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AAAAI Work Group Report: Current Approach to the Diagnosis and Management of Adverse Reactions to Foods

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The statement below is not to be construed as dictating an exclusive course of action nor is it intended to replace the medical judgment of healthcare professionals. The unique circumstances of individual patients and environments are to be taken into account in any diagnosis and treatment plan. This statement reflects clinical and scientific advances as of the date of publication and is subject to change.

Prepared by the AAAAI Adverse Reactions to Foods Committee (Scott H. Sicherer, M.D., Chair and Suzanne Teuber, M.D., Co-Chair)

Purpose: To provide a brief overview of the diagnosis and management of adverse reactions to foods.

Database: Recent review articles by recognized experts, consensus statements, and selected primary source documents.

Definitions
"Adverse food reaction" is a broad term indicating a link between an ingestion of a food and an abnormal response.

Reproducible adverse reactions may be caused by: a toxin, a pharmacological effect, an immunological response, or a metabolic disorder.

Food allergy is a term that is used to describe adverse immune responses to foods that are mediated by IgE antibodies that bind to the triggering food protein(s); the term is also used to indicate any adverse immune response toward foods (e.g., including cell mediated reactions).

Sensitization indicates demonstrable IgE antibody to a food but does not equate with clinical food allergy.

Epidemiology
Food allergy is more common in infants/children (~6% under age 3 years) than in adults (~2%) and appears to be increasing in prevalence.

Childhood food allergies to cow's milk, egg, wheat and soy are most often outgrown (~85% by age 5 years) while allergy to peanut, tree nuts and seafood are not commonly outgrown.

Severe and fatal reactions can occur at any age and even upon first known exposure to a food, but those at greatest risk for fatal food-induced anaphylaxis appear to be adolescents and young adults with asthma and a known food allergy to peanut, tree nut or seafood.

Adverse reactions to food additives (e.g., non-protein colors and preservatives) appears to be uncommon (<1%).

Virtually any food can trigger an allergic response.

The epidemiology of food allergy is influenced by cultural and geographical dietary influences. In US studies of young children, egg, cow's milk, peanut, wheat and soybean account for the majority (~90%) of significant reactions; for adults, peanuts, nuts from trees (e.g., walnut, Brazil nut, cashew), fish and shellfish account for the majority of significant reactions. Seeds such as sesame seem to be an emerging allergen.

Food allergy is partly genetically determined and often associated with a personal or family history of atopic disease.

Homologous proteins, or homologous glycan structures present on glycoproteins, among animal foods, plant foods, and between foods and certain airborne allergens may account for cross-sensitization that is sometimes clinically relevant. While variable, clinically-relevant cross-reactivity is more common (>20%) among related fruits (e.g. Rosaceae family), tree nuts, mammalian milks, and seafood than among grains and legumes.

Clinical manifestations
Clinical manifestations vary by disease pathophysiology, host factors, quantity of food ingested, ancillary factors (e.g., exercise, intake of other foods/alcohol) and may also vary in individuals over time.

Allergic reactions mediated by food-specific IgE antibodies usually result in symptoms that occur soon (on the order of minutes to 2 hours) following ingestion while cell-

mediated disorders may present with chronic symptoms or with a delayed onset (e.g., hours).

A variety of symptoms attributable to food allergy, and also clinical disorders defined by particular constellations of symptoms and/or pathophysiological responses, have been defined/described as follows:

Urticaria (and angioedema). Acute urticaria, angioedema, and flushing, are common manifestation of food allergy either alone or in combination with other symptoms. Food induced urticaria/angioedema is typically mediated by IgE antibodies. Contact urticaria describes lesions that occur at the site of direct contact with the food (that may or may not also induce a reaction when ingested). Chronic urticaria is not commonly associated with food allergy. Urticaria/flushing may be induced by means other than through binding of IgE antibodies (e.g., histamine-like chemicals in spoiled dark meat fish-scombroid poisoning).

Gastrointestinal "anaphylaxis". This term is used to describe isolated, acute gastrointestinal responses such as nausea, pain, vomiting and/or diarrhea induced by IgE-mediated mechanisms. Gastrointestinal anaphylaxis is uncommon but gastrointestinal symptoms commonly accompany other organ system manifestations of acute, IgE antibody mediated (anaphylactic) reactions to foods.

Pollen-food syndrome (oral allergy syndrome). Initial sensitization to pollen proteins may result in symptoms when homologous proteins in particular fruits/vegetables are ingested (e.g., ragweed associated with melons, birch pollen with Rosaceae fruits such as peach, apple). A sizeable proportion of pollen-allergic persons may be affected (~25-50%). Symptoms are usually limited to the oropharynx with pruritus and mild angioedema, but progression to a systemic reaction may occur. Causal proteins are presumably heat-labile since cooking the food typically abolishes reactions. The disorder must be distinguished from mild oral reactions to stable proteins and oral reactions that may be a first symptom of a more progressive allergic response. The selfsame foods causing this oral syndrome may induce systemic reactions in persons reactive to stable proteins in them (e.g., lipid transfer proteins).

Asthma. Isolated, chronic lower respiratory responses (asthma) are uncommonly caused by food allergy (ingestion of a food) but wheezing may be part of multi-organ system reactions. Inhalation of airborne allergenic proteins may induce respiratory reactions (e.g., seafood particles airborne during heating).

Anaphylaxis. Food is a common cause of anaphylaxis, an IgE antibody-mediated, systemic, often multi-organ system reaction. Fatal food-induced anaphylaxis may occur sometimes without skin symptoms and may follow a biphasic course with initial symptoms waning with recurrence of severe symptoms approximately 1-2 hours later. In some cases, anaphylaxis only occurs if exercise follows ingestion of the causal food

(food-associated, exercise-induced anaphylaxis) or more rarely with exercise after any meal.

Atopic dermatitis. Approximately 1 in three young children with moderate to severe atopic dermatitis has food allergy. Removal of triggering foods may improve the skin condition. IgE antibody-mediated mechanisms are typically involved, but a small subset of patients may react to foods to which IgE antibody is not detectable.

Contact dermatitis. Delayed type hypersensitivity skin reactions may occur from contact with foods in handling.

Dermatitis herpetiformis. A papulovesicular skin rash associated with Celiac disease caused by an immune response to gluten.

Allergic eosinophilic esophagitis/gastroenteritis. A group of disorders characterized by eosinophilic inflammation in the gastrointestinal tract. Symptoms overlap those of other gastrointestinal disorders and may include dysphagia, vomiting, diarrhea, obstruction, and malabsorption. A subset of patients are food-responsive, although implicated foods may or may not be associated with evidence of IgE antibody.

Food protein-induced proctocolitis. A disorder of infants characterized by mucous and blood in stools. Patients are breast-fed infants and the bleeding usually resolves with maternal exclusion of cow's milk. The disorder is generally not associated with detectable IgE antibody to milk and resolves by age 1 to 2 years.

Food protein-induced enterocolitis. Primarily a disorder of infants, it is characterized by a symptom complex of profuse vomiting and diarrhea (usually heme-positive), leading to failure to thrive, and potentially dehydration and shock during chronic ingestion of the causal protein. These infants also may develop acidemia and methemoglobinemia and present with a sepsis-like picture. Cow's milk and soy are most often responsible but grains are an increasingly recognized trigger. Ingestion of the causal protein after resolution of symptoms may lead to a delayed (about 2 hour) recurrence of symptoms that may be severe and include shock. IgE to the causal foods is typically not detectable.

Food protein-induced enteropathy. Features may include diarrhea, poor growth and edema due to hypoproteinemia caused by malabsorption. Enteropathy syndromes attributed to cow's milk protein usually resolve in 1-2 years. Celiac disease, a specific type of enteropathy, is caused by immune reactions to gluten (e.g., wheat, rye, barley) and is often associated with the HLA DQ2 haplotype and does not resolve. These disorders are not associated with IgE antibody to the causal proteins.

Food-induced pulmonary hemosiderosis. Heiner's syndrome describes a cow's milk-induced symptom complex of anemia, pulmonary infiltrates, recurrent pneumonia, poor and growth associated with precipitating (IgG) antibodies to cow's milk.

Several additional disorders have been attributed to food allergy in at least a subset of patients including: reflux, infantile colic, severe constipation.

Several disorders have not been convincingly or commonly linked to food allergy despite some comment in the literature including: behavioral symptoms, arthritis, headache.

Diagnosis

The clinician must consider if the problem under evaluation is consistent with an adverse reaction to food and, if so, determine the food(s) involved. If the disorder/reaction is consistent with an adverse reaction to food, a determination about possible pathophysiology (pharmacologic, toxic, immunological, metabolic) should be considered. The history is the key element in making the aforementioned determinations and a dietary diary may be helpful. The selection of particular additional tests follows from the potential pathophysiological cause of the problem and the importance of securing a diagnosis.

The physical examination may reveal features that signify an increased likelihood of an atopic disposition (e.g., atopic dermatitis) that may increase the risk that a food allergy is present or discount food allergy as a likely cause of the problem under evaluation.

The use of prick skin tests (PST) and/or serum tests for food-specific IgE antibodies is indicated to evaluate the role of specific foods in disorders that are associated with this pathophysiology (or to confirm that a disorder is not IgE antibody mediated in some cases).

Intradermal tests with foods are not recommended because they are overly sensitive (increased rates of false positive) and potentially dangerous.

The capability of a test for specific IgE antibody to confirm or refute a specific clinical reaction is dependant upon: the prior probability that a specific food would cause the problem under evaluation (based upon epidemiological and historical variables), and the intrinsic properties of the test (sensitivity and specificity).

Tests for specific IgE are highly sensitive (generally >90%) but only modestly specific (~50%) in regard to clinical reactivity. That is, a negative test is very good at confirming that an IgE mediated reaction would not occur. However, a positive test (defined, for example, as a 3 mm wheal on PST) may not signify a high likelihood of a clinical reaction. However, the interpretation is influenced by the prior probability that the food is causal. Therefore, the tests are well suited for use when suspicion of a particular food or foods is high, but are poor for the purpose of screening (e.g., using large panels of tests without consideration of likely causes).

The intrinsic predictive properties of the PST and serum IgE tests may be influenced by the quality of the test reagents (extracts, influence of homologous proteins among food extracts), and techniques used (e.g., assay types, skin test devices, location of test

placement, mode of measurement). These aspects must be appreciated in test interpretation. For example, commercial extracts may lack labile proteins that are relevant for evaluation of reactions to raw fruits/vegetables.

Recent studies indicate that increasingly higher concentrations of food-specific IgE antibodies (reflected by increasingly larger skin test size and/or higher concentrations of serum food-specific IgE antibody) correlates with an increasing risk for a clinical reaction. Studies are emerging to evaluate more and more foods in this manner. Such data are useful to provide more specific risk assessment that a particular food would or would not cause a reaction. Such studies may indicate, for example, that above a certain skin test wheal size or food-specific IgE serum concentration, a reaction is exceedingly likely (usually the test size does not correlate very well with severity of reactions) and depending upon the clinical scenario, such data may obviate the need for an oral food challenge to confirm reactivity. However, the interpretation of the results of the studies must be used with appreciation for the patient population (age, disease) to which they may apply. For example, a a particular size skin test or concentration of food-specific IgE antibody may be more indicative of true clinical reactivity in an infant compared to the identical result in an older child/adult. Since for many allergens the skin prick test is more sensitive that serum tests, if the a priori risk of a reaction is high but a serum test is negative, it may be prudent to additionally perform a PST (if not initially performed).

A trial elimination diet (where specific potentially causal foods are eliminated or a diet is devised that is essentially devoid of significant allergenic potential) may be helpful to determine if a disorder with frequent or chronic symptoms is responsive to dietary manipulation. The length of a trial depends upon the disorder under consideration (e.g., several weeks may be needed in eosinophilic gastroenteritis). If the symptoms do not abate, the likelihood that the eliminated foods are a strong contributor to the disorder is low, but it must be considered that foods maintained in the diet may be causing symptoms, even if some of the eliminated ones were also causal. If symptoms abate and several foods were eliminated, further evaluation to disclose the causal foods (e.g., oral food challenge) may be needed.

Oral food challenges provide the most definitive means to diagnose an adverse reaction to food. The double blind, placebo-controlled oral food challenge is considered the “gold standard” to diagnose food allergy but open feedings (or single blind challenges) are adequate for screening for reactivity (that may need to be confirmed by blinded challenge if positive, particularly for subjective symptoms). Various protocols have been published but such challenges are generally undertaken under physician supervision and with emergency treatments readily available by administering gradually increasing doses of the food. Tolerance of a serving size portion of the food is generally considered evidence of lack of reactivity.

As indicated above, the natural course of food allergies indicates that tolerance may occur over time so periodic re-evaluation is appropriate, according to the type of food and clinical history.

There are a number of tests under study, some of which have shown clinical utility but are not as well studied or yet a clear, standard part of clinical practice, as are the PST and serum tests. These include the atopy patch test (performed in a manner similar to patch testing for contact sensitizers but with foods), basophil histamine release assays, and tests for IgE binding to specific epitopes.

Some tests are considered unproven in regard to the diagnosis of specific food allergies. Those for which there is no evidence of validity include provocation-neutralization, cytotoxic tests, muscle response testing (applied kinesiology), electrodermal testing, the "reaginic" pulse test and chemical analysis of body tissues. Measurement of specific IgG antibodies to foods is also unproven as a diagnostic tool.

Ancillary tests may be needed to confirm the diagnosis of adverse reactions to foods that are not immune-mediated (e.g., performance of a breath hydrogen test) or provide evidence of immune reactions to foods (e.g., intestinal biopsy).

Therapy

The primary modality for treatment of food allergy is elimination of the causal foods from the diet. In some cases, even very small amounts of the causal protein may trigger a reaction.

Elimination of the targeted allergen from the diet is a difficult undertaking that requires education about reading labels of commercial food products (that may use terms unfamiliar to the patient), special care to inquire about the ingredients if eating outside of the home (e.g., restaurants and other food services) and preparation for children regarding schools and camps. In the US, the Food Allergy and Anaphylaxis Network (www.foodallergy.org; 800-929-4040) is a lay organization that has materials that may assist in the educational process required for successful dietary elimination programs.

The key drug for treatment of severe/potentially severe food allergic reactions is epinephrine. Delayed administration of epinephrine has been associated with poor outcomes, so provision of epinephrine for self-injection is an important intervention for those who have had, or are at risk for, food-induced anaphylaxis.

There is no previously published guideline for persons to whom self-injectable epinephrine should be prescribed. Considering the indication for those at increased risk for food-induced anaphylaxis, candidates may include: persons with prior food allergic reactions involving the respiratory or cardiovascular system; those with generalized urticaria/angioedema to foods, food-allergic persons with asthma of any severity or a history of wheezing; persons with allergy to peanut, nut or seafood; and persons with food allergy and a family history of others with severe food-allergic reactions.

Patients/caregivers should be taught how and when to use self-injectable epinephrine. While administration for reactions with any significant respiratory or cardiovascular

symptom is clearly warranted, and most experts would suggest administration to persons who ingested the allergen and have a history of a previous severe reaction to it, there is not yet clear consensus on administration of epinephrine in other circumstances. Physician judgment may be individualized for reactions with milder symptoms/milder histories and may vary by numerous circumstances such as the food involved, quantity ingested, person observing the reaction when considering a child, and other factors.

Intramuscular epinephrine injected into the lateral thigh provides a more favorable absorption profile than the subcutaneous route.

Self-injectable epinephrine is currently available in doses of 0.15 and 0.3 mg. The manufacturer provides suggested weights at which these are prescribed [e.g., 33-66 lbs (15-30 kg) for the 0.15 mg dose and over 66 lbs (30 kg) for the 0.3 mg dose] but some experts suggest that doses be individualized according to weight and history to balance potential side effects. For example, 0.15 mg for 10-20 kg, 0.3 mg for those over 28 kg and individualized by history of reactions for those 20-28 kg. Individualized dosing using ampule/syringe is a possible solution for more exact dosing, but when this approach was studied, parents and even health care workers demonstrated significant errors in dosing and lack of expediency in preparing the dose. Provision of more than one injector is generally recommended since a second dose may be needed prior to arrival to a medical facility for advanced care.

Additional therapies available to the patient outside of the hospital include oral antihistamine (e.g., diphenhydramine). Short acting bronchodilators may be administered to asthmatic patients experiencing systemic reactions.

Persons who have experienced a significant allergic reaction or have used self-injectable epinephrine should be directed to emergency medical services (e.g., call “911”) so that additional therapies such as oxygen, intravenous fluids, corticosteroids, respiratory support, inotropic agents, albuterol, H-2 blockers and other additional therapies are available. Patients should be observed for biphasic reactions that usually occur within 4 hours of the reaction.

Activated charcoal given orally has been suggested as an adjunctive therapy since in vitro studies show that it binds and inactivates peanut protein. Since such treatment may prevent the action of other oral medications (e.g., antihistamines), has not yet been studied extensively in humans, may be difficult to administer and carries risks of side effects, its place in outpatient management of accidental ingestion of food allergens remains unknown and potentially counter-productive. While the results of the in vitro study suggest that it be considered as an adjunct in therapy, it seems that consideration should be given to its use during physician-directed care when oral medications are not depended upon with understanding that its efficacy has not been studied as yet in any setting.

The clinical implications of food allergens (e.g., egg, gelatin, milk proteins, seed/nut proteins, etc) in vaccines and medications have been partly explored. Egg allergy is not a contraindication for administration of the measles, mumps and rubella vaccine. Protocols to approach influenza vaccination in persons with egg allergy have been suggested.

Future directions for diagnosis and treatment

Various studies toward improved diagnostic methods are underway including: analysis of IgE binding to specific epitopes that may indicate an increased risk for clinical reactions and/or persistent allergy, analysis of mediators in stool/blood that may indicate a chronic inflammatory process, studies of in vitro T cell responses to allergens and others.

A variety of immunotherapeutic approaches using engineered proteins, specific adjuvents, and novel delivery methods are under investigation. Therapy with humanized monoclonal anti-IgE antibodies is under investigation and may prove useful to prevent reactions from accidental exposure and allow administration of otherwise allergenic proteins for immunotherapy.

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