CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Food Allergy

Stacie M. Jones, M.D., and A. Wesley Burks, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

From the Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock (S.M.J.); and the Department of Pediatrics, University of North Carolina, Chapel Hill (A.W.B.). Address reprint requests to Dr. Burks at the University of North Carolina School of Medicine, Department of Pediatrics, 4032 Bondurant Hall, Campus Box 7000, Chapel Hill, NC 27599-7000, or at wburks@email.unc.edu.

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An 18-year-old basketball player with a known peanut allergy and moderate, persistent, controlled asthma has just played in a collegiate game. Cough, shortness of breath, and sneezing develop 10 minutes after he ingests a homemade sugar cookie at a party after the game. He immediately takes 50 mg of diphenhydramine, but hoarseness, throat tightness, worsening shortness of breath, rhinorrhea with copious clear mucus, and repetitive emesis continue to progress. He then administers 0.30 mg of epinephrine with the use of an autoinjector into his upper lateral thigh and four actuations of an albuterol inhaler (at a dose of 90 μg per actuation). The use of these agents results in immediate relief of the throat tightness and full resolution of the other symptoms within 15 minutes. What would you advise at this point? Could his symptoms have been prevented?

THE CLINICAL PROBLEM

IgE-mediated food allergy is a global health problem that affects millions of persons and multiple aspects of a person's life.[1,2] Prevalence rates are uncertain, but food allergy is estimated to affect 15 million Americans — approximately 4% of children and 1% of adults — and studies suggest an increased prevalence in the past two decades.[1-4] Food allergy probably results from a breakdown of or a delay in the development of oral tolerance, or a lack of clinical reactivity to a food substance, in persons who are genetically and possibly environmentally predisposed to the development of atopic disease.[5] Eight foods (milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish) are the most common food allergens in the United States.[1] Peanut allergy is typically lifelong; fewer than 20% of persons who receive a diagnosis in childhood outgrow the allergy. In contrast, milk and egg allergy is typically outgrown by school age.[8]

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Peanut allergy, which affects approximately 1% of persons in the United States, is the leading cause of fatal and near-fatal anaphylaxis.[6,7] Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death[9]; it involves multiple organ systems, including the respiratory tract, gastrointestinal tract, and skin (Table 1).[9] Risk factors that are most strongly associated with fatal or near-fatal anaphylaxis (Table 2) include the type of allergenic food, adolescence or young adulthood, the presence of concomitant asthma, and the delayed use of or lack of access to an epinephrine autoinjector.[6,9] In addition, several factors, including exercise, viral infections, menses, emotional stress, and alcohol consumption, place some persons at increased risk by lowering the reaction threshold after exposure to an allergen.[11]

KEY CLINICAL POINTS

FOOD ALLERGY

- Food allergy, which affects 15 million Americans, has a substantial effect on many aspects of daily living.
- Peanuts are the most common food allergen associated with fatal and near-fatal anaphylaxis.
- Obtaining an appropriate medical history and collaborating with an allergist to interpret the results of clinical tests are important for the diagnosis and management of food allergy.
- Medical management currently focuses on the following: recognition of signs and symptoms of anaphylaxis; ready availability of an epinephrine autoinjector, with early use when signs or symptoms of anaphylaxis are present, followed by immediate evaluation in an emergency facility for monitoring after use; strict avoidance of culprit food allergens; and education about safe food products.
- Early introduction of peanuts in the first year of life in many children reduces the risk of peanut allergy considerably.

Table 1. Diagnostic Criteria for Anaphylaxis.*

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled
Criterion 1
Onset of an illness within minutes to several hours after possible exposure to an allergen, with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, or swollen lips, tongue, or uvula) and at least one of the following signs or symptoms:
Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia or collapse, syncope, or incontinence)
Criterion 2
Two or more of the following signs or symptoms that occur rapidly (within minutes to several hours) after exposure to a likely allergen:
Involvement of the skin or mucosal tissue (e.g., generalized hives, itching or flushing, or swollen lips, tongue, or uvula)
Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
Reduced blood pressure or associated symptoms of hypotension (e.g., hypotonia or collapse, syncope, or incontinence)
Persistent gastrointestinal symptoms (e.g., crampy abdominal pain or vomiting)
Criterion 3
Reduced blood pressure within minutes to several hours after exposure to a known allergen:
Infants and children: low systolic blood pressure (age-specific) or >30% decrease in systolic blood pressure
Adults: systolic blood pressure of <90 mm Hg or >30% decrease from the person's baseline blood pressure

* Data are from Berin.[10]

Food allergy–associated anaphylaxis is an IgE-mediated reaction. In a previously sensitized person with food-specific IgE on mast cells and basophils, the food allergen is ingested and absorbed into the local tissue and then cross-links IgE, resulting in immediate release of preformed mediators.[1,10,12] This immune response is rapid; the onset of symptoms typically occurs within 5 to 60 minutes after exposure to the food.

An anaphylactic reaction requires the involvement of multiple organ systems (Table 1), and it may rapidly progress to severe symptoms (e.g., hypotension or respiratory collapse) and death.[9] Although cutaneous manifestations such as hives and pruritus are the most common, they are absent in 20% of persons who have anaphylaxis. Thus, a high index of suspicion is required when other signs and symptoms such as cough, wheezing, laryngeal edema, vomiting, diarrhea, and hypotension are present.

STRATEGIES AND EVIDENCE

EVALUATION

The most important step in diagnosing a food allergy is obtaining a thorough medical history

Table 2. Risk Factors for Food-Induced Anaphylaxis.

Risks associated with fatal and near-fatal food-induced anaphylaxis
Most common risk factors
Delayed treatment with epinephrine
Allergy to peanuts, tree nuts, fish, or shellfish
Adolescence or young adulthood
Asthma
Other risk factors
Cardiovascular disease in middle or older age
Pregnancy
Absence of skin symptoms during reaction
Coexisting conditions and factors associated with increased risk of food-induced anaphylaxis or increased severity of reaction
Asthma
Chronic lung disease
Systemic mastocytosis
Use of beta-adrenergic blocker, angiotensin-converting–enzyme inhibitor, or alpha-adrenergic blocker

that includes the type of food ingested, the type of symptoms, and the timing of the reaction.[1,13] Testing typically includes a skin-prick test for allergen-specific IgE, in vitro allergen-specific IgE tests, or both. If used alone and without a medical history, these tests have a greater than 90% negative predictive value but an approximately 50% positive predictive value.

Oral food challenges are indicated when the clinical history and testing do not indicate a high likelihood that the person has a food allergy. Since many food allergies are outgrown later in life, food challenges are most often used to establish that the person is no longer allergic to the culprit food.

PREVENTION

The Learning Early About Peanut Allergy (LEAP) trial and follow-up studies tested the hypothesis that regular consumption of peanut-containing products, when started during infancy, would elicit a protective immune response (instead of an allergic immune reaction) that would be sustained over time.[14,15] In the LEAP trial, 640 children who were 4 to 11 months of age and who were at high risk for peanut allergy (i.e., those who had severe atopic dermatitis, egg allergy, or both) were randomly assigned to consume peanuts or to avoid them until 5 years of age. Children in the consumption group ate a food containing peanuts at least three times weekly.

The rate of peanut allergy by 5 years of age was only 1.9% among children who ate peanuts, as compared with 13.7% among those who avoided peanuts. Overall, sustained consumption of peanuts beginning in the first 11 months of life was highly effective in preventing the development of peanut allergy. On the basis of these results, new dietary guidelines recommend the introduction of peanuts in the first 4 to 6 months of life.[16]

MANAGEMENT

The current management of peanut allergy and other food allergies involves dietary and medical management, ongoing education, and scheduled follow-up (Table 3).[1] Strict avoidance of food allergens requires continual vigilance before ingestion. This vigilance includes reading and interpreting labels, avoiding cross-contamination, and communicating with other persons who are preparing foods (e.g., in restaurants and school cafeterias).[17]

Medical intervention is focused on the availability of epinephrine as the initial drug of choice for treatment of food-induced anaphylaxis.[1] Epinephrine is the most effective treatment to prevent death from anaphylaxis, but it has a short half-life (minutes) and often requires a second dose for treatment of persistent or recurrent symptoms.[18] Despite its recognized benefit in preventing fatal anaphylaxis, epinephrine continues to be vastly underprescribed and underutilized by health care providers and patients, whereas antihistamines are commonly overused in treating reactions.[18,19] The use of epinephrine earlier in the development of anaphylactic symptoms would most likely prevent more serious reactions and complications.[18] Medications such as antihistamines, glucocorticoids, and inhaled beta-agonists are considered to be adjunctive medications that are used to reduce symptoms, but they should not be used as first-line treatment for anaphylaxis.[1,20,21] The most common reason for morbidity in systemic allergic reactions is that epinephrine is not administered early in the course of the allergic reaction.

Guidelines for the management of food-induced anaphylaxis recommend activation of the local emergency medical services system for

Table 3. Management of Food Allergy.

Strategy	Standard Management	Additional Strategies
Diet	Strict avoidance of culprit foods	Some limited forms of food (e.g., baked products containing milk and egg) may be safely consumed, but this safety must be confirmed clinically with a medically observed feeding or food challenge
Medication	First-line treatment: epinephrine administered with the use of an autoinjector	Adjunctive treatment: antihistamines, beta-agonists, glucocorticoids
Education	Education on label reading, cross-contamination, cross-contact, access to safe foods, and use of medical-alert jewelry; creation of patient-specific action plan for food allergy anaphylaxis	Information provided in schools, workplaces, restaurants, and the food service industry; change in labeling laws for food industry
Scheduled clinical follow-up	Planned follow-up with provider who has experience in treating food allergies (may include allergist); ongoing education, including review of technique for administering epinephrine and use of anaphylaxis action plan; evaluation for resolution of allergy or change in disease with management of coexisting conditions; review of therapeutic plan	Review of emerging treatment options; consideration of participation in clinical trials if applicable

transport of the person to an emergency facility once anaphylaxis occurs, epinephrine is administered, or both. Owing to the potential for biphasic or protracted reactions that can occur 4 to 24 hours after the initial reaction in 10 to 15% of persons, immediate evaluation in an emergency medical facility, with close observation for 4 to 6 hours or longer according to the severity of the reaction or if additional symptoms develop, is recommended.[1]

Currently, no proactive specific treatment is available for persons with food allergy. However, during the past decade, substantial progress has been made toward the development of allergen-specific immunotherapy for food allergy.[22] Scientific investigation and recent clinical trials have focused on three major forms of treatment (oral, sublingual, and epicutaneous immunotherapy), each of which targets a different aspect of the mucosal surface. All these treatments remain experimental.[23] These therapies have a tremendous safety advantage over traditional subcutaneous immunotherapy[24,25] and newer forms of mucosal immunotherapy[26] that have been associated with high rates of serious side effects and have been dismissed as potential treatment options in their current forms.

In order to understand the effects of emerging therapies for food allergy, an understanding of the definitions of clinical desensitization, sustained unresponsiveness, and oral tolerance is essential.[23] "Desensitization" is defined as an increase in the reaction threshold to a food allergen during active therapy; this increase provides some protection from accidental ingestions. Desensitization is achieved after only months of therapy and requires ongoing therapy.

"Sustained unresponsiveness," which is defined as a lack of a clinical reaction to a food allergen after active therapy has been discontinued, requires some level of continued exposure to the allergen to maintain the unresponsive state. Achievement of sustained unresponsiveness requires years of therapy and has been seen only in subgroups of persons.[27,28]

"Oral tolerance," which is used to describe a specific type of immunologic response that does not produce any clinical reactivity after ingestion of a food allergen, typically occurs naturally early in life.[5] Current data suggest that true immunologic and clinical tolerance in patients who have received experimental immunotherapies for food allergy is unlikely to develop; this point is important in understanding the clinical outcomes and potential future implications of immunotherapy.

Table 4. Immunotherapies under Investigation in Clinical Trials for Treatment of Food Allergy.

Feature	Oral Immunotherapy	Sublingual Immunotherapy	Epicutaneous Immunotherapy
Form of study product (protein dose)	Allergen powder (300–4000 mg per day)	Allergen extract drops (2–7 mg per day)	Allergen patch (100–500 μg per day)
Clinical effect			
Desensitization	Large effect	Moderate-to-small effect	Variable effect
Sustained unresponsiveness	Occurs in subgroups of persons	Not known (studies under way)	Not known
Side effects	Oral or gastrointestinal; potential for anaphylaxis in persons with fever, infection, or menses and during exercise after receipt of a dose of oral immunotherapy	Oral or pharyngeal (local effects)	Skin (local effects)
Immune modulation: antibody and cellular changes	Substantial	Small or moderate	Small or moderate

Oral Immunotherapy

The use of oral immunotherapy (Table 4) against a variety of food allergens has been studied, but most randomized, controlled trials have focused on oral immunotherapy for the treatment of peanut, milk, and egg allergies.[22,28-35] This form of immunotherapy, which can be administered over a period of years, requires daily ingestion of an allergen powder (e.g., peanut protein) mixed with another food. The initial dose of peanut protein is measured in micrograms, building up to reach maintenance doses ranging from 300 to 4000 mg of peanut protein.

Oral immunotherapy has resulted in the highest rates of desensitization and sustained unresponsiveness of all therapies studied as of this writing, but it is also associated with a risk of serious adverse events, including episodic anaphylaxis, eosinophilic esophagitis (among <5% of participants in clinical trials of oral immunotherapy), and dose-limiting gastrointestinal side effects (among approximately 20% of the trial participants).[36,37] Oral immunotherapy may be associated with a higher risk of adverse events and a lower effectiveness in persons with seasonal allergies than in those with food allergies who do not have seasonal allergies.[38] In addition, in persons with a viral illness or menses and in those who exercise within minutes to 2 hours after receiving an oral dose of immunotherapy, reductions in the amounts of allergenic protein used in oral immunotherapy are frequently required to maintain safety.[11,30] Adjunctive therapy with omalizumab, a monoclonal anti-IgE antibody, during the induction stages of treatment has proved to be beneficial in reducing short-term side effects, but studies have not shown that the use of this agent has a major influence on eventual outcomes.[39-41]

Sublingual Immunotherapy

The use of sublingual immunotherapy has been evaluated in clinical trials for the treatment of peanut allergy and allergies to a few other foods. It requires the application of an allergen extract under the tongue on a daily basis for a period of years, with doses ranging from 2 to 7 mg of protein. Sublingual immunotherapy leads to clinical desensitization in most people after 1 year of treatment and to moderate immunologic changes; data are limited from longer-term studies of sustained unresponsiveness.[42-46] This form of immunotherapy has few side effects and minimal adverse effects, which are typically limited to oropharyngeal itching or tingling.

Epicutaneous Immunotherapy

Epicutaneous immunotherapy, which has been investigated for the treatment of peanut and milk allergy, involves application of an allergen patch to the back or upper arm at 24-hour intervals, with doses ranging from 250 to 500 μg of protein. Therapy can continue over a period of years.[47-49] Epicutaneous immunotherapy for peanut allergy is associated with some benefit in clinical desensitization after 1 year of treatment in children, especially those who are 4 to 11 years of age. It has been associated with only modest

desensitization and immunologic changes, and it has not been associated with sustained unresponsiveness.[49] Epicutaneous immunotherapy is associated with minimal adverse effects, with only mild skin irritation at the patch site in most persons, and no systemic allergic reactions have been reported as of this writing.[48,49]

Of the three forms of immunotherapy, the greatest likelihood of clinical desensitization and also the highest frequency of adverse events occur with the use of oral immunotherapy. Sublingual immunotherapy is associated with a lower likelihood and frequency than oral immunotherapy. Epicutaneous immunotherapy is associated with the lowest likelihood of clinical desensitization and the lowest frequency of adverse events.[22,50]

AREAS OF UNCERTAINTY

A recent National Academy of Medicine report, "Finding a Path to Safety in Food Allergy," outlines the difficulties in stating the true prevalence of food allergy.[2] In studies in which participants report having received a diagnosis of food allergy, the prevalence of food allergy among adults is at least 15%, whereas in well-defined studies, the prevalence is 4% among children and 1% among adults. Although most physicians and public health and school administrators would attest to the increase in numbers of persons with food allergy, data are lacking from systematic studies with a sufficient sample size, and in various populations, to determine the true prevalence.[2]

The apparent increases in the prevalence of food allergy and overall allergic disease are unexplained. Changing practices in food manufacturing (e.g., alterations in the production of processed foods), decreases in microbial exposure early in life, and the changing microbiome are speculated to contribute to increases in the prevalence of allergic disease.[5,51,52]

Clear and accurate diagnostic testing in patients with food allergy remains a challenge. The emergence of recombinant testing such as allergen component testing or DNA testing has allowed for broader testing, but its role in clinical practice remains unclear owing to difficulty with interpretation of test results in persons with multiple allergic sensitivities (e.g., those with a pollen allergy or additional food allergies). Additional biomarkers of disease activity and severity are needed to improve diagnostic accuracy.

Regulatory policies for food labeling, including statements such as "may contain" or "manufactured in the same plant as," which are intended to minimize acute allergic reactions, often produce more confusion and anxiety than benefit.[53,54] Efforts to define minimal reaction thresholds for food allergens are under way and may guide the development of improved policies for food manufacturing, preparation, and labeling.

Questions remain about the best management of food allergy, both in the short term and long term. With respect to epinephrine autoinjectors, there are few data on the potential for alternative routes of delivery (intramuscular vs. sublingual or inhaled), the need for the availability of additional doses (currently the doses in the United States are 0.15 mg and 0.30 mg), consideration of an alternative needle length or injection site for severely overweight or underweight persons, determination of best practice for the appropriate number of autoinjectors prescribed per patient, and clear guidelines regarding which persons should receive a prescription for an autoinjector.

Substantial knowledge gaps also remain with respect to the use of immunotherapy in the management of food allergy.[55,56] Most clinical trials have been small and have involved primarily homogeneous populations. Phase 3 clinical trials of oral and epicutaneous immunotherapy for the treatment of peanut allergy are ongoing. Longer-term data regarding the effectiveness of immunotherapy are limited to a small number of studies assessing sustained unresponsiveness after successful treatment with immunotherapy for peanut, egg, or milk allergy.[28,32]

Other forms of allergen-specific and allergen-nonspecific treatment have been studied or are in various stages of development, including Chinese herbal therapy; probiotic treatment, prebiotic treatment, or both; recombinant protein-based, peptide-based, or epitope-based immunotherapy; and anti-IgE therapy. If any of these immunotherapies is approved, clinicians will need to decide on an individual patient basis between careful avoidance (with the potential risk of inadvertent exposure) and the use of immunotherapy with potentially adverse effects and an

uncertain duration of effectiveness without ongoing treatment.[57]

GUIDELINES

Recommendations are outlined in the U.S.[1] and European[20] guidelines for the diagnosis and management of food allergy. Disease-specific practice guidelines and position statements regarding food allergy and anaphylaxis are also available.[9,21]

In addition, important findings noted above in the LEAP trial and follow-up studies in the United Kingdom[14,15] have resulted in the dissemination of updated dietary recommendations for the prevention of peanut allergy. These recommendations classify infants into three categories according to risk.[16] In infants with the highest risk — those with severe eczema, egg allergy, or both — allergy testing should be performed and, if appropriate according to their development and feeding abilities, peanuts then should be introduced in these infants at as early as 4 to 6 months of age. In infants with mild-to-moderate eczema, who are also at increased risk for peanut allergy, peanuts should be introduced at approximately 6 months of age, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy. In infants without an increased risk (i.e., those who do not have eczema or a food allergy), peanuts can be introduced freely into the diet with other solid foods and in accordance with family preferences and cultural practices.

CONCLUSIONS AND RECOMMENDATIONS

The young man described in the vignette had an anaphylactic reaction after eating a cookie. He was at high risk for illness and death owing to his peanut allergy, age, risk-taking behavior (i.e., eating food without investigating its ingredients or cross-contamination), and concomitant asthma.

Persons with food allergy should be educated and reminded to ask about food ingredients and preparation to avoid cross-contamination and to avoid ingestion when this information is not known. They should be instructed regarding the immediate use of intramuscular epinephrine if symptoms or signs suggest an impending systemic anaphylactic reaction, and they should be informed about the need to immediately seek medical care after they administer epinephrine. If food-allergen immunotherapy is ultimately approved by the Food and Drug Administration, such treatment would warrant consideration in such persons, although there are limited data regarding long-term effectiveness.

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