

CME Reviews

Phenotypes and endotypes of food allergy: A path to better understanding the pathogenesis and prognosis of food allergy



Mary Grace Baker, MD; Hugh A. Sampson, MD

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

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Key Messages

- Proper identification of phenotypes and endotypes of IgE-mediated food allergy may allow for more meaningful investigation of underlying pathobiologic mechanisms that can ultimately improve our approach to treatment.
- Both phenotype and endotype are determined by genotype, inherited epigenetic factors and environmental factors.
- Proposed phenotypes and respective endotypes include: Classic (persistent, transient, food-dependent exercise-induced, NSAID-dependent, alcohol-dependent), Intermittent and Cross-Reactive, Aerosol Sensitization (local reactions to aerosolized cross-reactant antigens, systemic reactions to aerosolized forms of food-specific antigens), α -Gal syndrome and Sensitized Nonreactive.
- A formalized cluster analysis of patients with food allergy to refine phenotype and endotype identification remains an area of opportunity in our field.

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Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize the diverse pathobiologic phenomena and clinical manifestations implicated in food allergy.
- Propose a classification scheme for phenotypes and endotypes of food allergy.

Reprints: Hugh A. Sampson, MD, Division of Allergy/Immunology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, One Gustave L Levy Place, New York, NY 10029-6574; E-mail: hugh.sampson@mssm.edu.

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Author

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- Mary Grace Baker, MD
- Hugh A. Sampson, MD

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Introduction

According to the 2010 Expert Panel of the National Institute of Allergy and Infection Disease, food allergy is defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”¹ This definition is broad, and patients with diagnosed food allergy exhibit great diversity in their clinical presentation, biomarker expression, natural history, and potential to respond to novel therapies. This variation among patients creates a challenge when educating patients about the natural history of their condition and devising an appropriate management plan. To better refine our ability to evaluate patients and treat them appropriately, it is imperative that we gain more insight into specific pathophysiologic mechanisms. Proper identification of phenotypes and endotypes of patients with food allergy is integral to the meaningful study and care of patients with food allergy, with the goals of better elucidating pathophysiologic mechanisms and devising appropriate therapeutic plans.

For this review, we use the following definitions. A phenotype is any observable characteristic or trait of a disease, such as morphology, development, biochemical, or physiologic properties or behavior, without any implication for the responsible mechanism. An endotype is a subtype of a phenotype and is defined by a distinct

functional or pathobiologic mechanism. It is envisaged that patients with a specific endotype present within phenotypic clusters of disease. Phenotype and endotype are determined by genotype, inherited epigenetic factors, and environmental factors.

We are proposing a system of food allergy phenotypes and endotypes based on clinical and basic laboratory characteristics (Table 1). The focus of this article is immunoglobulin E (IgE)-mediated food allergy, although non-IgE-mediated food allergy is discussed briefly. Of note, this classification is not based on a formalized cluster analysis, and such work represents a significant area of opportunity in our field. The following phenotypes of IgE-mediated food allergy are proposed: classic, intermittent and cross-reactive allergy, aerosolized sensitization, galactose- α -1,3-galactose (alpha-gal) syndrome or mammalian meat allergy, and sensitized nonreactive allergy (Fig 1).

Classic Phenotype

The classic phenotype of food allergy encompasses patients with typical IgE-mediated food allergy. In these patients, oral ingestion of food or contact on inflamed skin leads to a loss of or a failure to develop tolerance, resulting in the typical signs and symptoms of

Table 1
Phenotypes and Endotypes of Food Allergy

Phenotype	Endotype	Skin prick test result	Specific IgE	Symptoms
Classic	persistent	++ to ++++	++ to ++++	typical IgE-mediated symptoms
Classic	transient	+ to +++	+ to ++	typical IgE mediated symptoms
Classic	food dependent + exercise induced	+ to ++	+ to ++	typical IgE-mediated symptoms ^a after ingestion of an allergen + exercise
Classic	NSAID or aspirin dependent	+ to ++	+ to ++	typical IgE-mediated symptoms ^a after ingestion of an NSAID or aspirin + an allergen
Classic	alcohol dependent	+ to ++	+ to ++	typical IgE-mediated symptoms ^a after ingestion of alcohol + an allergen
Intermittent and cross-reactive allergy	N/A	+ to +++	+ to +++	typical IgE-mediated symptoms
Aerosol sensitization	local reactions to aerosolized cross-reactant antigens (pollen-food allergy syndrome or oral allergy syndrome)	±	±	limited oral and pharyngeal pruritus, mild edema of lips and tongue
Aerosol sensitization	systemic reactions to aerosolized forms of food specific antigens (psyllium)			typical IgE-mediated symptoms after ingestion after sensitization to aerosolized rather than ingested protein
α-Gal syndrome	N/A	+ to +++	++ to +++	classic IgE-mediated symptoms, delayed 3–6 h
Sensitized nonreactive	N/A	+ to ++	+ to ++	sensitized but nonreactive

Abbreviations: α-Gal, galactose-α-1,3-galactose; IgE, immunoglobulin E; N/A, not applicable; NSAID, nonsteroidal anti-inflammatory drug.

^aTypical IgE-mediated symptoms include urticaria, angioedema, rhinoconjunctivitis, bronchospasm, acute gastrointestinal spasm, hypotension, dizziness, uterine cramping, feeling of “pending doom,” and anaphylactic shock.

an allergic reaction.^{2,3} In a state of tolerance, dendritic cells in the gut and skin transport the antigen to regional lymph nodes, permitting the induction of regulatory T cells.^{4,5} In patients with food allergy, induction of regulatory T cells is believed to be superseded by the development of antigen-specific T-helper type 2 (T_H2A) cells that drive IgE class switching and T_H2 inflammatory mediators.⁶ Cross-linking of food-specific IgE on mast cells and basophils leads to a release of inflammatory mediators, resulting in the systemic manifestations of classic food allergy, including urticaria, angioedema, rhinoconjunctivitis, bronchospasm, acute gastrointestinal (GI) spasm, hypotension, dizziness, uterine cramping, feeling of “pending doom,” and, in the most severe cases, anaphylactic shock.^{1,5}

Diagnosis is suggested in the setting of a reported reaction to an ingested food and established based on positive serum IgE, skin prick test (SPT), and, in some cases, oral food challenge (OFC) results.³ Currently, the cornerstone of management remains avoidance of responsible foods and any significant cross-reacting antigens.¹ For patients with relatively low serum IgE and small wheals in reaction to the SPT, an OFC can be performed to distinguish between this classic phenotype and the sensitized nonreactive type.^{7–9} For patients with evidence of persistent reactivity and a strong desire for therapy, different potential treatments, including oral, sublingual, and epicutaneous immunotherapy, can be considered.²

Within the classic phenotype, we recognize 5 endotypes: persistent, transient, food-dependent exercise-induced allergy (FDEIA), nonsteroidal anti-inflammatory drug (NSAID)- or aspirin-induced allergy, and alcohol-dependent allergy. The persistent and transient endotypes distinguish patients with IgE-mediated food allergy who differ in the expected natural history of their allergy (Fig 2). The persistent phenotype refers to patients who do not “outgrow” their food allergy over time. For example, it is estimated that more than 80% of children with allergy to peanut, tree nuts, and seafood will have persistent allergy throughout their lifetime.^{10–12} The study of patients with peanut allergy has greatly shaped our understanding about the natural history of food allergy. Mapping of epitopes through microarray immunoassays has shown a series of sequential (linear) allergenic (IgE-binding) epitopes on major peanut component proteins (Ara h 1, Ara h 2, and Ara h 3).¹³ In a prospective study conducted by the Consortium for Food Allergy Research (CoFAR), 125 infants considered at high risk for the development of food allergy were enrolled for serial clinical and immunologic evaluation.¹⁴ In the first 12 months of life, some children exhibited high specific IgE (sIgE) to peanut with reactivity primarily to conformational epitopes but not sequential (linear) epitopes. It is

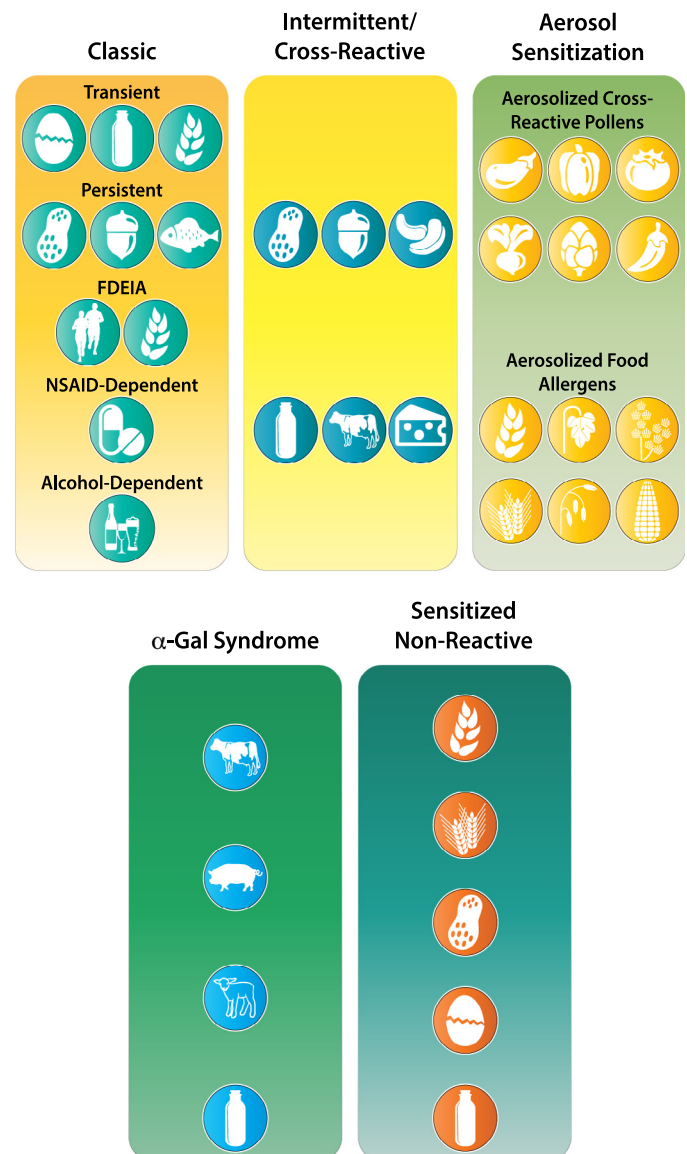


Figure 1. Phenotypes and respective endotypes. α-Gal, galactose-α-1,3-galactose; FDEIA, food-dependent exercise-induced allergy; NSAID, nonsteroidal anti-inflammatory drug.

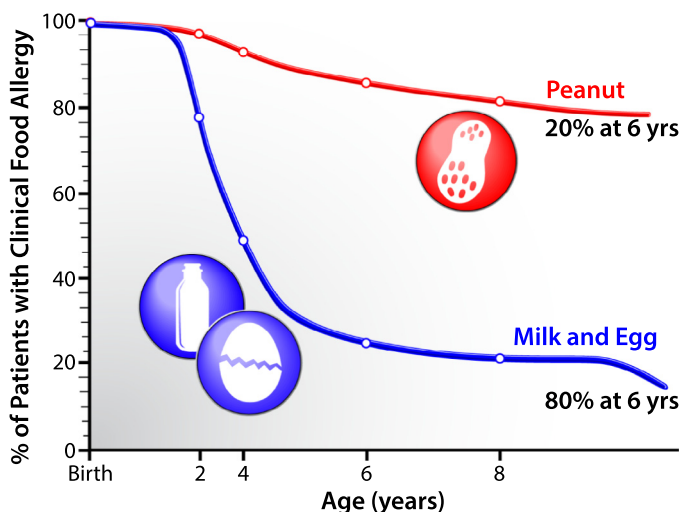


Figure 2. Natural history of food allergy. In patients with transient food allergy, clinical allergy is outgrown over time with resolution in most patients. For persistent allergy, clinical reactivity lingers with resolution in a minority of patients.

presumed that these patients react despite recognition of only conformational epitopes due to increased GI absorption and/or low IgG4 and IgA levels. As children with persistent food allergy mature, they develop sIgE to sequential epitopes, leading to permanence of the allergy over time. Recognition of sequential epitopes has been associated with greater basophil activation at lower antigen concentrations and more severe clinical reactions.^{15,16} This is substantiated by unpublished data from the LEAP cohort. At enrollment, the children were found to have little to no sIgE to peanut, and the IgE antibody that was present was directed at conformational epitopes. The children who ate peanut during the study period did not develop IgE to sequential epitopes over time, whereas the children who avoided peanut were more likely to develop IgE to sequential epitopes. The 2 groups produced IgG4 antibodies to peanut epitopes, although this antibody production took place later in children avoiding peanut. Although persistent allergy to milk and egg is less common, risk factors have been identified. Various standard laboratory procedures suggestive of persistent allergy include SPT wheal reaction larger than 15 mm and/or IgE level higher than 25 kU_A/L for milk, egg, peanut, and tree nuts, Ara h 2 IgE level higher than 5 kU_A/L, and IgE level higher than 50 kU_A/L for wheat. Clinical factors associated with persistent allergy include a history of severe atopic dermatitis (especially of early onset), multiple food allergies, and a history of severe anaphylactic reactions.³

This is in contrast to the transient phenotype, in which most patients are expected to lose clinical reactivity over time. Examples of this type of allergy include children with egg, soy, and wheat allergy, of whom approximately 90% are expected to outgrow their allergy, and those with milk allergy, of whom more than 80% outgrow their allergy.¹⁷ Notably, most patients with milk and egg allergies can tolerate these foods when extensively heated as ingredients in baked goods.^{18,19} It is believed that these patients tolerate the foods because they develop IgE antibodies primarily to conformational epitopes, which after exposure to high temperature (ie, baking), undergo a change in their tertiary structure (Fig 3).^{20–22} It also is believed that allergenic proteins might aggregate under these conditions and therefore be less available to IgE antibodies on effector cells (mast cells, basophils, dendritic cells) when prepared in a food matrix.^{21,22} In addition, it has been found that serving baked milk and egg to tolerant children can accelerate the development of tolerance to all forms of milk and egg.^{18,19} Although a meta-analysis found that the data tend to be observational,²³ a recent study

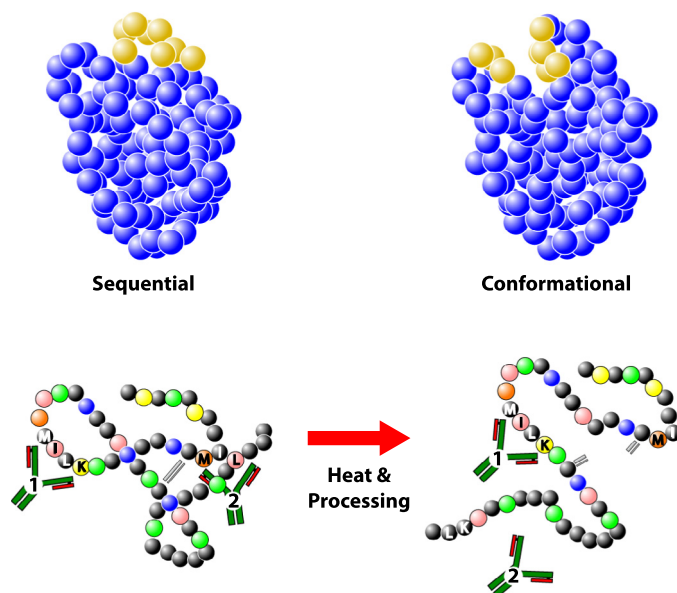


Figure 3. Epitopes and conformational changes with heating. Epitopes can be sequential or conformational. When a protein is heated, it can undergo conformational changes. This decreases the allergenicity of conformational epitopes but does not affect reactivity with exposure to sequential epitopes.

by Nowak-Węgrzyn et al²⁴ showed that with regular incorporation of baked milk at home, half the children tolerant of baked milk go on to develop tolerance to non-baked liquid milk within 36 months, with a median time to tolerance of 18 months. IgE testing to casein (casein <4.95 kU_A/L) and ovomucoid (ovomucoid <4.40 kU_A/L) aids in the identification of children likely to tolerate baked milk and egg, respectively.^{19,25,26}

Other endotypes within the classic phenotype are defined by augmentation factors that elicit an allergic reaction when exposure occurs in proximity to ingestion of a culprit food. These include FDEIA, NSAID- or aspirin-induced, and alcohol-induced allergic reactions. In the FDEIA endotype, vigorous exercise within 2 to 4 hours of ingestion of specific foods elicits urticaria or anaphylaxis.²⁷ Young adults are most commonly affected, although FDEIA can occur at any age. A female predominance has been observed.²⁸ The food most frequently associated with this disorder is wheat, but cases also have been reported with shellfish, milk, soy, celery, etc.^{3,28,29} These reactions are mediated by preformed food-specific IgE antibodies, and the reaction can be provoked if a large enough quantity of the food is consumed or if other augmentation factors are present even in the absence of exercise.³⁰ It is believed that exercise provokes a reaction by increasing GI absorption or lowering the activation threshold of mast cells and/or basophils in sensitized individuals.^{31–33} Positive SPT and/or IgE antibody reactions are typically present to the culprit food.²⁷ The cornerstone of management is identification of the culprit food and lifestyle modification to avoid exercise and other augmentation factors in temporal proximity to possible ingestion of a causative food. There are ongoing studies examining the potential role of omalizumab and misoprostol as pharmacotherapies to prevent symptoms.

It has been established that other augmentation factors including the use of NSAIDs (eg, ibuprofen, naproxen, celecoxib), aspirin, and/or alcohol can increase the likelihood and severity of allergic reactions before ingestion of a culprit food.³⁴ Intake of NSAIDs has been hypothesized to increase absorption by altering intestinal permeability and to induce direct effects on mast cells and basophils to amplify their activation.^{31,35} Recent research by Pascal et al³⁵ has bolstered the latter hypothesis, demonstrating that NSAIDs act to

activate basophils. Notably, this effect was observed with aspirin but not with selective cyclooxygenase-2 inhibitors, suggesting that the mechanism might require the inhibition of cyclooxygenase-1 to release leukotriene mediators resulting in the signs and symptoms of an allergic reaction.

Alcohol consumption also has been implicated in increasing the severity of allergic reactions.^{2,21,36} It is believed that this is due to alcohol's effect in increasing the absorption of allergens and increasing the amount of protein absorbed or the rapidity with which it enters the circulation and activates immunologic pathways. In addition, alcohol's effect to decrease one's inhibitions places individuals with food allergy at risk for inadvertent consumption of food allergens. Other notable augmentation factors that merit mention include infection, antacid use, and menstruation.

Intermittent and Cross-Reactive Allergy Phenotype

The intermittent and cross-reactive allergy phenotype is an independent entity with no clear endotypes. It has been observed that among patients with food allergy, patients can exhibit evidence of sensitization to other foods that share homologous proteins.³⁷ An example of this occurs among legumes and especially peanut, lupine, and soy. Previous work has shown the presence of multiple homologous proteins in peanut and soy.³⁸ In addition, it has been shown that patients with peanut allergy will frequently demonstrate positive SPT and sIgE antibody reactions to soy.^{39,40} A study by Bock and Atkins³⁹ of patients with peanut allergy undergoing OFCs to soy showed a positive OFC reaction in just 1 of 32 patients, although 17 of these patients were found to have positive SPT reactions to soy. It is currently estimated that approximately 5% of children with peanut allergy will react to soy and other legumes.^{37,41} Personal observation suggests that in some cases, ingestion of large quantities of concentrated soy can increase the likelihood of a reaction.

A similar phenomenon has been observed in patients with cow's milk allergy. In 1 study, allergic reactions to beef were documented in up to 10% of patients with cow's milk allergy.⁴² Reactions were more likely when the beef was rare or less well cooked, and it has been shown that thorough cooking alters the allergenicity of beef.⁴³ It is believed that patients with cow's milk allergy who tolerate well-cooked but not rare beef can continue to consume well-cooked beef without fear of developing an adverse reaction.

In addition to these classic examples, there are other commonly observed patterns of cross-reactivity. Many patients with allergy to 1 tree nut show cross-reactivity to other tree nuts, especially in the setting of birch sensitivity.^{37,44} This has been shown to occur at higher frequency for cashew and pistachio and for walnut and pecan.^{45–48} Patients with allergy to finned fish typically also demonstrate significant cross-reactivity among species, often due to the antigen parvalbumin.^{37,49} These patients merit careful evaluation because they might tolerate some species despite evidence of allergy to several others. In addition, high rates of cross-reactivity are observed for patients with shellfish allergy, which includes crustaceans and mollusks. Allergy to crustaceans is often due to invertebrate tropomyosin, which is fairly homologous among crustaceans and results in high rates of cross-sensitization and often cross-reactivity. Some patients with allergy to crustaceans might tolerate mollusks and vice versa.

Aerosol Sensitization

In contrast to the classic and intermittent and cross-reactive phenotypes in which sensitization to a food antigen occurs after ingestion of a culprit food, it has been observed that patients can become sensitized to foods through exposure to homologous airborne plant pollens or aerosolized food protein. In the aerosol sensitization phenotype, airborne exposure to an antigen results in

sensitization to an antigen present in a food protein or a homologous antigen protein in a plant pollen that cross-reacts with food. Two endotypes have been identified within this phenotype: local reactions to aerosolized cross-reactant antigens and systemic reactions to aerosolized forms of food-specific antigens.

In pollen-food allergy syndrome, also known as oral allergy syndrome, patients report symptoms that are largely localized to the oropharynx but rarely involve systemic symptoms after ingestion of a specific fruit, vegetable, or tree nut.⁵⁰ This is believed to be due to IgE-mediated reactions after exposure to proteins that are homologous to or cross-react with pollen proteins to which they have already been sensitized.⁵¹ Commonly reported culprit foods include raw apple, almond, hazelnut, peanut, and other fruits in the Rosaceae family in patients with birch allergy; melons, banana, and kiwi in patients with ragweed allergy; and melon and tomato in patients with grass allergy.⁵⁰ Many other foods and associated environmental allergens have been identified (Table 2).^{37,52–54} Diagnosis is established based on clinical history of symptoms provoked by ingestion of a fruit, vegetable, or tree nut and the finding of positive SPT (prick and prick) reaction to the fresh food or positive allergy test reaction to a corresponding pollen.⁵⁵ Note that conformational epitopes in commercial extracts are easily degradable and frequently do not yield credible results. An OFC might be considered in ambiguous cases. Once diagnosed, it is generally recommended that patients avoid raw forms of the culprit food.⁵² Select patients might avoid symptoms by peeling the fruit because homologous proteins appear to be concentrated below the skin, whereas others can tolerate these foods only when microwaved or thoroughly cooked.^{56,57} It is believed that the loss of reactivity is due to conformational changes with heating.⁵⁸ Peanuts and tree nuts are notable exceptions, because in many cases they have been shown to be more allergenic when roasted.⁵⁹ There has been great interest in treating the pollen-food allergy syndrome with immunotherapy to pollens to prevent symptoms with ingestion of associated foods, but the benefits have not been consistent.^{52,60–63}

We also propose an endotype called systemic reactions to aerosolized food-specific antigens. This has been best demonstrated with reactions to psyllium. In the early 1990s, multiple cases of allergic reactions including anaphylaxis were reported after ingestion of a psyllium-based cereal. Interview of the affected individuals showed that these reactions most commonly affected health care workers

Table 2
Oral Allergy Syndrome Pollens and Cross-reactant Foods

Pollens	Family	Cross-reactant foods
Birch	Rosaceae	apple, peach, nectarine, plum, pear, cherry, apricot, almond
	Apiaceae	carrot, celery, parsley, caraway, fennel, coriander, aniseed
	Fabaceae	soybean, peanut
	Betulaceae	hazelnut
Ragweed	Juglandaceae	walnut
	Cucurbitaceae	cantaloupe, honeydew, watermelon, zucchini, cucumber
	Musaceae	banana
Mugwort	Actinidiaceae	Kiwi
	Apiaceae	celery, carrot, parsley, caraway, fennel, coriander, aniseed
	Solanaceae	bell pepper
Orchard	Piperaceae	black pepper
	Brassicaceae	mustard, cauliflower, cabbage, broccoli
	Liliaceae	garlic, onion
	Rosaceae	Peach
	Cucurbitaceae	cantaloupe, honeydew, watermelon
	Fabaceae	peanut
Timothy	Solanaceae	white potato, tomato
	Amaranthaceae	Swiss chard
	Rutaceae	orange

who previously had occupational exposure to aerosolized psyllium (eg, Metamucil; Procter & Gamble, Cincinnati, Ohio) when caring for patients.^{64,65} It is notable that at least 20% of these reactions were severe and required epinephrine. Multiple studies of patients with these reactions to psyllium have highlighted psyllium hypersensitivity as an occupational risk with sensitization occurring after inhalation.⁶⁶

Similarly, occupational exposure and sensitization to aerosolized wheat has been widely reported among bakers, with baker's asthma being one of the most reported causes of occupational asthma worldwide.⁶⁷ Examination of bakers with rhinitis and asthma has shown that 60% to 70% of subjects have sIgE to wheat and/or rye.⁶⁸ The diagnosis is established based on work-related asthma symptoms, the finding of sIgE or positive SPT reaction to a relevant allergen, and, in some cases, bronchial challenge.^{69,70} Notably, large case series have demonstrated that despite the presence of sIgE to wheat components and provocation of symptoms with aerosolized exposure, no symptoms have been reported with ingestion of wheat products.^{68,70,71} Other reported but less common causes of baker's asthma include molds, yeast, egg, sesame, nuts, soy, insects, and dust mites.^{67,72}

Alpha-Gal Syndrome or Mammalian Meat Allergy

In 2004, there were multiple reports of cases of atypical, idiopathic urticaria, angioedema, or anaphylaxis in the southeastern United States.⁷³ When the same region was affected by a disproportionate number of infusion reactions to the chemotherapeutic agent cetuximab, intensive investigation led to the discovery that the affected patients demonstrated sensitization to the alpha-gal carbohydrate moiety present on the biologic and that this sensitization occurred before beginning their oncologic treatment.⁷⁴ It ultimately became clear that many cases of presumed "idiopathic anaphylaxis" were almost always associated with a meal of beef, pork, or lamb hours before the reaction, and it seemed likely that these patients were reacting to the alpha-gal sugar present on these mammalian meat products.⁷⁵

Although these reactions are mediated by IgE, they merit distinction from the classic phenotype for a number of atypical features. Foremost, it is notable that alpha-gal is a carbohydrate, unlike the vast majority of clinically significant epitopes in food allergy, which are glycoproteins.⁷⁵ In addition, unlike in the classic phenotype in which sensitization occurs after ingestion of an allergenic food, it has been shown that sensitization occurs after tick bites, with the *Amblyomma americanum* or Lone Star tick being the most significant vector in the United States.⁷⁶

There are many unique features of the allergic reactions to alpha-gal. As alluded to earlier, unlike classic IgE-mediated allergy in which symptom onset typically occurs within minutes of ingestion, patients report symptoms 3 to 6 hours after the ingestion of a meat-containing meal.⁷⁵ Although many possible explanations for this have been examined, it is believed that this is due to delayed entry into the circulation after processing in the lymphatics, specifically the thoracic duct.⁷³ As a consequence of this delay, the clinical manifestations of allergy can prove quite dramatic, often waking patients in the middle of the night several hours after dinner. In addition, it is important to note that the reactions are not always consistent with meat ingestion and could appear idiosyncratic. Although patients with classic IgE-mediated food allergy develop symptoms reliably after ingestion of a food allergen, patients often report being able to tolerate some meat meals and developing severe symptoms with others. It is believed that the type of meat could contribute to the likelihood, severity, and rapidity of a reaction. As described earlier, an increased risk of a reaction has been noted with cofactors such as alcohol, NSAIDs, and exercise.⁷⁷ Patients occasionally

demonstrate clinical reactivity to cow's milk, although many more patients exhibit evidence of sensitization than report reactions.^{75,78}

When the diagnosis of mammalian meat allergy is considered, it is important to note the limited utility of commercial extracts to the mammalian meats. Skin testing with fresh meat and intradermal testing with meat extracts yield more accurate results. In addition, patients will exhibit positive serum IgE to alpha-gal, beef, pork, lamb, cow's milk, cat, and dog.

Much remains to be learned about the natural history of patients with mammalian meat allergy. There is evidence that repeated tick bites result in an increase in sIgE to alpha-gal.⁷⁹ For patients able to avoid tick bites, it has been shown that the sIgE to alpha-gal decreases over time, and patients have gone on to reintroduce mammalian meat into the diet without signs or symptoms of allergy.

Sensitized Nonreactive Phenotype

The final IgE-mediated food hypersensitivity phenotype that is important to consider is the sensitized nonreactive type. These patients demonstrate a potential sign of food allergy based on at least 1 positive food-specific IgE test result. However, with a clinical history of consumption without symptoms or the successful passage of an OFC, it is clear that the food is tolerated and does not activate an allergic response.

The mechanism by which some patients with sIgE antibodies to a food can tolerate that food, whereas others cannot, remains uncertain. These patients might have had clinically reactive food allergy in the past but outgrew their allergy and demonstrate mild residual positive SPT and/or sIgE reactions after resolution of clinical allergy. For some patients, there also could be a relation between cross-reactive allergens. In these cases, the presence of allergy to cross-reacting antigens results in positive sIgE test results but no evidence of clinical reactivity. Moreover, the lack of absorption of an antigen could play a role in the absence of allergic reactivity and certain aspects of a patient's digestion might affect that patient's likelihood of reacting. This remains an area of limited research, although there are some mouse data to suggest that GI absorption is key. For example, in many murine models of IgE sensitivity, feeding the animal the food allergen often will fail to induce symptoms, but if the food is injected intraperitoneally, bypassing the need for GI absorption, the mouse will experience anaphylaxis.⁸⁰

Non-IgE-Mediated Food Allergy

Although the focus of this review is the classification of IgE-mediated food allergy, allergic conditions related to food ingestion but not mediated by IgE merit discussion. These include atopic dermatitis, contact dermatitis, eosinophilic esophagitis (EoE) and gastroenteritis, dietary protein-induced proctocolitis, food protein-induced enterocolitis syndrome, celiac disease, and Heiner syndrome.

Atopic dermatitis typically presents in infancy and is often the harbinger of future atopy.⁸¹ Although atopic dermatitis can have a relapsing and remitting course without clear provocation, it has been observed that patients with atopic dermatitis often have elevated food-specific and total IgE, and it has been shown that children with regular ingestion of foods to which they are allergic have basophil release of histamine and symptom flares.⁸² A targeted elimination diet can lead to clearing of active eczema. Because of concern about excessive dietary restriction, it has been suggested that possible food allergens be eliminated for 2 to 3 weeks with a daily symptom diary.⁸¹ If a compelling correlation is detected, the food should be eliminated with subsequent allergy testing, including OFC under physician supervision, before reintroduction.

Various other cutaneous manifestations of non-IgE-mediated food allergy have been reported. These include irritant contact dermatitis, allergic contact dermatitis, and phototoxic contact

dermatitis.⁸³ Reactions are most common in persons who frequently handle food including bakers, chefs, butchers, fisherman, farmers, etc. Irritant contact dermatitis is most common. This occurs most often with regular exposure in patients with frequent hand-washing, and the incidence is increased in patients with atopic dermatitis.^{84,85} It is believed that defects in skin barrier function increase one's predisposition. The hands and face are most affected, and implicated foods include garlic, onion, citrus fruits, potato, pineapple, carrot, corn, and spices.⁸⁶

Although rare, foods have been identified as a cause of allergic contact dermatitis. These are cell-mediated type IV hypersensitivity reactions, and antigens tend to be low-molecular-weight molecules requiring haptenization.⁸⁷ "Mango dermatitis" is the best-known example, and symptoms are elicited by exposure to the skin, leaves, or stem but not the juice. It is believed that patients are sensitized during exposure to other plants in the Anacardiaceae family, such as poison ivy, because all contain urushiol. Other foods reported to cause allergic contact dermatitis include garlic, onion, citrus fruits, asparagus, broccoli, cauliflower, artichoke, endive, lettuce, and spices.^{84,86}

Phototoxic dermatitis occurs in areas of skin that have been exposed to food and UVA rays. The reaction presents as streaks of erythema, vesicles, and bullae and can leave residual pigmentation changes.^{83,84} Reported culprit foods include citrus fruits, celery, parsnip, parsley, and fig. All these foods contain bergamot or 5-methoxypsoralen.

Numerous GI manifestations of non-IgE-mediated food allergy have been identified. According to consensus guidelines, EoE is a "chronic, immune/antigen-mediated disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation."⁸⁸ Presentation is highly variable with age, but infants frequently demonstrate poor feeding, children experience vomiting and abdominal pain, and adults report dysphagia, food impaction, and abdominal pain. Patients often have a history of atopy, autoimmune disease, or connective tissue disease.^{89–92} Although much remains to be learned about the pathogenesis of EoE, it is believed to be a T_H2-mediated disorder with impaired epithelial barrier function.^{89,93–95} The relation between EoE and trigger foods is well established, and an elimination diet is one of the cornerstones of management. Although 6- or 8-food elimination diets have been the standard of care, recent data have suggested that a 4-food elimination diet with avoidance of cow's milk, wheat, egg, and soy leads to symptomatic improvement and histologic remission in most patients.⁹⁶ A limited number of patients eventually tolerate foods previously associated with active EoE.⁹⁷

Dietary protein-induced proctocolitis is a condition of infancy in which children are noted to have streaks or specks of blood mixed with mucus in their stool.⁹⁸ They are otherwise healthy with no apparent symptoms and normal growth and development. Most affected infants are breastfed. Avoidance of cow's milk usually results in symptom resolution, although soy and egg have been reported as culprit foods as well. In fewer than 10% of cases, an elemental formula might be required.⁹⁹ There has not been an association with elevated food-specific or total IgE. The avoided food can generally be reintroduced at home after 1 year of age.

Food protein-induced enterocolitis syndrome is recognized as a non-IgE-mediated form of food allergy in which ingestion of a food results in repetitive vomiting 1 to 4 hours after feeding, sometimes severe enough to result in significant dehydration and even shock.¹⁰⁰ The age at onset depends on exposure to the antigen, although it is often in the first year of life.⁹⁹ The most common triggers are cow's milk and soy, but rice, oat, egg, and other foods have been reported. Although the acute manifestations are often dramatic, symptoms can be persistent if the culprit food is not recognized and eliminated. In these cases, children can have episodes of emesis,

bloody diarrhea, lethargy, dehydration, and failure to thrive.¹⁰¹ Laboratory results have shown anemia, hypoalbuminemia, and a leukocytosis with a left shift and eosinophilia, and methemoglobinemia in more severe cases.¹⁰² Although the pathogenesis remains uncertain, it is postulated that food protein-induced enterocolitis syndrome is cell-mediated with a role of intestinal permeability. Some patients have comorbid IgE-mediated food allergy.¹⁰⁰

Celiac disease is a non-IgE-mediated food allergy in which ingestion of gluten elicits symptoms.¹⁰³ A predisposition has been observed among patients with the HLA-DQ2 and HLA-DQ8 haplotypes.¹⁰⁴ Symptoms include abdominal pain, diarrhea, and bloating from enteropathy; dermatitis herpetiformis; failure to thrive; nutritional deficiencies and their sequelae; and neuropsychiatric concerns. The disease is believed to be mediated by the response of the innate and adaptive immune systems to undigested gliadin produced during the breakdown of gluten.¹⁰⁵ Complete dietary elimination of wheat, rye, and barley generally alleviates symptoms.¹⁰³

In 1960, Heiner and Sears¹⁰⁶ observed that ingestion of milk appeared to contribute to chronic pulmonary disease in some patients. We now recognize Heiner syndrome as a rare condition, typically caused by ingestion of milk, that results in pulmonary infiltrates; upper respiratory symptoms including cough, wheezing, hemoptysis and dyspnea; GI symptoms including vomiting, diarrhea or colic; failure to thrive; and iron-deficiency anemia.^{1,107} Although much remains to be learned about the pathogenesis, it is characterized by precipitating antibodies to milk protein, and it is believed to be due to alveolar vasculitis mediated by cellular mechanisms and immune complexes. Although the diagnosis can be suggested based on clinical features, it is established based on the finding of serum milk precipitins and iron-laden macrophages on bronchoalveolar lavage, lung biopsy, and/or gastric aspirate.¹⁰⁸ Patients show improvement with a milk elimination diet, and they are likely to eventually tolerate milk after a period of avoidance.

Conclusion

Given the diversity of allergic reactions to food, the proper identification of relevant phenotypes and endotypes is essential to further our understanding of underlying pathophysiologic mechanisms, which is necessary for the proper diagnosis and management of patients with food allergy. The classification scheme proposed in this article is intended to stimulate conversation and provide a potential framework to approach this topic. Future research should lead to further refinement and modifications of this scheme. Specifically, it should be emphasized that this classification is based on clinical characteristics and known immunologic mechanisms. There are a number of studies of patients with asthma and other non-communicable diseases that have identified endotypes of disease based on formalized cluster analyses, which also can be applied to food allergy.

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