 1,200 articles, abstracted nearly 900 articles, and included 348 articles in the final RAND report. The full version of the report with a complete list of references is available at http://www.rand.org/pubs/working_papers/WR757-1/.

1.3.4. Assessing the quality of the body of evidence. In addition to assessing the quality of each of the included studies, RAND assessed the quality of the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which was developed in 2004. GRADE provides a comprehensive and transparent methodology to develop recommendations for the diagnosis, treatment, and management of patients. In assessing the body of evidence, GRADE considers study design and other factors, such as the precision, consistency, and directness of the data. Using this approach, GRADE then provides a grade of high, moderate, or low for the quality of the body of evidence.

1.3.5. Preparation of the draft Guidelines and Expert Panel deliberations. All 43 clinical recommendations drafted by the EP received 90% (or higher) agreement. Sections 3, 5, and 6 of the Guidelines also contain "In summary" statements. These statements are intended to provide health care professionals with significant information that did not warrant a recommendation, or are in place of a recommendation when the EP or the CC could not reach consensus. All "In summary" statements received 90% (or higher) agreement.

1.3.6. Public comment period and draft Guidelines revision. The draft Guidelines were posted to the NIAID Web site in March 2010 for a period of 60 days to allow for public review and comment. More than 550 comments were collected

and reviewed by the CC, the EP, and NIAID. The EP revised the Guidelines in response to some of these comments. The final Guidelines were published in the December 2010 issue of the *Journal of Allergy and Clinical Immunology* and are publically available at www.jacionline.org.

1.4. Defining the strength of each clinical guideline

The EP has used the verb "recommends" or "suggests" in each clinical guideline. These words convey the strength of the guideline, defined as follows:

- **Recommend** is used when the EP strongly recommended for or against a particular course of action.
- **Suggest** is used when the EP weakly recommended for or against a particular course of action.

1.5. Summary

The Guidelines are intended to assist health care professionals in making appropriate decisions about patient care in the United States. The recommendations are not fixed protocols that must be followed. Health care professionals should take these Guidelines into account when exercising their clinical judgment. However, this guidance does not override their responsibility to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient, guardian, or caregiver. Clinical judgment on the management of individual patients remains paramount. Health care professionals, patients, and their families need to develop individual treatment plans that are tailored to the specific needs and circumstances of the patient. This document is intended as a resource to guide clinical practice and develop educational materials for patients, their families, and the public. It is not an official regulatory document of any government agency.

SECTION 2. DEFINITIONS, PREVALENCE, AND EPIDEMIOLOGY OF FOOD ALLERGY

2.1. Definitions

2.1.1. Definitions of food allergy, food, and food allergens. The EP came to consensus on definitions used throughout the Guidelines.

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.

A **food** is defined as any substance—whether processed, semi-processed, or raw—that is intended for human consumption, and includes drinks, chewing gum, food additives, and dietary supplements. Substances used only as drugs, tobacco products, and cosmetics (such as lip-care products) that may be ingested are not included.

Food allergens are defined as those specific components of food or ingredients within food (typically proteins, but sometimes also chemical haptens) that are recognized by allergen-specific immune cells and elicit specific immunologic reactions, resulting in characteristic symptoms. Some allergens (most often from fruits and vegetables) cause allergic reactions primarily if eaten when raw. However, most food allergens can still cause reactions even after they have been cooked or have undergone digestion in the stomach and intestines. A phenomenon called

cross-reactivity may occur when an antibody reacts not only with the original allergen, but also with a similar allergen. In FA, cross-reactivity occurs when a food allergen shares structural or sequence similarity with a different food allergen or aeroallergen, which may then trigger an adverse reaction similar to that triggered by the original food allergen. Cross-reactivity is common, for example, among different shellfish and different tree nuts.

Food oils—such as soy, corn, peanut, and sesame—range from very low allergenicity (if virtually all of the food protein is removed in processing) to very high allergenicity (if little of the food protein is removed in processing).

2.1.2. Definitions of related terms. Because individuals can develop allergic sensitization (as evidenced by the presence of allergen-specific IgE (sIgE)) to food allergens without having clinical symptoms on exposure to those foods, an sIgE-mediated FA requires *both* the presence of sensitization *and* the development of specific signs and symptoms on exposure to that food. Sensitization alone is not sufficient to define FA.

These Guidelines generally use the term **tolerate** to denote a condition where an individual has either naturally outgrown an FA or has received therapy and no longer develops clinical symptoms following ingestion of the food. This ability to tolerate food does not distinguish between these 2 possible clinical states. Individuals may tolerate food only for a short term, perhaps because they have been desensitized by exposure to the food. Alternatively, they may develop long-term tolerance. The specific term **tolerance** is used in these Guidelines to mean that an individual is symptom free after consumption of the food or upon oral food challenge weeks, months, or even years after the cessation of treatment. The immunological mechanisms that underlie tolerance in humans are poorly understood.

Although many different foods and food components have been recognized as food allergens, these Guidelines focus on only those foods that are responsible for the majority of observed adverse allergic or immunologic reactions. Moreover, foods or food components that elicit reproducible adverse reactions but do not have established or likely immunologic mechanisms are not considered food allergens. Instead, these non-immunologic adverse reactions are termed **food intolerances**. For example, an individual may be allergic to cow's milk (henceforth referred to as milk) due to an immunologic response to milk protein, or alternatively, that individual may be intolerant to milk due to an inability to digest the sugar lactose. In the former situation, milk protein is considered an allergen because it triggers an adverse immunologic reaction. Inability to digest lactose leads to excess fluid production in the gastrointestinal (GI) tract, resulting in abdominal pain and diarrhea. This condition is termed lactose intolerance, and lactose is not an allergen because the response is not immune based. It should be noted that the words **tolerance** and **intolerance** are unrelated terms, even though the spelling of the words implies that they are opposites.

2.1.3. Definitions of specific food-induced allergic conditions. The reader is referred to the Guidelines for the definitions of the following:

- **Food-induced anaphylaxis**
- **GI food allergies and several specific syndromes**
 - Immediate GI hypersensitivity
 - Eosinophilic esophagitis (EoE)

- Eosinophilic gastroenteritis
- Food protein-induced allergic proctocolitis (AP)
- Food protein-induced enterocolitis syndrome (FPIES)
- Oral allergy syndrome (OAS)
- **Cutaneous reactions to foods**
 - Acute urticaria
 - Angioedema
 - The increase in atopic dermatitis (AD) symptoms
 - Allergic contact dermatitis
 - Contact urticaria
- **Respiratory manifestations**
- **Heiner syndrome**

2.2. Prevalence and epidemiology of food allergy

The true prevalence of FA has been difficult to establish for several reasons.

- Although more than 170 foods have been reported to cause IgE-mediated reactions, most prevalence studies have focused on only the most common foods.
- The incidence and prevalence of FA may have changed over time, and many studies have indeed suggested a true rise in prevalence over the past 10 to 20 years.
- Studies of FA incidence, prevalence, and natural history are difficult to compare because of inconsistencies and deficiencies in study design and variations in the definition of FA.

2.2.1. Systematic reviews of the prevalence of food allergy. (Not summarized here; refer to Guidelines.)

2.2.2. Prevalence of allergy to specific foods, food-induced anaphylaxis, and food allergy with comorbid conditions. The following is a summary of prevalence data for the most common food allergies and anaphylaxis:

Peanut

- Prevalence of peanut allergy in the United States is about 0.6% of the population.
- Prevalence of peanut allergy in France, Germany, Israel, Sweden, and the United Kingdom varies between 0.06% and 5.9%.

Tree nuts

- Prevalence of tree nut allergy in the United States is 0.4% to 0.5% of the population.
- Prevalence of tree nut allergy in France, Germany, Israel, Sweden, and the United Kingdom varies between 0.03% and 8.5%.

Seafood

- Prevalence rates in the United States are significantly lower for children than for adults: fish allergy, 0.2% for children vs 0.5% for adults; crustacean shellfish allergy, 0.5% vs 2.5%; any seafood allergy, 0.6% vs 2.8%.
- Prevalence rates in the United States are higher for women than for men: crustacean shellfish allergy, 2.6% for women vs 1.5% for men; any fish, 0.6% vs 0.2%.

Milk and hen's egg

- In a Danish cohort, allergy to milk was confirmed in 2.2%. Of these, 54% had IgE-mediated allergy, and the remaining 46% were classified as non-IgE mediated.
- In a Norwegian cohort, the prevalence of hen's egg (henceforth referred to as egg) allergy was estimated to be 1.6%, and most egg reactions were IgE mediated.

Food-induced anaphylaxis

- Several studies in the United States assessed the incidence of anaphylaxis related to food. These studies found wide differences in the rates (from 1/100,000 population to as high as 70/100,000 population) of hospitalization or emergency department visits for anaphylaxis, as assessed by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes or medical record review.
- The proportion of anaphylaxis cases thought to be due to foods also varied between 13% and 65%, with the lowest percentages found in studies that used more stringent diagnostic criteria for anaphylaxis.

The EP agreed that any estimate of the overall US incidence of anaphylaxis is unlikely to have utility because such an estimate fails to reflect the substantial variability in patient age, geographic distribution, criteria used to diagnose anaphylaxis, and the study methods used.

SECTION 3. NATURAL HISTORY OF FOOD ALLERGY AND ASSOCIATED DISORDERS

The EP reviewed the literature on the natural history of FA and summarized the available data for the most common food allergens in the United States: egg, milk, peanut, tree nuts, wheat, crustacean shellfish, and soy. Natural history data for fish allergy were unavailable as of the completion of the systematic literature review (September 2009). It should be noted that many published studies addressing the natural history of FA typically come from selected populations (for example, from a single clinic or hospital) that may not be representative of the general or community-based patient population with a specific FA condition. Thus, the findings of these studies may not necessarily be extrapolated to all patients with the condition.

3.1. Natural history of food allergy in children

In summary: Most children with FA eventually will tolerate milk, egg, soy, and wheat; far fewer will eventually tolerate tree nuts and peanut. The time course of FA resolution in children varies by food and may occur as late as the teenage years. A high initial level of sIgE against a food is associated with a lower rate of resolution of clinical allergy over time.

3.2. Natural history of levels of allergen-specific IgE to foods in children

In summary: For many patients, sIgE antibodies to foods appear within the first 2 years of life. Levels may increase or decrease; a decrease is often associated with the ability to tolerate the foods.

3.3. Natural history of food allergy in adults

In summary: FA in adults can reflect persistence of pediatric FAs (for example, milk, peanut, and tree nuts) or *de novo* sensitization to food allergens encountered after childhood. Although there is a paucity of data from US studies, FA that starts in adult life tends to persist.

3.4. Natural history of conditions that coexist with food allergy

In summary: FA may coexist with asthma, AD, EoE, and exercise-induced anaphylaxis. In patients with asthma, the coexistence of FA may be a risk factor for severe asthma exacerbations. Moreover, food may be a trigger for exercise-induced anaphylaxis. Elimination of food allergens in sensitized individuals can improve symptoms of some comorbid conditions.

3.4.1. Asthma.

In summary: Asthma and FA often coexist in pediatric and adult patients. FA is associated with severe asthma.

3.4.2. Atopic dermatitis.

In summary: AD and FA are highly associated. When tolerance develops to a food, the reintroduction of the food in the diet will not result in recurrence or worsening of the AD.

3.4.3. Eosinophilic esophagitis.

In summary: EoE is commonly associated with sensitization to foods. The natural history of EoE is that of a chronic condition that resolves spontaneously or with therapy, and then relapses. There are insufficient data to judge the impact of food sensitization on the natural history of EoE, and vice versa. Only retrospective data exist that support a beneficial effect of dietary changes on the histopathologic changes in the esophagus in EoE.

3.4.4. Exercise-induced anaphylaxis.

In summary: Exercise-induced anaphylaxis in adults is triggered by foods in about one third of patients and has a natural history marked by frequent recurrence of the episodes.

3.5. Risk factors for the development of food allergy

In summary: Family history of atopy and the presence of AD are risk factors for the development of both sensitization to food and confirmed FA.

3.6. Risk factors for severity of allergic reactions to foods

In summary: The severity of allergic reactions to foods is multifactorial and variable. The severity of a reaction cannot be accurately predicted by the degree of severity of past reactions nor by the level of sIgE or the size of the wheal from the skin prick test (SPT). The factor most commonly identified with the most severe reactions is the coexistence of asthma.

3.7. Incidence, prevalence, and consequences of unintentional exposure to food allergens

In summary: Self-reported reactions to food frequently occur in patients with a known diagnosis of FA. Although a subset of these reactions is due to intentional exposure, most are due to unintentional exposure. Both types of exposure can be life-threatening. There is no evidence that unintentional or intentional exposures to the food allergen alter the natural history of the FA.

SECTION 4. DIAGNOSIS OF FOOD ALLERGY

4.1. When should food allergy be suspected?

Guideline 1: The EP recommends that FA should be considered:

TABLE I. Symptoms of food-induced allergic reactions

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

GI, Gastrointestinal.

Note: This table is presented as Table IV in the Guidelines.

- In individuals presenting with anaphylaxis or any combination of symptoms listed in Table I that occur within minutes to hours of ingesting food, especially in young children and/or if symptoms have followed the ingestion of a specific food on more than 1 occasion
- In infants, young children, and selected older children diagnosed with certain disorders, such as moderate to severe AD, EoE, enterocolitis, enteropathy, and allergic proctocolitis
- In adults diagnosed with EoE

4.2. Diagnosis of IgE-mediated food allergy

4.2.1. Medical history and physical examination.

Guideline 2: The EP recommends using medical history and physical examination to aid in the diagnosis of FA.

- **Medical history:** The EP recommends using a detailed medical history to help focus the evaluation of an FA. Although the medical history often provides evidence for the type of food-induced allergic reaction and the potential causative food(s) involved, history alone cannot be considered diagnostic of FA.
- **Physical examination:** The EP recommends performing a focused physical examination of the patient, which may provide signs consistent with an allergic reaction or disorder often associated with FA. However, by itself, the physical examination cannot be considered diagnostic of FA.

Guideline 3: The EP recommends that parent and patient reports of FA must be confirmed, because multiple studies demonstrate that 50% to 90% of presumed FAs are not allergies.

4.2.2. Methods to identify the causative food.

4.2.2.1. Skin prick test.

Guideline 4: The EP recommends performing an SPT (also known as a skin puncture test) to assist in the identification of foods that may be provoking IgE-mediated food-induced allergic reactions, but the SPT alone cannot be considered diagnostic of FA.

4.2.2.2. Intradermal tests.

Guideline 5: The EP recommends that intradermal testing should *not* be used to make a diagnosis of FA.

4.2.2.3. Total serum IgE.

Guideline 6: The EP recommends that the routine use of measuring total serum IgE should *not* be used to make a diagnosis of FA.

4.2.2.4. Allergen-specific serum IgE.

Guideline 7: The EP recommends sIgE tests for identifying foods that potentially provoke IgE-mediated food-induced allergic reactions, but alone these tests are *not* diagnostic of FA.

4.2.2.5. Atopy patch test.

Guideline 8: The EP suggests that the atopy patch test (APT) should *not* be used in the routine evaluation of non-contact FA.

4.2.2.6. Use of skin prick tests, sIgE tests, and atopy patch tests in combination.

Guideline 9: The EP suggests *not* using the combination of SPTs, sIgE tests, and APTs for the routine diagnosis of FA.

4.2.2.7. Food elimination diets.

Guideline 10: The EP suggests that elimination of 1 or a few specific foods from the diet may be useful in the diagnosis of FA, especially in identifying foods responsible for some non-IgE-mediated food-induced allergic disorders, such as FPIES, AP, and Heiner syndrome, and some mixed IgE- and non-IgE-mediated food-induced allergic disorders, such as EoE.

4.2.2.8. Oral food challenges.

Guideline 11: The EP recommends using oral food challenges for diagnosing FA. The double-blind placebo-controlled food challenge is the gold standard. However, a single-blind or an open-food challenge may be considered diagnostic under certain circumstances: if either of these challenges elicits no symptoms (ie, the challenge is negative), then FA can be ruled out; but when either challenge elicits objective symptoms (ie, the challenge is positive) *and* those objective symptoms correlate with

medical history *and* are supported by laboratory tests, then a diagnosis of FA is supported.

4.2.2.9. Nonstandardized and unproven procedures.

Guideline 12: The EP recommends *not* using any of the following nonstandardized tests for the routine evaluation of IgE-mediated FA:

- Basophil histamine release/activation
- Lymphocyte stimulation
- Facial thermography
- Gastric juice analysis
- Endoscopic allergen provocation
- Hair analysis
- Applied kinesiology
- Provocation neutralization
- Allergen-specific IgG₄
- Cytotoxicity assays
- Electrodermal test (Vega)
- Mediator release assay (LEAP diet)

4.3. Diagnosis of non-IgE-mediated immunologic adverse reactions to food.

4.3.1. Eosinophilic gastrointestinal diseases.

Guideline 13: The EP suggests that SPTs, sIgE tests, and APTs may be considered to help identify foods that are associated with EoE, but these tests alone are *not* sufficient to make the diagnosis of FA. The role of these tests in the diagnosis of other eosinophilic GI disorders has not been established.

4.3.2. Food protein-induced enterocolitis syndrome.

Guideline 14: The EP recommends using the medical history and oral food challenge to establish a diagnosis of FPIES. However, when history indicates that infants or children have experienced hypotensive episodes or multiple reactions to the same food, a diagnosis may be based on a convincing history and absence of symptoms when the causative food is eliminated from the diet.

4.3.3. Food protein-induced allergic proctocolitis.

Guideline 15: The EP recommends using the medical history, resolution of symptoms when the causative food is eliminated from the diet, and recurrence of symptoms following an oral food challenge to diagnose allergic proctocolitis.

4.3.4. Food protein-induced enteropathy syndrome.

(Not summarized here; refer to Guidelines.)

4.3.5. Allergic contact dermatitis.

Guideline 16: The EP recommends using the medical history, including the absence of symptoms while the causative food is avoided, and positive patch tests to diagnose allergic contact dermatitis.

4.3.6. Systemic contact dermatitis.

Guideline 17: The EP suggests using the medical history, including the resolution of symptoms while the causative food is avoided, and positive patch tests to establish the diagnosis of systemic contact dermatitis.

4.4. Diagnosis of IgE-mediated contact urticaria

Guideline 18: The EP suggests using the medical history, including the absence of symptoms while the causative food is avoided, positive sIgE tests or SPTs, and positive immediate epicutaneous skin tests (for example, positive immediate responses to APTs), to establish the diagnosis of food-induced IgE-mediated contact urticaria.

Contact urticaria can be of 2 types, either IgE mediated or non-IgE mediated. In IgE-mediated contact urticaria, substances present in foods interact with sIgE bound to cutaneous mast cells, leading to the release of histamine and other inflammatory mediators. Localized or generalized urticaria, as well as systemic symptoms, may result. sIgE-mediated contact urticaria may be assessed with APTs, SPTs, or sIgE tests, although there is no standardization of diagnostic methodology. In non-IgE-mediated contact urticaria to food, systemic symptoms are rarely seen.

SECTION 5. MANAGEMENT OF NONACUTE ALLERGIC REACTIONS AND PREVENTION OF FOOD ALLERGY

5.1. Management of individuals with food allergy

5.1.1. Dietary avoidance of specific allergens in IgE-mediated food allergy.

Guideline 19: The EP recommends that individuals with documented IgE-mediated FA should avoid ingesting their specific allergen or allergens.

5.1.2. Dietary avoidance of specific allergens in non-IgE-mediated food allergy.

Guideline 20: The EP recommends that individuals with documented non-IgE-mediated FA should avoid ingesting their specific allergen or allergens.

5.1.3. Effects of dietary avoidance on associated and comorbid conditions, such as atopic dermatitis, asthma, and eosinophilic esophagitis.

Guideline 21: In individuals with documented or proven FA who also have 1 or more of the following—AD, asthma, or EoE—the EP recommends avoidance of their specific allergen or allergens.

Guideline 22: In individuals without documented or proven FA, the EP does *not* recommend avoiding potentially allergenic foods as a means of managing AD, asthma, or EoE.

5.1.4. Food avoidance and nutritional status.

Guideline 23: The EP recommends nutritional counseling and regular growth monitoring for all children with FA.

5.1.5. Food labeling in food allergy management.

Guideline 24: The EP suggests that individuals with FA and their caregivers receive education and training on how to interpret ingredient lists on food labels and how to recognize labeling of the food allergens used as ingredients in foods. The EP also suggests that products with precautionary labeling, such as “this product may contain trace amounts of allergen,” be avoided.

5.1.6. When to re-evaluate patients with food allergy.

Guideline 25: The EP suggests follow-up testing for individuals with FA depending on the specific food to which the individual is allergic. Whether testing is done annually or at other intervals depends on the food in question, the age of the child, and the intervening medical history.

5.1.7. Pharmacologic intervention for the prevention of food-induced allergic reactions.

5.1.7.1. IgE-mediated reactions.

Guideline 26: There are *no* medications currently recommended by the EP to prevent IgE-mediated food-induced allergic reactions from occurring in an individual with existing FA.

5.1.7.2. Non-IgE-mediated reactions.

Guideline 27: There are *no* medications currently recommended by the EP to prevent non-IgE-mediated food-induced allergic reactions from occurring in an individual with existing FA.

5.1.8. Pharmacologic intervention for the treatment of food-induced allergic reactions. Allergen avoidance is the first line of treatment for FA, and use of antihistamines, as needed, remains the mainstay of managing (as opposed to preventing) symptoms of nonsevere food-induced allergic reactions. However, drug therapy has been used to treat FA in cases where allergen avoidance is extremely difficult or results in nutritional deficiencies. Drugs that alter the immune response to the allergen are commonly considered the most likely candidates for such therapy in the future, but these treatments are not currently recommended (see Guideline 28).

5.1.9. Immunotherapy for food allergy management.

5.1.9.1. Allergen-specific immunotherapy.

Guideline 28: The EP does *not* recommend using allergen-specific immunotherapy to treat IgE-mediated FA.

5.1.9.2. Immunotherapy with cross-reactive allergens.

Guideline 29: The EP does *not* recommend immunotherapy with cross-reactive allergens for treating IgE-mediated FA.

5.1.10. Quality-of-life issues associated with food allergy.

Guideline 30: The EP recommends that patients with FA and their caregivers be provided with information on food allergen avoidance and emergency management that is age and culturally appropriate.

5.1.11. Vaccinations in patients with egg allergy.

In summary: Patients who have generated IgE antibodies to an allergen are at risk for anaphylaxis with systemic exposure to that allergen. Thus, patients who have IgE-mediated egg allergy are at risk for anaphylaxis if injected with vaccines containing egg protein. More detailed information about specific egg-containing vaccines (MMR, MMRV, influenza, yellow fever, and rabies) is provided in sections 5.1.11.1-5.1.11.4 of the Guidelines.

The EP recognizes that changes in these recommendations may occur in the future as there is an increased understanding of the risk factors for allergic reactions and as vaccine manufacturing processes improve and decrease the final egg protein content of vaccines. For the most current recommendations, health care professionals should refer to the Web sites of the American Academy of Pediatrics (AAP) and Advisory Committee for Immunization Practices (ACIP):

- <http://aapredbook.aappublications.org/>
- <http://www.cdc.gov/vaccines/recs/acip/>

5.1.11.1. Measles, mumps, rubella, and varicella vaccine.

Guideline 31: The EP recognizes the varying consensus recommendations of the different organizations on this particular vaccine and recommends that children with egg allergy, even those with a history of severe reactions, receive vaccines for measles, mumps, and rubella (MMR) and for MMR with varicella (MMRV). The safety of this practice has been recognized by ACIP and AAP and is noted in the approved product prescribing information for these vaccines.

5.1.11.2. Influenza vaccine.

In summary: The EP concludes that insufficient evidence exists to recommend administering influenza vaccine, either inactivated or live-attenuated, to patients with a history of severe reactions to egg proteins. Severe reactions include a history of hives, angioedema, allergic asthma, or systemic anaphylaxis to egg proteins (or chicken proteins). Less severe or local manifestations of allergy to egg or feathers are not contraindications. However, the EP notes that egg allergy is relatively common

among the very patients who would highly benefit from influenza vaccination. Such patients include children and young adults (from 6 months to 18 years old for seasonal influenza, and from 6 months to 24 years old for H1N1 influenza) and all patients with asthma. It should be noted that live-attenuated vaccine is not licensed for use in patients with asthma.

Although ACIP and AAP, and also the vaccine manufacturers, do not recommend influenza vaccination in patients who are allergic to egg, several publications have described different approaches to giving the influenza vaccine to patients with severe allergic reactions to egg. These approaches, which depend on the ovalbumin content and the results of SPTs or intradermal tests with the vaccine, include a single dose of vaccine, 2 doses of vaccine, or multiple doses. However, the evidence supporting these approaches is limited by the small numbers of patients included in each study. Moreover, data indicate that, although the vaccines are relatively safe, there remains some, albeit low, risk of systemic reactions. Also, negative SPT results do not accurately predict safety of vaccination, in that 5% of patients with negative SPTs had systemic reactions to vaccination.

5.1.11.3. Yellow fever vaccine.

In summary: The EP recognizes the current guidelines from the different organizations and recommends *against* administering yellow fever vaccine to patients with a history of hives, angioedema, allergic asthma, or systemic anaphylaxis to egg proteins, unless an allergy evaluation and testing with the vaccine is done first. This approach has been recognized by ACIP and AAP and is noted in the approved product prescribing information for this vaccine.

5.1.11.4. Rabies vaccines.

In summary: The EP recognizes the current guidelines from the different organizations and recommends *against* administering rabies vaccines to patients with a history of hives, angioedema, allergic asthma, or systemic anaphylaxis to egg proteins, unless an allergy evaluation and testing with the vaccine is done first. This approach has been recognized by ACIP and AAP and is noted in the approved product prescribing information for these vaccines.

5.2. Management of individuals at risk for food allergy

5.2.1. Nonfood allergen avoidance in at-risk patients.

Guideline 32: The EP suggests that patients *at risk* for developing FA do *not* limit exposure to potential nonfood allergens (for example, dust mites, pollen, or pet dander). Patients *at risk* for developing FA are defined as those with a biological parent or sibling with existing, or history of, allergic rhinitis, asthma, AD, or FA. This definition of “*at risk*” is used throughout sections 5.2 and 5.3.

5.2.2. Dietary avoidance of foods with cross-reactivities in at-risk patients.

Guideline 33: The EP suggests that patients *at risk* for developing FA do *not* need to limit exposure to foods that may be cross-reactive with the 8 major food allergens in the United States (milk, egg, peanut, tree nuts, soy, wheat, fish, and crustacean shellfish).

5.2.3. Testing of allergenic foods in patients at high risk prior to introduction.

In summary: The EP concludes that insufficient evidence exists to recommend routine FA testing prior to the introduction of highly allergenic foods (such as milk, egg, and peanut) in children

who are *at high risk* of reacting to the introduction of such foods. The definition of children *at high risk*, in this specific situation, is children with pre-existing severe allergic disease and/or a family history of FA. Nevertheless, there may be some value in FA evaluations that include an oral food challenge for a select group of patients with certain risk factors, such as having a sibling with peanut allergy or evidence of another underlying FA (for example, testing for tree nut allergy in a child with peanut allergy). It is possible that an FA evaluation prior to introduction of a food could potentially prevent allergic reactions. However, widespread SPTs and sIgE tests are not recommended because of their poor predictive value. These tests would lead to many clinically irrelevant results and unnecessary dietary restrictions, especially if unconfirmed by oral food challenges. Overall, the risk-to-benefit ratio of FA evaluation should be considered on an individual basis, especially for the highly allergenic foods in *high-risk* young children.

Guideline 34: The EP suggests that the general population of children *not* be tested for FA to highly allergenic foods prior to their introduction into the diet. The general population of children does not have pre-existing severe allergic disease and also does not have a family history of FA.

5.2.4. Testing in infants and children with persistent atopic dermatitis.

Guideline 35: The EP suggests that children less than 5 years old with moderate to severe AD be considered for FA evaluation for milk, egg, peanut, wheat, and soy, if *at least 1* of the following conditions is met:

- The child has persistent AD in spite of optimized management and topical therapy.
- The child has a reliable history of an immediate reaction after ingestion of a specific food.

5.3. Prevention of food allergy

5.3.1. Maternal diet during pregnancy and lactation.

Guideline 36: The EP does *not* recommend restricting maternal diet during pregnancy or lactation as a strategy for preventing the development or clinical course of FA.

5.3.2. Breast-feeding.

Guideline 37: The EP recommends that all infants be exclusively breast-fed until 4 to 6 months of age, unless breast-feeding is contraindicated for medical reasons.

5.3.3. Special diets in infants and young children.

5.3.3.1. Soy infant formula versus cow's milk formula.

Guideline 38: The EP does *not* recommend using soy infant formula instead of cow's milk infant formula as a strategy for preventing the development of FA or modifying its clinical course in *at-risk* infants ("*at risk*" is defined in Guideline 32).

5.3.3.2. Hydrolyzed infant formulas versus cow's milk formula or breast-feeding.

Guideline 39: The EP suggests that the use of hydrolyzed infant formulas, as opposed to cow's milk formula, may be considered as a strategy for preventing the development of FA in *at-risk* infants who are not exclusively breast-fed ("*at risk*" is defined in Guideline 32). Cost and availability of extensively hydrolyzed infant formulas may be weighed as prohibitive factors.

5.3.4. Timing of introduction of allergenic foods to infants.

Guideline 40: The EP suggests that the introduction of solid foods should *not* be delayed beyond 4 to 6 months of age. Potentially allergenic foods may be introduced at this time as well.

SECTION 6. DIAGNOSIS AND MANAGEMENT OF FOOD-INDUCED ANAPHYLAXIS AND OTHER ACUTE ALLERGIC REACTIONS TO FOODS

6.1. Definition of anaphylaxis

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. Typically, IgE-mediated food-induced anaphylaxis is believed to involve systemic mediator release from sensitized mast cells and basophils. The term **anaphylactoid** has been used in the past to indicate adverse reactions that are not IgE mediated and typically are not life-threatening. This term is imprecise and will not be used in these Guidelines.

6.2. Diagnosis of acute, life-threatening, food-induced allergic reactions

Guideline 41: The EP recommends that the health care professional considering a diagnosis of food-induced anaphylaxis should understand:

- The signs and symptoms characteristic of anaphylaxis
- The timing of symptoms in association with food ingestion/exposure
- Comorbid conditions, such as asthma, that may affect treatment and outcome
- The limited utility of laboratory parameters in the acute-care setting

6.3. Treatment of acute, life-threatening, food-induced allergic reactions

6.3.1. First-line and adjuvant treatment for food-induced anaphylaxis.

Guideline 42: The EP recommends that treatment for food-induced anaphylaxis should focus on the following:

- Prompt and rapid treatment after onset of symptoms (see Table II)
- Intramuscular (IM) epinephrine as first-line therapy
- Other treatments, which are adjunctive to epinephrine dosing

Epinephrine is the first-line treatment in all cases of anaphylaxis. All other drugs have a delayed onset of action. When there is suboptimal response to the initial dose of epinephrine, or if symptoms progress, repeat epinephrine dosing remains first-line therapy over adjunctive treatments.

The cornerstones of initial management should begin with the following *concurrent* steps:

- Elimination of additional allergen exposure
- IM injection of epinephrine
- Call for help (summon a resuscitation team in the hospital setting, call 911 or an equivalent service in the community setting), although attempts to summon help should not delay use of epinephrine

These actions should be quickly followed by these additional steps:

- Placement of the patient in a recumbent position (if tolerated), with the lower extremities elevated
- Provision of supplemental oxygen
- Administration of intravenous (IV) fluid (volume resuscitation)

TABLE II. Summary of the pharmacologic management of anaphylaxis (modified)

Note: These treatments often occur concomitantly, and are not meant to be sequential, with the exception of epinephrine as first-line treatment.

In the outpatient setting

- First-line treatment:
 - Epinephrine, IM; auto-injector *or* 1:1,000 solution
 - Weight 10 to 25 kg: 0.15 mg epinephrine autoinjector, IM (anterior-lateral thigh)
 - Weight >25 kg: 0.3 mg epinephrine autoinjector, IM (anterior-lateral thigh)
 - Epinephrine (1:1,000 solution) (IM), 0.01 mg/kg per dose; maximum dose, 0.5 mg per dose (anterior-lateral thigh)
 - Epinephrine doses may need to be repeated every 5-15 minutes
- Adjunctive treatment:
 - Bronchodilator (β_2 -agonist): albuterol
 - MDI (child: 4-8 puffs; adult: 8 puffs) *or*
 - Nebulized solution (child: 1.5 ml; adult: 3 ml) every 20 minutes or continuously as needed
 - H₁ antihistamine: diphenhydramine
 - 1 to 2 mg/kg per dose
 - Maximum dose, 50 mg IV or oral (oral liquid is more readily absorbed than tablets)
 - Alternative dosing may be with a less-sedating second generation antihistamine
 - Supplemental oxygen therapy
 - IV fluids in large volumes if patient presents with orthostasis, hypotension, or incomplete response to IM epinephrine
 - Place the patient in recumbent position if tolerated, with the lower extremities elevated

In the hospital-based setting

- First-line treatment:
 - Epinephrine IM as above, consider continuous epinephrine infusion for persistent hypotension (ideally with continuous non-invasive monitoring of blood pressure and heart rate); alternatives are endotracheal or intra-osseous epinephrine
- Adjunctive treatment:
 - Bronchodilator (β_2 -agonist): albuterol
 - MDI (child: 4-8 puffs; adult: 8 puffs) *or*
 - Nebulized solution (child: 1.5 ml; adult: 3 ml) every 20 minutes or continuously as needed
 - H₁ antihistamine: diphenhydramine
 - 1 to 2 mg/kg per dose
 - Maximum dose, 50 mg IV or oral (oral liquid is more readily absorbed than tablets)
 - Alternative dosing may be with a less-sedating second generation antihistamine
 - H₂ antihistamine: ranitidine
 - 1 to 2 mg/kg per dose
 - Maximum dose, 75 to 150 mg oral and IV
 - Corticosteroids
 - Prednisone at 1 mg/kg with a maximum dose of 60 to 80 mg oral *or*
 - Methylprednisolone at 1 mg/kg with a maximum dose of 60 to 80 mg IV
 - Vasopressors (other than epinephrine) for refractory hypotension, titrate to effect
 - Glucagon for refractory hypotension, titrate to effect
 - Child: 20-30 μ g/kg
 - Adult: 1-5 mg
 - Dose may be repeated or followed by infusion of 5-15 μ g/min
 - Atropine for bradycardia, titrate to effect
 - Supplemental oxygen therapy
 - IV fluids in large volumes if patients present with orthostasis, hypotension, or incomplete response to IM epinephrine
 - Place the patient in recumbent position if tolerated, with the lower extremities elevated

Therapy for the patient at discharge

- First-line treatment:
 - Epinephrine auto-injector prescription (2 doses) and instructions
 - Education on avoidance of allergen
 - Follow-up with primary care physician
 - Consider referral to an allergist
- Adjunctive treatment:
 - H₁ antihistamine: diphenhydramine every 6 hours for 2-3 days; alternative dosing with a non-sedating second generation antihistamine
 - H₂ antihistamine: ranitidine twice daily for 2-3 days
 - Corticosteroid: prednisone daily for 2-3 days

IM, Intramuscular; IV, intravenous; MDI, metered-dose inhaler.

Note: This table is presented as Table VI in the Guidelines.

In summary: The use of antihistamines is the most common reason reported for not using epinephrine and may place a patient at significantly increased risk for progression toward a life-threatening reaction.

6.3.2. Treatment of refractory anaphylaxis. No published prospective studies exist on the optimal management of refractory anaphylactic shock. Repeated use of epinephrine, as well as IV fluids, corticosteroids, and vasopressor agents, may be needed. Prompt transfer to an acute-care facility and intensive-care unit for treatment and monitoring is essential.

6.3.3. Possible risks of acute therapy for anaphylaxis. There are no absolute contraindications to epinephrine use in anaphylaxis. However, there are subgroups of patients who might theoretically be at higher risk for adverse effects during epinephrine therapy. Because the risk of death or serious disability from anaphylaxis itself usually outweighs other concerns, existing evidence clearly favors the benefit of epinephrine administration in most situations. Some level of decision making regarding the risk-to-benefit ratio may be warranted for patients under specific circumstances (described in the Guidelines).

6.3.4. Treatment to prevent biphasic or protracted food-induced allergic reactions. Very little information exists that defines the mechanism of biphasic or protracted allergic reactions. Similarly, little information exists to support specific therapy to prevent biphasic or protracted food-induced allergic reactions. In general, induction and recruitment of inflammatory cells and release of preformed, long-acting mediators from mast cells have been implicated as mechanisms. Due to their anti-inflammatory properties, systemic corticosteroids are often recommended to prevent biphasic or protracted food-induced allergic reactions, but little data support their use.

6.3.5. Management of milder, acute food-induced allergic reactions in health care settings. Milder forms of allergic reactions, such as flushing, urticaria, isolated mild angioedema, or symptoms of OAS, can be treated with H₁ and H₂ antihistamine medications. When antihistamines alone are given, ongoing observation and monitoring are warranted to ensure a lack of progression to more significant symptoms of anaphylaxis. If progression or increased severity is noted, epinephrine should be administered immediately. Additionally, if there is a history of a prior severe allergic reaction, epinephrine should be administered promptly and earlier in the course of treatment (for example, at the onset of even mild symptoms).

6.4. Management of food-induced anaphylaxis

Guideline 43: The EP recommends that the management of food-induced anaphylaxis should focus on the following:

- Dosing with IM epinephrine followed by transfer to an emergency facility for observation and possible further treatment
- Observation for 4 to 6 hours or longer based on severity of the reaction
- Education for patient and family on:
 - Allergen avoidance
 - Early recognition of signs and symptoms of anaphylaxis
 - Anaphylaxis emergency action plan implementation
 - Appropriate IM epinephrine administration
 - Medical identification jewelry or an anaphylaxis wallet card
- Epinephrine auto-injector prescription and training provided at the time of discharge

- Continuation of adjunctive treatment after patient discharge:
 - H₁ antihistamine: diphenhydramine every 6 hours for 2-3 days; alternative dosing with a non-sedating second generation antihistamine
 - H₂ antihistamine: ranitidine twice daily for 2-3 days
 - Corticosteroid: prednisone daily for 2-3 days
- Follow-up appointment with primary health care professional (after the food-induced anaphylactic reaction), with consideration for additional follow-up with a clinical specialist such as an allergist/immunologist

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1. Boyce JA, Assa'ad A, Burks WA, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel. *J Allergy Clin Immunol* 2010;126(suppl 1): S1-58.

APPENDIX A. PRIMARY AUTHOR AFFILIATIONS AND ACKNOWLEDGMENTS

Primary authors

*Joshua A. Boyce, MD

Division of Rheumatology, Immunology and Allergy
Brigham and Women's Hospital
Department of Medicine Harvard Medical School
Boston, Mass

*Amal Assa'ad, MD

Division of Allergy and Immunology
Cincinnati Children's Hospital Medical Center
University of Cincinnati
Cincinnati, Ohio

*A. Wesley Burks, MD

Division of Allergy and Immunology
Department of Pediatrics
Duke University Medical Center
Durham, NC

*Stacie M. Jones, MD

Division of Allergy and Immunology
Department of Pediatrics
University of Arkansas for Medical Sciences
Arkansas Children's Hospital
Little Rock, Ark

*Hugh A. Sampson, MD

Elliot and Roslyn Jaffe Food Allergy Institute
Division of Allergy and Immunology
Department of Pediatrics
Mount Sinai School of Medicine
New York, NY

*Robert A. Wood, MD

Division of Allergy and Immunology
Department of Pediatrics
The Johns Hopkins University School of Medicine
Baltimore, Md

Marshall Plaut, MD

Division of Allergy, Immunology, and Transplantation

National Institute of Allergy and Infectious Diseases National
Institutes of Health
Bethesda, Md

Susan F. Cooper, MSc

Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Md

Matthew J. Fenton, PhD

Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Md

Authors who are members of the Expert Panel are denoted with
an asterisk (*) in this list.

For additional information, please contact the National Institute
of Allergy and Infectious Diseases at daitinfo@niaid.nih.gov.

Acknowledgments

NIAID-sponsored Expert Panel

S. Hasan Arshad, MBBS, MRCP, DM, FRCP

School of Medicine
University of Southampton
Southampton, UK
The David Hide Asthma and Allergy Research Centre
St. Mary's Hospital
Newport, Isle of Wight, UK
Southampton University Hospital NHS Trust
Southampton, UK

Sami L. Bahna, MD, DrPH

Department of Pediatrics
Allergy and Immunology Section
Louisiana State University Health Sciences Center
Shreveport, La

Lisa A. Beck, MD

Department of Dermatology
University of Rochester Medical Center
Rochester, NY

Carol Byrd-Bredbenner, PhD, RD, FADA

Department of Nutritional Sciences
Rutgers University
New Brunswick, NJ

Carlos A. Camargo, Jr, MD, DrPH

Department of Emergency Medicine and Division of
Rheumatology, Allergy and Immunology
Department of Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, Mass

Lawrence Eichenfield, MD

Division of Pediatric and Adolescent Dermatology
Rady Children's Hospital
San Diego, Calif
Departments of Pediatrics and Medicine

University of California, San Diego
San Diego, Calif

Glenn T. Furuta, MD

Section of Pediatric Gastroenterology, Hepatology, and
Nutrition
Digestive Health Institute
Children's Hospital Denver
Aurora, Colo
Department of Pediatrics
National Jewish Health
Denver, Colo
Department of Pediatrics
University of Colorado Denver School of Medicine
Aurora, Colo

Jon M. Hanifin, MD

Department of Dermatology
Oregon Health and Science University
Portland, Ore

Carol Jones, RN, AE-C

Asthma Educator and Consultant
Allergy and Asthma Network
Mother's of Asthmatics
McLean, Va

Monica Kraft, MD

Division of Pulmonary, Allergy and Critical Care Medicine
Department of Medicine
Duke University Medical Center
Durham, NC

Bruce D. Levy, MD

Partners Asthma Center
Pulmonary and Critical Care Medicine Division
Brigham and Women's Hospital and Harvard Medical School
Boston, Mass

Phil Lieberman, MD

Division of Allergy and Immunology
Department of Medicine
University of Tennessee
College of Medicine
Memphis, Tenn

Stefano Luccioli, MD

Office of Food Additive Safety
US Food and Drug Administration
College Park, Md

Kathleen M. McCall, BSN, RN

Children's Hospital of Orange County
Orange, Calif

Lynda C. Schneider, MD

Division of Immunology
Children's Hospital Boston
Boston, Mass

Ronald A. Simon, MD

Division of Allergy, Asthma and Immunology
Scripps Clinic
San Diego, Calif

F. Estelle R. Simons, MD

Departments of Pediatrics and Child Health and Immunology
Faculty of Medicine
University of Manitoba
Winnipeg, Manitoba, Canada

Stephen J. Teach, MD, MPH

Division of Emergency Medicine
Children's National Medical Center
Washington, DC

Barbara P. Yawn, MD, MPH, MSc

Department of Research
Olmsted Medical Center
Rochester, Minn
Department of Family and Community Health
University of Minnesota
School of Medicine
Minneapolis, Minn

NIAID staff**Julie M. Schwaninger, MSc**

Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Md

APPENDIX B. LIST OF ABBREVIATIONS

AAP: American Academy of Pediatrics
ACIP: Advisory Committee on Immunization Practices
AD: Atopic dermatitis
AP: Allergic proctocolitis
APT: Atopy patch test
CC: Coordinating Committee
COI: Conflict of interest
EoE: Eosinophilic esophagitis
EP: Expert Panel
FA: Food allergy
FPIES: Food protein-induced enterocolitis syndrome
GI: Gastrointestinal
GRADE: Grading of Recommendations Assessment, Development and Evaluation
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
IM: Intramuscular
IV: Intravenous
MDI: Metered-dose inhaler
MMR: Measles, mumps, and rubella
MMRV: Measles, mumps, rubella, and varicella
NIAID: National Institute of Allergy and Infectious Diseases
OAS: Oral allergy syndrome
sIgE: Allergen-specific IgE
SPT: Skin prick test