Common food allergens and cross-reactivity

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ABSTRACT

The most clinically relevant food allergens are cow's milk, hen's egg, peanut, tree nuts, wheat, soy, fish, shellfish, and seeds. Heat-stable food allergens have molecular characteristics that enhance protein stability and gastrointestinal absorption and thus are more likely to cause systemic reactions on ingestion. In contrast, heat-labile food allergens lack these characteristics and do not typically elicit reactions if sufficiently altered by heat or acid. Immunologic cross-sensitization between food allergens is more common than clinical cross-reactivity. However, certain groups of food allergens, such as tree nuts, fish, and shellfish, are associated with high rates of clinical cross-reactivity. Knowing the rates of clinical cross-reactivity is important when providing guidance to patients with food allergy and families on what foods can be safely added to the diet and what foods should be avoided.

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Although geographic differences exist, the most clinically relevant food allergens are cow's milk, hen's egg, peanut, tree nuts, wheat, soy, fish, shellfish, and seeds. These allergens are responsible for the majority of clinically significant immunoglobulin E (IgE) mediated reactions to foods. Although allergies to fruits and vegetables are commonly reported in adults, most reactions are mild and associated with pollen-food allergy syndrome.[1] Here we review the most common food allergens, examine rates of cross-sensitization and clinical cross-reactivity between different foods, and discuss implications for clinical management.

BACKGROUND

Food allergens can generally be divided into heat-stable and heat-labile allergens. Most heat-stable food allergens are glycoproteins with a molecular mass of 10–70 kDa.[2] Heat-stable food allergens have molecular properties that confer conformational stability, such as disulfide bonds, protein glycation, and the ability to bind lipids. These properties can protect food allergens from degradation by heat, acid, and proteases, thereby enhancing uptake of intact protein in the gastrointestinal tract.[2] In contrast, heat-labile allergens are highly sensitive to heat and acid. Sensitization to heat-labile allergens in plant-based foods is thought to result from exposure to homologous proteins in pollens, which leads to the development of pollen-food allergy syndrome.[1,2] However, some common food allergens, such as cow's milk and hen's egg, also contain heat-labile allergens that are denatured during extensive heating.[3] Table 1 contains a list of important food allergens and their clinical significance.

Structural homology between allergens can result in binding of cross-reactive IgE antibodies, which is referred to as cross-sensitization. Cross-sensitization to food allergens can cause positive allergen specific IgE test results (*e.g.*, skin-prick testing or *in vitro* IgE testing), which may or may not be of clinical significance. In contrast to cross-sensitization, clinical cross-reactivity refers to the elicitation of symptoms consistent with an IgE-mediated food allergy and is less common than cross-sensitization.[4] It is thought that protein allergens must share at least a 70% amino acid sequence identity for clinical cross-reactivity to occur.[2] Other factors that impact clinical cross-reactivity include patient characteristics and the dose and route of exposure.[2,4] The rates of clinical cross-reactivity for common food allergens are presented in Table 2.

COW'S MILK

Cow's milk allergy is one of the most common food allergies and affects up to 2% of children and adults in the United States. The major allergens in cow's milk include caseins (~80% of all milk protein) and the whey proteins alpha-lactalbumin, beta-lactoglobulin, and bovine serum albumin.[2] Approximately 75% of children with milk allergy tolerate extensively heated milk in baked products.[3] Caseins tend to be more heat resistant; as such, high casein-specific IgE is associated with reactivity to baked milk.[3] There is extensive

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Table 1 **Important food allergens**

	Food Allergen	Clinical Significance
Cow's milk	Alpha-casein (Bos d 8)	Bos d 8 is associated with reactivity to extensively heated milk and persistent allergy
	Alpha-lactalbumin (Bos d 4)	
	Beta-lactoglobulin (Bos d 5)	
	Bovine serum albumin (Bos d 6)	
Hen's egg	Ovomucoid (Gal d 1)	Gal d 1 is associated with reactivity to extensively heated egg and persistent allergy
	Ovalbumin (Gal d 2)	Gal d 5 is implicated with bird-egg syndrome
	Ovotransferrin (Gal d 3)	
	Alpha-livetin (Gal d 5)	
Peanut	Ara h 1	Ara h 1, 2, 3, 6 have a higher risk for systemic reactions
	Ara h 2	Ara h 2 may gain favor over whole peanut extract in diagnostic testing
	Ara h 3	
	Ara h 6	
	Ara h 8	Ara h 8 is a Bet v 1 homologue
	Ara h 9	
Soy	Gly m 3	
	Gly m 4	Gly m 4 is a Bet v 1 homologue but may still provoke severe reactions
	Gly m 5	
	Gly m 6	
Hazelnut	Cor a 1	Cor a 1 is a Bet v 1 homologue
	Cor a 8	Cor a 8, 9, 14 are associated with severe reactions
	Cor a 9	
	Cor a 14	
Wheat	Omega-5-gliadin	Omega-5-gliadin is implicated in wheat-dependent, exercise-induced anaphylaxis and severe reactions
	Tri a 36	Tri a 36 associated with immunoglobulin E–mediated allergy
Shrimp	Tropomyosin (Pen a 1)	May cross-react with proteins in dust mite and cockroach

clinical cross-reactivity between the ruminant mammal milks (goat, sheep, buffalo), and results of studies indicate that >90% of children allergic to cow's milk react to goat's milk.[4,5] In contrast, donkey, horse, and camel milk are likely to be tolerated by patients with cow's milk allergy.[5] Although mammalian meats share some proteins with cow's milk, only ~10% of children with cow's milk allergy react to beef.[6]

HEN'S EGG

Hen's egg allergy is a common IgE-mediated allergy in childhood. Approximately 70% of children with hen's egg allergy are able to ingest extensively heated forms in baked goods.[3] The major allergens are the egg-white proteins ovomucoid, ovalbumin, and ovotransferrin.[2] Ovomucoid is resistant to heat, and, thus, high levels of ovomucoid specific IgE are associated with an increased likelihood of reactivity to baked egg.[3] The yolk protein alpha-livetin has been implicated in rare clinical cross-reactivity between chicken egg, feathers, and poultry.[2] Although cross-sensitization has been described among avian eggs (hen, duck, goose), clinical cross-reactivity is thought to be rare, and patients are not routinely advised to avoid other bird eggs.[7]

LEGUMES

Legumes belong to the Fabaceae family, with peanut, soy, chickpea, and lupin being most clinically relevant. Peanut allergy affects 1–2% of children and typically persists into adulthood. Peanut contains 32 proteins, of which at least 16 have been reported to bind peanut specific IgE.[8] The major peanut allergens are seed storage proteins and include Ara h 1, Ara h 2, and Ara h 3. Ara h 6 is another seed storage protein with homology to Ara h 2. Sensitization to Ara h 2 and Ara h 6 is highly predictive of clinical reactivity and is associated with more severe allergic reactions.[9] Ara h 8 is a pathogen-related 10 family protein and homologous to the birch pollen allergen Bet v 1; as such, sensitization to Ara h 8 is typically associated with tolerance or pollen-food allergy syndrome.[1,10]

Table 2 **Rates of clinical cross-reactivity for common food allergens**

Food	Rates of Clinical Cross-Reactivity	Considerations
Cow's milk	Goat milk, >90%	Goat, sheep, and buffalo milks should be avoided
	Mare milk, 4%	Donkey, camel, and mare milks are likely tolerated
	Beef, ~10%	Extensively heated or processed beef likely tolerated compared with uncooked and medium rare forms
Peanut	Other legumes, 5%	Results of limited studies indicate increased risk for lupin cross-reactivity
	Tree nuts, 30–40%	
	Lupin, 4–29%	
Lentil	Chickpea, green pea, 81%	
Tree nuts	Pistachio-cashew, 34–100%	>97% of patients with pistachio allergy react to cashew, but only 34–83% of patients with cashew allergy will react to pistachio
	Walnut-pecan, 75–100%	>97% of patients with pecan allergy will react to walnut, but only 75–91% of patients with walnut allergy will react to pecan
	Peanut or other tree nuts, 20–60%	
Fish	Other fish, 50%	Canned fish is less allergenic
Shellfish	Crustacean-mollusk, 10–20%	
	Mollusk-mollusk, 50%	
	Crustacean-crustacean, 50%	
Wheat	Rye, barley, 20%	Rice, oat, and corn are more likely tolerated than rye and barley
	Rice, oats, corn, <5%	
Fruits	Peach and other Rosaceae fruits (apple, cherry, plum, pear, apricot, almond, apricot), 50%	Sensitization to peach associated with both systemic reactions and pollen-food allergy syndrome
	Melons (watermelon, cantaloupe, honeydew) and kiwi, avocado, peach and banana; 90%	30–50% of patients with latex allergy react to certain fruits or vegetables (e.g. avocado, banana, kiwi, peach, potato, tomato, bell pepper), but only 10% of patients with primary allergy to these foods react to latex
Beef	Cow's milk, 90%	

Soy allergy primarily affects infants and children, with most cases resolving before adulthood. Similar to peanut, seed storage proteins (Gly m 5 and Gly m 6) seem to be the most clinically significant allergens. Gly m 2 and Gly m 3 are birch pollen homologues and can be associated with pollen-food allergy syndrome.[2] Cross-sensitization between peanut and soy is common but clinical cross-reactivity is <5%.[2,4] Some studies show that up to 80% of subjects with peanut allergy are sensitized to lupin, a legume commonly consumed in Mediterranean countries, but estimated rates of clinical reactivity range from 4 to 29%.[11] Less is known with regard to clinical cross-reactivity for other legumes, although one study found that ~80% of patients with lentil allergy react to chickpea, green pea, or both.[5] There are also reports of peanut clinical cross-reactivity with fenugreek, a legume frequently used as a spice in Asian and Mediterranean cooking.[12]

TREE NUTS AND SEEDS

Tree nut allergy affects up to 1% of the population and is usually life-long. The most common tree nut allergens in the United States are walnut and cashew, whereas hazelnut

is more common in Europe.[13] Similar to legumes, seed storage or lipid transfer proteins are typically responsible for systemic reactions, whereas labile birch pollen analogues may produce symptoms of pollen-food allergy syndrome.[2] For example, sensitization to the hazelnut allergens Cor a 9 and Cor a 14 is associated with more severe symptoms.[13,14] Sensitization to Cor a 8 is also associated with severe symptoms in Mediterranean populations.[13] In contrast, sensitization to Cor a 1, a Bet v 1 homolog, is associated with pollen-food allergy syndrome.[13]

Results of studies demonstrated high rates of cross-sensitization among tree nuts and peanuts due to shared homologous proteins, but rates of clinical cross-reactivity are less clear. Closely related tree nuts, such as cashew and pistachio or walnut and pecan, have high rates of cross-sensitization (>90%) but variable rates of clinical cross-reactivity.[15–17] Recently, a multicenter European study, the Pronuts study,[15] reported that 97% of children with pistachio allergy were allergic to cashew, whereas only 83% of children allergic to cashew reacted to pistachio, as determined by food challenge. In contrast, another European study found that only 34% of individuals sensitized to cashew had clinically significant pistachio allergy.[16] With regard to clinical cross-reactivity between walnut and pecan, results of studies showed that 97–100% of subjects with pecan allergy were allergic to walnut but only 75–91% of children with walnut allergy reacted to pecan.[15,17] Clinical cross-reactivity among other tree nuts, as well as between peanut and any tree nut, has been estimated to range between 20 and 60%.[2,4,13]

Sesame and mustard seed are the most common seed allergies reported, although rates vary significantly depending on geographic location. Cross-sensitization between different seeds as well as between seeds, peanuts, and tree nuts has been reported but data on clinical cross-reactivity are limited.[18] The Pronuts study[15] found that the food challenge–proven rate of coexistent sesame, peanut, and/or tree nut allergy was ~60%.

FISH AND SHELLFISH

Fish and shellfish allergies are estimated to affect ~0.9% and 2.9% of the United States population, respectively, and are more common in adults than in children. Fish refers to finned fish such as cod, salmon, and tuna. In patients allergic to one fish, ~50% are cross-reactive to another or multiple types of fish.[4] Parvalbumin is the primary allergen in finned fish responsible for clinical cross-reactivity, although patients reactive to a single fish may be sensitized to other proteins.[2] Some patients are able to tolerate canned or highly heated forms, which also suggests sensitization to less-stable proteins. Importantly, some fish allergens may be altered during creation of standardized extracts for testing and thus prick-to-prick skin testing to fresh fish should be considered in the appropriate clinical context.[5]

Shellfish includes crustaceans (crab, lobster, shrimp) and mollusks (squid, snail, and bivalves [*e.g.*, clam, mussel, scallop, oyster]). Tropomysins are the major allergens in shrimp and possibly other shellfish.[2] Similar to fish, clinical cross-reactivity is common among shellfish because ~50% of patients with either crustacean or mollusk allergy will react to other animals within the same category.[2,4] Studies are limited with regard to rates of clinical cross-reactivity between crustaceans and mollusks, but 10–20% of patients with either mollusk or crustacean allergy are estimated to be allergic to a food in the other category.[5] Because clinical cross-reactivity between fish and shellfish is low, patients with fish allergy need not avoid shellfish and vice versa, although they should be vigilant for possible cross-contamination. Tropomysins are found in other invertebrates, such as dust mites and cockroaches, and cross-sensitization between these allergens and shellfish has been reported.[19] Although a common misconception, there is no cross-reactivity between seafood and radiocontrast material.

GRAINS

IgE-mediated reactions to cereal grains, including wheat, barley, and rye, have been described. Major allergens in wheat include alpha-amylase inhibitor (associated with baker's asthma), lipid transfer proteins, and gliadins.[2] Sensitization to omega-5-gliadin (Tri a 19) is predictive of severe reactions to wheat in children and is also associated with wheat-dependent, exercise-induced anaphylaxis. Cross-sensitization among grains is common, but clinical cross-reactivity to two or more grains is unusual except for wheat, barley, and rye.[5] In one study of subjects with wheat allergy, 55% reacted to barley but all tolerated rice and corn.[20] There is a high degree of homology between grain allergens and grass pollens, which is likely responsible for most cases of clinically insignificant sensitization to wheat and other grains.

FRUITS AND VEGETABLES

IgE-mediated reactions to fruits and vegetables are the most commonly reported food allergies in adults. Most patients are sensitized to heat-labile pathogen-related proteins with homology to pollen allergens. These patients generally develop symptoms of pollen-food allergy syndrome on ingestion of fresh fruits or vegetables to which they are sensitized, whereas cooked forms of the culprit foods are usually tolerated.[1] Some patients, particularly those with peach allergy, are sensitized to stable lipid transfer proteins and may develop systemic reactions on ingestion of the culprit food.[21] There are also certain groups of fruits associated with high rates of clinical cross-reactivity. For example, ~50% of patients with peach allergy will react to other Rosaceae fruits (apple, cherry, plum, pear, apricot, almond). In addition, ~90% of patients with allergies to

melons (watermelon, cantaloupe, honeydew) will react to kiwi, avocado, peach, and banana.[4]

Similar to pollen-food allergy syndrome, exposure to natural rubber latex can sensitize some individuals to fruits and vegetables, such as avocado, banana, kiwi, chestnut, peach, potato, tomato, and bell pepper. Roughly 30–50% of patients with latex allergy will exhibit clinical cross-reactivity to those foods. In contrast, only ~10% of patients with allergies to avocado, kiwi, or banana will have a concurrent latex allergy.[22]

MAMMALIAN MEATS

Mammalian meat allergies are generally rare, with beef allergy being the most common. The major protein allergens in mammalian meat are serum albumins and immunoglobulins.[23] Cross-sensitization has been described between the meats of different mammalian species, but patterns of clinical cross-reactivity have not been well studied. More than 90% of children with beef allergy are reactive to cow's milk, with sensitization to bovine serum albumin being the primary predictor of reactivity.[5] Clinical cross-reactivity between mammalian meat and animal epithelia due to homologous albumins can also occur, as has been described in patients with "pork-cat" syndrome.[23] Finally, the carbohydrate antigen galactose alpha-1,3,-galactose that is present in all nonprimate mammalian meats has been increasingly identified as responsible for delayed anaphylaxis after consumption of red meat in the southeastern United States.[24]

CLINICAL PEARLS

- Patients allergic to cow's milk are >90% likely to cross-react to goat and sheep milk, and ~10% likely to react to beef.
- Clinical cross-reactivity between peanuts and tree nuts is common; patients allergic to one or more of these foods should be tested for cross-sensitization to the other foods if not already tolerating them in their diet.
- Patients with peanut allergy do not typically need to avoid other legumes, although caution should be exercised if lupin is introduced.
- Patients with shellfish allergy and fish allergy should generally avoid other foods within the same category; however, patients with shellfish allergy do not need to avoid fish and *vice versa*.
- Patients with wheat allergy may react to rye or barley but are likely to tolerate oats, rice, and/or corn.

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