

Hidden and Cross-Reacting Food Allergens

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KEY CONCEPTS

- False assumptions of multiple food allergy may derive from reactions to hidden ingredients, or from positive allergy tests to cross-reactive foods.
- Hidden or unexpected exposure to food allergens may occur from undeclared ingredients, cross-contact with an allergen, or from exposures not expected to carry food proteins, such as kissing, from airborne proteins, or in medications and cosmetics.
- Among related foods, cross-sensitization (positive tests) is more common than clinical cross-reactivity.
- Clinical cross-reactivity is more common (>35%) among tree nuts, fish, shellfish, certain mammalian milks, and certain fruits, than among grains and legumes (<20%).
- Individualization by testing and oral food challenge may be needed to confirm tolerance of potentially cross-reactive foods.

Introduction

The physician is often challenged by the patient who experiences reactions to multiple foods that are sometimes phylogenetically related and sometimes apparently unrelated. The two topics discussed in this chapter, hidden and cross-reacting food allergens, are ones that may lead to a conclusion of multiple food allergies. Table 25.1 lists several of the considerations for evaluating multiple food hypersensitivity. For the two general categories presented here, hidden food allergens may lead to the false assumption of multiple food hypersensitivities, because one or more previously identified food allergens are responsible for reactions to seemingly diverse food products through exposure in an unexpected manner. On the other hand, cross-reactivity may account for reactions to a variety of related foods of plant or animal origin based on immune reactions toward homologous proteins shared among them. Topics concerning the specific food proteins that frequently account for cross-reactions, oral allergy syndrome, and diagnostic methods and management of food allergy will not be emphasized here; rather, this chapter will introduce concepts and provide information to enhance the evaluation of patients with

possible multiple food allergies, in regard to hidden and cross-reacting food allergens.

Hidden food allergens

For the purpose of this chapter, the term “hidden food allergens” will refer to a variety of unexpected ways in which an individual may be exposed to food allergens [1–3]. Of course, a “hidden” food allergen may only be unknown to the consumer, not necessarily to a manufacturer or chef who provided the food. The use of peanut flour to thicken and provide unique flavor to tomato sauce or chili is one such example that underscores the importance of maintaining a clear line of communication when an allergic individual is depending on food provided from a restaurant or other commercial source without ingredient labels. Food proteins can also turn up in many unexpected ways. For example, a teacher may use egg white to make finger paints smoother or wheat may be an ingredient in modeling clay. Table 25.2 lists the ways in which exposure may occur within the context of hidden food allergens.

Commercial food products: manufacturing and labeling issues

Consumers with a known food allergy depend on accurate food label ingredient lists to determine the safety of their food. Their safety is predicated both on the accuracy of the

Table 25.1 Considerations when evaluating patients with apparent MFA

Type	Cause	Example
<i>True reactions to multiple food types</i>		
True MFA	True allergic reactions to multiple, diverse food allergens. Usually in highly atopic patients	Reactions to egg, milk, wheat, and soy in one child
Intolerance	Non-immune-mediated conditions causing adverse reactions when various foods are ingested	Intolerance of fat resulting in gastrointestinal upset to fatty meats; lactase deficiency resulting in symptoms from milk; fructose/sorbitol intolerance resulting in "acidic" diarrhea from multiple fruits
Cross-reactivity	Homologous proteins among foods and between foods and environmental allergens	Pollen-allergy syndrome, latex–fruit syndrome, panallergens in related foods
<i>False assumption of multiple food allergy</i>		
Multiple positive prick skin tests/RAST	Multiple tests for IgE antibody are positive and reactions are assumed to be related without further evaluation (history, oral challenge)	Atopic individual inappropriately tested to a wide battery of allergens has numerous positive tests and told to avoid all of the foods
Hidden ingredients	Reactions to apparently diverse products because of exposure to a hidden/unexpected source of one or a few previously identified allergens	Milk-allergic child reacts to soy desserts and canned tuna because they contain casein
Unproven tests	Use of unproven/experimental tests that identify multiple problematic foods for potentially vague symptoms	IgG antibody tests identify 43 foods purported to cause weakness in an elderly patient
Psychological	Previous food-allergy-related traumatic event generalizes to increasing numbers of reactions that are based on psychological triggers	A severe peanut-allergic patient develops paleness and syncope when exposed to products that she thought contained peanut, but did not
Misperception	Chronic complaints attributed to adverse reactions to a variety of foods without a pathophysiological explanation	Patient with perception that his headaches are triggered by orange foods (carrot, sweet potato, squash, orange soda)

MFA, multiple food allergies.

Table 25.2 Modes of exposure to hidden/unexpected food allergens

Mode of exposure	Examples
Hidden ingredient in manufactured product	Undeclared ingredient, contaminant, ambiguous label, non-standard terminology
Non-food item	Pet food, shampoo, ointment
Medications	Egg, soy, and milk (often in clinically irrelevant concentrations) in a variety of medications (carriers)
Cross-contact	Shared equipment in restaurant/bakery causes contamination
Non-food allergen found in food	Dust mite contamination of grains
Unexpected exposure route	Skin contact from residual food on table/chair, inhalation of fumes during cooking, exchange of saliva (kissing, shared straws, etc.)

label and their ability to decipher the statements on the label. Errors on both fronts can occur. Sometimes mistakes are apparent from simple misunderstandings: egg substitutes may catch the eye of an egg-allergic consumer who

may assume the product is egg-free and not realize that egg is clearly labeled as an ingredient. In other cases, the consumer simply cannot trust the label since ingredient labels may not accurately reflect the presence of allergens. In January 2001, the US Food and Drug Administration (FDA) reported an investigation of 85 selected food companies in Minnesota and Wisconsin [4]. The investigation was, in part, in response to a significant increase in the number of recalls of products for undeclared allergens. The firms investigated were small, medium, and large bakeries; candy manufacturers; and ice cream manufacturers and they were reviewed for their approach to food allergens. Assays were conducted to determine the presence of peanut and egg in finished products. They found that 25% of products contained undeclared allergenic ingredients, often from cross-contamination, and 47% of the firms did not check their products to ensure that the labels were accurate. The medical literature contains reports of clinical reactions to foods with allergen contamination not declared on the ingredient label for several allergens including egg, milk, and peanut [2,5–8]. The potential for minor ingredients to cause severe reactions has been recognized for decades [3,9].

Governmental oversight of manufactured products varies worldwide [10–12]. In the United States, regulations pertaining to the declaration of food ingredients and the impact on the declaration of allergens are evolving. Until January 2006, allergens may have been referred to with scientific names such as “casein” or with ambiguous terms such as “natural flavor.” Several studies have described allergic reactions and confusion ascribed to these labeling practices [13,14]. The recognized deficiencies in manufacturing and labeling in the United States came under scrutiny by a variety of professional, public, governmental, and lay organizations with a variety of suggestions for improvements, resulting in new labeling laws. Labeling laws changed in the United States as the Food Allergen Labeling and Consumer Protection Act of 2004 came into effect in January 2006. The law requires that the eight major allergens or allergenic food groups – milk, egg, fish, shellfish, tree nuts, wheat, peanut, and soy – must be declared on ingredient labels using plain English words. The law requires that the specific type of allergen, in regard to grouped allergens such as nuts, fish, or shellfish, be named. The law still allows terms such as “natural flavor” or “whey” on labels, but plain English must additionally disclose a major allergen. While the law includes the listed eight major allergens/allergenic food groups, additional allergens, for example garlic, sesame, poppy, etc., may not be disclosed clearly. For example, the word “spice” may be used for these allergens. Of note, some countries include sesame as a major allergen that must be disclosed. The US law applies to all types of packaged foods except for meat, egg, and poultry products, and raw agricultural foods such as fruits and vegetables in their natural state. The plain English words used to identify the foods may be placed within the ingredient list or as a separate statement “contains.” In regard to soy, terms such as soybean, soy, and soya are considered interchangeable.

The FALCPA legislation has not defined a safe “threshold” of included allergen and several food ingredients may now be included on labels that did not previously disclose them. Processing aids such as soy lecithin, a fatty derivative of soy oil which may contain minute quantities of soy protein, may now be disclosed. The law acknowledges that certain forms of highly processed oils may not contain any appreciable protein, for example, soy oil. The law which is likely to be revised by petition and updates is available from the Center for Food Safety and Applied Nutrition, a branch of the FDA (www.cfsan.fda.gov). Studies on consumer interpretation of labels and actions based on the wording used on labels indicate that the law should result in reduced allergic reactions, but will also likely result in avoidance of foods that were safely consumed before labeling was required for potential trace protein contamination [15]. In some cases where ambiguous terms remain, a manufacturer may need to be called by a consumer to clarify ingredients.

Provisionary cautions used on labels, such as “may contain,” are not regulated by the FALCPA legislation. These statements have been used by companies when a particular allergen is not an ingredient of the food, but that allergen may contact or become a part of the food despite good manufacturing processes. Labeling for the possibility of allergen contact is voluntary, and various terms are used at the discretion of the manufacturer such as “processed on shared equipment with...,” “manufactured in a facility that processes...,” and many others. The risk is impossible to determine for the consumer. In practical terms, food-allergic individuals, specifically teenagers and young adults, are increasingly ignoring these precautionary warnings; in a study of 174 adolescent subjects, 42% were willing to eat foods labeled “may contain” an allergen [16]. The degree of risk may vary by the product/manufacturer and the degree and frequency of reactions among persons with allergies who are not heeding these warnings is unknown.

Cross-contact

Cross-contact (cross-contamination) is an issue that is relevant in and out of commercial manufacturing. Small quantities of allergens can trigger reactions, including amounts that may be carried over in various ways from an “unsafe” food to one that is purportedly free of the allergen. Simple examples of this problem abound. In the home setting, a knife used to spread peanut butter could next contact and contaminate jelly. In restaurants, shared grills, pans, food processors, and other equipment used without thorough cleaning between preparations may be a source of cross-contact. Bakeries pose similar problems as shared bowls, mixing equipment, and pans may allow for cross-contact. In ice cream shops, dipping scoops from one flavor to the next can cross-contaminate otherwise safe flavors. In the school setting, cross-contact has been identified as a possible source of inadvertent exposures to peanut and tree nut through shared utensils and cross-contact of foods [17]. A problematic issue of cross-contact, combined with false assumptions by consumers is demonstrated by “pareve” labeled products [2]. Pareve is a religious term meaning non-dairy and does not ensure absence of milk proteins. These products are often sought out by unknowing milk-allergic consumers and consequently reactions are described to products with this label due to cross-contamination by cow’s milk.

Restaurant meals also pose challenges for those with food allergies. The author and colleagues evaluated allergic reactions in peanut- and tree-nut-allergic subjects that were associated with restaurants and food from establishments such as bakeries and ice cream shops [18]. Of 5149 voluntary registrants in the US National Peanut and Tree Nut Allergy Registry, 13.7% indicated that they had experienced a reaction in these types of establishments. A review of 156 episodes among 129 randomly selected registrants revealed that 39% of reactions were due to peanut

or tree nut hidden in the food and not overtly identifiable to the patron (e.g. in sauces, dressing, egg rolls). In 22% of cases, cross-contact was involved primarily due to the use of shared cooking/serving supplies. There were particular problems regarding cross-contact in desserts, Asian cooking, and buffets.

The lessons learned from the study of reactions in restaurants and food establishments highlight several important issues concerning allergen exposure in these settings and others. Ideally, procedures would be in place to manage food-allergic patrons. Personnel would receive training about food allergy, the potential for trace protein contamination to trigger reactions, a variety of methods to avoid cross-contamination and how to activate emergency assistance in the event of a reaction. A clear line of communication among the patron, server, and those preparing the foods must be established and maintained. Menu items should include a description of the ingredients in the food. In addition, the restaurant personnel would be advised about the potential for cross-contamination (shared fryers/blenders/utensils/mixers/pans/grills, contamination by garnishing bars, hands, and gloves) and methods to avoid this problem (use freshly cleaned, separate equipment, change gloves). For prevention of reactions due to cross-contact to be efficacious in any setting, education of the allergic individual about these issues is paramount.

Unexpected sources of food proteins in non-food items and in medications

Allergenic food proteins may be components of a variety of items not meant for ingestion by humans. Pet foods may contain a variety of classically allergenic food proteins such as milk, peanut, soy, and seafood. Inadvertent ingestion by young children must be considered when these foods are left on the floor for household pets with curious allergic youngsters in the vicinity. A number of hair-care products and topical skin-care products contain food proteins (e.g. almond, soy). Reactions to these products applied topically are usually not severe.

Patients with food allergies and their physicians must always consider that a drug (or vaccine) reaction may be induced by a food ingredient in the drug. Well-known examples of this phenomenon include egg protein [19,20] in influenza and yellow fever vaccines and gelatin [21] in a variety of other vaccines. The measles–mumps–rubella (MMR) vaccine is no longer considered to contain appreciable egg protein. It may be administered to egg-allergic persons without increased risk, as indicated in the Red Book 2006 Report of the Committee on Infectious Diseases of the American Academy of Pediatrics. A study on influenza vaccine in children with egg allergy evaluated the risk using a vaccine with a known amount of egg protein [20] and suggested a split, two-dose (one-tenth then nine-tenths) regimen for safety. Since the amount of egg in the vaccine may vary from lot to lot, and may be unknown, the two-dose regimen may

not be universally applicable. Allergists may perform skin testing with the vaccine to better define risks. The Red Book 2006 Report of the committee on Infectious Diseases of the American Academy of Pediatrics suggests a regimen of gradual dosing in persons who are deemed to require influenza or yellow fever vaccination despite their anaphylactic egg allergy. Of note, the nasal influenza vaccine contains a higher amount of egg protein than the injection and should not be used in persons with egg allergy. Vaccines that may include gelatin include some of the diphtheria, tetanus, and pertussis vaccines; influenza vaccine; Japanese encephalitis; mumps; measles, mumps and rubella; typhoid; varicella (chicken pox) and yellow fever vaccines.

Many other food-related ingredients used in medications have not been well studied in terms of their allergic potential. Pharmaceutical-grade lactose is used in many medications and the clinical relevance of possible residual milk protein has not been well established. One report identified milk protein in the lactose used in several dry-powdered inhalers used for asthma [22]. Egg or soy lecithin and soy oil are found in a variety of medications, but the clinical relevance to most individuals with these allergies remains unexplored.

Non-food allergens in foods

There are case reports of non-food allergen contamination of foods resulting in allergic reactions. For example, dust mites may contaminate flour mixtures and cause severe reactions when ingested by dust-mite-allergic patients [23,24]. This appears to be a particular problem in tropical climates. The use of latex gloves by food handlers has resulted in unexpected reactions when these foods are ingested by latex-allergic individuals [25,26]. Indeed, latex allergens are detectable on food products following handling with powdered latex gloves [27]. Insofar as parasites are not intentionally consumed, it is worthwhile to note that the nematode *Anisakis simplex* that infests fish can induce allergic reactions. This appears to be a problem particularly in Spain and other countries with high fish consumption and is associated with undercooking [28].

Non-standard exposure routes to food allergens

There appear to be exceptional cases where topical exposure to foods result in systemic reactions [29]. More commonly, however, topical exposure leads primarily to isolated, local skin reactions. In such cases, residual food proteins on tables and chairs may induce rashes. Although not truly hidden or unexpected, school craft projects using peanut butter (peanut butter covered pine cone birdfeeders) are commonly responsible for reactions despite school's awareness about avoiding peanut as an ingestant [17].

Airborne exposure to food allergens is not unexpected in a variety of industrial food-processing settings (e.g. baker's asthma) but is a potential hidden source outside of these settings. There are several published case reports of acute allergic reactions to airborne food particles such as string

bean [27], lentil [28], meats [30], and seafood [31] usually during cooking (rapidly boiling milk, frying eggs, steaming soups, sizzling fried seafood, etc). Reactions have been verified in challenge settings [32]. There are also a few reports concerning peanut reactions to inhalation of peanut dust during commercial airline flights [33–35]. In airliners, the hypothesis is that the powdery material from roasted peanuts becomes airborne [36] and can induce reactions in that setting of a closed space when many bags are being opened simultaneously. These reactions are generally isolated to the upper and sometimes lower respiratory tract.

Another source of unintended and unexpected oral exposure is through saliva from an individual who ingested an allergen, for example, through contact during kissing or sharing cups, straws, or utensils. Kissing, in particular passionate kissing, is a common route of exposure. Of 379 allergy patients in the United States with peanut/tree nut/legume or seed allergy, 5.3% reported reactions from kissing [37]. Of 839 food-allergy patients in Denmark (self-reported) who recalled possible kissing, 16% reported a reaction [38]. These two reports also support the notion that the food was usually, but not always, recently ingested and that brushing teeth may not be sufficient for removing the allergen. A study was undertaken to determine the time course of peanut protein (a marker protein Ara h 1) in saliva after a meal of peanut butter and possible methods for cleaning [39]. Detection of Ara h 1 was performed by a monoclonal-based ELISA (detection limit, 15–20 ng/ml). Most (87%) subjects with detectable peanut after a meal had undetectable levels by 1 hour with no interventions. None had detectable levels several hours later following a peanut-free lunch. This result indicates (95% confidence) that 90% would have undetectable Ara h 1 in saliva under these circumstances. Piloted cleaning procedures only led to undetectable levels in 1 in 5 subjects, but the methods with a waiting period reduced salivary Ara h 1 to undetectable in 8 of 10 (wait-brush) and 8 of 9 (wait, gum) subjects. The studies were performed with peanut butter and results may vary with other allergens or forms of peanut. There is one case report [40] of a mild reaction to peanut despite a 2-hour wait, brushing teeth, and chewing gum. Food-allergic reactions from blood transfusion or semen are theoretically possible but highly unlikely.

Cross-reacting food allergens

When an allergic response is established toward a particular protein, presentation of a homologous form of that protein in another substance also may trigger an allergic response (cross-reaction). Hence, true allergic reactions to multiple foods may follow initial sensitization caused by one food. The initial sensitization may occur by the oral or inhaled route. In fact, as discussed in Chapter 7, the appropriate immunological response to ingested proteins is tolerance, and for most individuals food allergies do not occur despite other atopic

respiratory illnesses. However, one way that immune tolerance to foods may be bypassed is by initial sensitization that occurs to homologous proteins that contact the respiratory tree (e.g. pollen-allergy syndrome). In this way, IgE antibody toward the respiratory allergen can also induce disease when the homologous protein is ingested. As will be discussed below, the scenario of respiratory sensitization resulting in food allergy may apply to pollens, latex, and insect emanations that are airborne allergens with homologous proteins in foods. In addition to sensitization by the airborne route, typical sensitization to a particular food through the gastrointestinal tract can result in reactions to, usually related, foods containing homologous proteins. Reactions in this setting are typically more severe because they involve proteins that are capable of sensitization by ingestion and these are proteins that are typically more stable to digestion and able to enter the systemic circulation [41]. In some cases, more distantly related foods or environmental allergens contain common (conserved) homologous (pan)allergens. To complicate matters further, however, there may be homologous, allergenically important sequences (epitopes) shared even among more distantly related foods that may trigger reactions in some individuals (e.g. seed storage proteins in peanut, sesame, and tree nuts) [42].

Plant-derived proteins responsible for allergy include various families of pathogenesis-related proteins, protease and α -amylase inhibitors, peroxidases, profilins, seed storage proteins, thiol proteases, and lectins [43,44] while homologous animal proteins include muscle proteins, enzymes, and various serum proteins. Remarkably, typical food allergens derive from just these few, out of thousands, of protein families. Over 70% identity in primary sequence is generally needed for cross-reactivity [45]. The biochemical attributes of these proteins will not be discussed here, but the focus will rather be on the clinical relevance of potential cross-reactivity.

To elicit a clinical response, it is presumed that the causal food protein must maintain the ability to present the epitope in question in an immunologically relevant form. That is, evidence that there is IgE binding to a potentially cross-reactive food protein (sensitization demonstrated by prick skin test or RAST) is not evidence of clinically relevant allergy to the food. In fact, it is quite common to find food-specific IgE antibody by prick skin tests or RASTs to foods related to the one causing the index reaction. For example, using RASTs, Barnett *et al.* [46] screened sera from 40 peanut-allergic patients against 10 other legumes and demonstrated IgE binding to multiple legumes for 38% of patients. Similarly, Bernhisel-Broadbent and colleagues [47] studied 62 children with allergy to at least one legume and found that 79% had serological evidence of IgE binding to more than one, and 37% bound all six legumes. The scenario is similar for tree nuts [48–50]. In our studies of tree-nut-allergic children [48], 92% of 111 patients with peanut and/or tree

nut allergy had IgE antibody to more than one tree nut. In all of these cases, however, it is much more common to find that the food to which there is cross-sensitization is actually tolerated when ingested [51]. Factors that determine the clinical appearance of allergy in the face of sensitization are complex and relate to the host (immune response, target organ hyperreactivity) and the allergen (liability, digestibility) [41]. Presumably, these factors also bear upon the clinical relevance of potentially cross-reactive foods. The information to follow may be of particular value in deciding on the best approach to diagnose potential allergy to cross-reactive foods (the utility of *in vivo* and *in vitro* tests).

Cross-reactions among specific foods/food families

Legumes

Despite the high rate of cross-sensitization to legumes (beans), clinical cross-reactions are uncommon. Peanut and soy represent two of the most highly allergenic legumes that are dietary staples in North America, and yet the rate of clinical cross-reactivity is low. However, Bock and Atkins [52] studied 32 children with peanut allergy confirmed by DBPCFCs and found that 10 (31%) had a positive skin test to soy, but only one (3% of those with peanut allergy) had a clinical reaction to soy. In considering a wider variety of legumes, only 3 (1.8%) of 165 children with atopic dermatitis evaluated with DBPCFCs reacted to more than one legume despite 19% reacting to at least one [53]. Bernhisel-Broadbent and Sampson [47] specifically addressed the issue of legume cross-reactivity by performing open or DBPCFCs in 69 highly atopic children with at least one positive skin test to a legume. Oral challenges to the 5 legumes (peanut, soybean, pea, lima bean, green bean) resulted in 43 reactions in 41 patients (59%). Only 2 of 41 with any one positive challenge reacted to more than one legume (5%).

There are limited data to suggest that particular legumes are more likely than others to trigger reactions and also that the types of beans consumed in various cultures (e.g. lupine used whole or as flour in breads) also impact the rate of cross-reactions [54–57]. For example, 11 of 24 (44%) French children with peanut allergy [56] had positive skin tests to lupine, and of 8 subjects who underwent DBPCFCs (6 children) or labial challenges (2 children) to lupine, 7 reacted. As a probable reflection of cultural and geographical influences on the diet, allergy to lentil is more common than to peanut in Spain [58]. Furthermore, of 22 Spanish children with lentil allergy evaluated for reactions to other legumes [59], 6 had a history of reacting to chick pea, 2 to pea, and 1 to green bean. These findings raise suspicion for multiple legume allergy in those reacting to lentil, lupine, and chick pea, but more studies in a variety of geographic settings utilizing blinded challenges to confirm reactivity are needed to quantify the risks.

In regard to a clinical approach, it is clear that multiple legume allergy is relatively uncommon, but it is common to observe positive skin tests to multiple legumes in an atopic patient with reaction to one. Thus, it is not appropriate to assume that a particular patient has multiple legume allergy; rather, a more definitive evaluation should be undertaken to ensure tolerated beans are available as personal preferences would indicate. Furthermore, tests for specific IgE antibody in this scenario may be helpful primarily when they are negative, because positive tests are common despite clinical tolerance. It must be appreciated that an individual with more than one legume allergy is at higher risk for even more legume reactions and that lentil, lupine, and chick pea may be slightly more likely to be involved in this scenario than others (pea, string bean).

Tree nuts

Clinical reactions to tree nuts can be severe [60], potentially fatal, and can occur from a first apparent exposure to a nut in patients allergic to other nuts [61]. Due to the frequency of severe reactions, there are no comprehensive studies on clinical cross-reactivity among tree nuts. Bock and Atkins [52] performed challenges to one or more nuts in 14 children and at least 2 reacted to multiple nuts (as many as 5 types). Ewan [60] reported allergy to multiple tree nuts in over a third of 34 patients evaluated for tree nut allergy. Similarly, our group noted that in 54 children with a tree nut allergy, reactions to more than one nut occurred in 37% [48]. Some nut allergens may be homologous and cause reactions (e.g. in pistachio/cashew [62]) while others may be homologous but rarely elicit clinical cross-reactivity (e.g. proteins in coconut and walnut [63]).

Legume/tree nuts/seeds

Co-sensitization to allergenic foods such as peanut, tree nuts, and seeds (sesame, poppy, mustard) is common. In a study of 731 subjects in the United Kingdom, 59% sensitized to peanut were also sensitized to hazelnut and/or Brazil nut [49]. Although clinically significant cross-reacting proteins have not yet been described, it is known that some amino acid sequences (epitopes) are highly homologous among some of the seed storage proteins that constitute the major allergens in these foods [42]. Co-allergy to peanut and tree nut has been reported between 23% and 50% in referral populations of atopic patients [48,60,64,65]. This observation raises the question: Is this high rate of co-reactivity due to homologous proteins or to expected allergies to intrinsically allergenic foods among highly atopic patients? The tools are available to answer this important question and the methodical searches are underway. Until more data are available, the clinician must consider the age of the patient, history, and sensitization in considering categorical elimination of these allergenic foods [66]. Reactions to seeds such as sesame, mustard, and poppy are being increasingly

reported [50,67–69], and cross-reactivity with foods (hazel, kiwi, other seeds) and pollens is potentially important.

The full clinical implications of possible cross-reactivity among peanuts, tree nuts, and seeds are not yet established. From a practical perspective, considering the potential severity of the allergy and issues with accurate identification of particular nuts in prepared foods, caution would seem prudent and total elimination of the nut family (perhaps with the exception of previously tolerated nuts eaten in isolation) is often suggested [48,70]. These recommendations are potentially over-restrictive. There is no consensus as to whether seeds should be considered as highly likely to elicit reactions among individuals with peanut/tree nut allergy, but based on the studies thus far, some caution is warranted.

Fish

In a prevalence study in the United States [71], reactions to multiple fish among those with any fish allergy was 67%. Among those with fish allergy ($n = 58$), 19 reported a reaction to only one type, 5 to 2 types, 13 to 3–9 types and the remainder were uncertain. In serological studies of 10 subjects with codfish allergy, sensitization to salmon was strong while sensitization to halibut, flounder, tuna, and mackerel were lower [72]. To best evaluate clinical cross-reactivity, it would be necessary to perform oral food challenges to multiple types of fish, shellfish, or mollusks in persons allergic to at least one type. The clinical studies concerning fish allergy mirror those of tree nut allergy in that clinical reactions to multiple fish is a common phenomenon, high cross-sensitization rates are even more common, and the allergic reactions tend to be severe [73–75]. A few studies have utilized DBPCFCs challenges to evaluate fish allergy. In 10 US children evaluated with DBPCFCs to 4–6 species of fish, and in whom reactions were confirmed to at least 1 species, 3 reacted to more than one type [73]. Hansen and colleagues [76] evaluated 8 adults with codfish allergy proven by DBPCFCs. Sensitization to plaice, herring, and mackerel was nearly 100% and among patients exposed to each (6, 5, and 6 patients, respectively), all had a history of clinical reactions. In a study of 6 adults from Denmark with a positive DBPCFC to at least one of 3 fish (catfish, codfish, snapper) and challenged to at least 2 types, 4 reacted to more than one species [74]. Several studies that did not utilize DBPCFCs provide additional information that is in agreement with these formal studies. In 61 children with a history of fish allergy exposed to 2–8 species, 34 (56%) reacted to all and 27 (44%) tolerated some types [75]. In a study of 20 codfish-allergic Italian children [77], a high frequency of positive skin tests (from 5% to 100% for each of 9 species tested) was documented. For those who ingested the fish to which antibody was detected, the clinical reaction rate per fish based on history was 25–100% depending on the species. Some fish were more problematic than others in these cod-allergic children. Eel, bass, sole, and tuna

most frequently provoked reactions and salmon, sardine, and dogfish were least likely to induce symptoms. Regional exposure patterns are relevant. Pascual and colleagues [78] from Spain evaluated the relevance of cross-reactivity among 6 regionally important species in 79 children with fish allergy where codfish is not a common food. While all subjects had positive skin tests to multiple species, only 31 of 79 (39%) had clinical reactions, and hake and whiff had the highest while albacore had the lowest reaction rates. In contrast to the studies that indicate a high likelihood of multiple fish allergy, several reports demonstrate that isolated allergy to a single species of fish occurs (e.g. tropical sole [79], swordfish [80]). This apparently occurs because of immune responses toward species-specific allergens since there is relative absence of IgE antibody to the common fish allergens (Gad c 1). Formal studies of fish hypersensitivity have also indicated that fish proteins may be denatured when heated (canned) or lyophilized, and this must be appreciated when considering a history of specific fish that appear to be tolerated in some forms, for example reactive to salmon but not reactive to canned salmon [81].

In summary, a fish-allergic patient is at high risk for reactions to other fish, but may tolerate some fish species, and may therefore deserve further evaluation with supervised oral challenges if desirous of ingesting other fish. The facts that fish allergy can be severe and that cooking/canning and other processing can alter allergenicity must be considered during these evaluations [81].

Shellfish

The clinical impression is that reactions to multiple crustaceans are fairly common, but there are few clinical studies addressing this issue. In a prevalence study in the United States [71], reaction to multiple Crustacea for those with allergy to any was 38%, and for mollusks was 49%; only 14% with crustacean allergy reported a mollusk allergy. In that study, estimation of the rate of allergies to multiple types of seafood was complicated by the fact that not all participants were exposed to all types of seafood and, after a reaction, avoidance of multiple types of seafood was often undertaken. Among those with allergy to shrimp, lobster, and/or crab who indicated specific knowledge of an allergy among these ($n = 232$), 62% indicated allergy to one, 20% to 2, and 18% to all 3 types. Among scallops, clams, oysters, and mussels ($n = 67$), 51% reacted to one, 19% to 2, 8% to 3 and 22% to all 4 types. Forty-one persons with shellfish allergy (14%) reported an allergy to both one or more Crustaceae and one or more mollusks/bivalves.

The major shared allergenic protein is invertebrate tropomyosin found in crustaceans (shrimp, crab, lobster) [82–84] and mollusks (oyster, scallop, and squid) [85]. Not surprisingly, the rate of cross-sensitization is high. In 16 atopic, shrimp-allergic patients, >80% had positive PSTs to crab, crayfish, and lobster [86]. Unfortunately, formal clinical

studies to determine the rate of clinical reactivity are lacking. In a study of 11 patients with immediate reactions to shrimp ingestion, the reaction rate to lobster, crab, and crayfish was 50–100% per species [87]. On the other hand, there are individuals who react not only to shrimp alone, but to specific species of shrimp [88].

Also poorly defined is the risk of mollusk allergy for Crustaceae or mollusk-allergic individuals. Lehrer and McCants [89] reported a study of six oyster-sensitive, seven oyster and Crustacea, and 12 Crustacea-sensitive patients in whom serologies were evaluated. Most of the reactions to oyster were isolated to the gastrointestinal tract and not associated with oyster-specific IgE antibody. However, among 19 patients with sensitivity to Crustacea, 47% had positive RASTs to oyster, indicating potential cross-reactivity. In another study evaluating 9 patients with shrimp anaphylaxis, binding to tropomyosin of 13 crustaceans and mollusks was universal [85]. These studies only evaluated serologies, so the rate of clinical reactivity is unclear but apparently not great.

Invertebrate tropomyosin is also found in airborne insect allergens found in cockroach and dust mite [85,90,91], which raises the possibility of sensitization by the respiratory route. There is a case report of a seafood restaurant worker who developed IgE to tropomyosin and occupational asthma to both scallop (mollusk) and shrimp (crustacean) [92]. In a report of wheezing induced by snail consumption in 28 patients, RAST inhibition studies indicated that house dust mite sensitization was the likely initial sensitizing event [91]. There are several reports linking allergen immunotherapy with *D. pteronyssinus* to development of severe reactions to mollusks and crustaceans. Five of six patients from the Canary Islands with anaphylaxis to limpet, a mollusk, had received immunotherapy with dust mite [93]. In a prospective study, two of 17 patients receiving dust mite immunotherapy developed cross-reactive IgE antibodies to tropomyosin and oral symptoms to shrimp [94].

Overall, Crustaceae species represent an increased risk of cross-reactivity with a potential for severe reactions and a potentially high rate of clinical symptoms. However, there are individuals who tolerate most types, so individualization, done cautiously, may be warranted. Allergy to mollusks is less well established and appears less common. Allergy to, and immunotherapy with, dust mite may be an additional risk factor, but determination of the precise risks requires further investigation.

Cereal grains

Wheat, rye, barley, and oat share homologous proteins with grass pollens and with each other [95,96] and this may account for the high rate of co-sensitization among these foods [95]. Among children with at least one grain allergy undergoing DBPCFCs to multiple grains, 80% were tolerant of all other grains. Caution is warranted, but clinical

reactivity to multiple grains appears uncommon and individualization warranted for these common foods.

Avian and mammalian food products

For avian foods such as chicken, sensitization has been described to α -livetins found in feathers, egg, and meat [97]. Reactions to chicken meat is often based on reactivity to this protein (22–32%) [97,98]. Chicken meat allergy is uncommon [99], but when it occurs in the absence of egg allergy, the risk of reaction to multiple species of avian meats (turkey, pheasant, quail) may be increased. This observation is probably because a meat-specific protein, rather than within species meat–egg specific protein, is causally related to reactions [100,101]. Cross-reactive proteins among various avian eggs are also common [102], but the clinical implications have not been systematically studied. Conversely, allergy to one egg type may not guarantee reactions to others; reactions to duck and goose egg, in the absence of hen's egg allergy has been described [103].

Some patients with allergy to mammalian milks also react to mammalian meats [104]. This observation may be due to homologous proteins or, more likely, proteins that are identical and are found in meat and milk from the same animal. A study employing oral challenges showed that 10% of 62 cow's milk-allergic (CMA) children reacted to beef [105]. Heating and other cooking processes can reduce the allergenicity of beef [106], so well-cooked beef is less likely to cause a problem for those with CMA. Reactions to multiple mammalian milks are more common than milk–meat reactions. *In vitro* studies showed extensive cross-reactivity among sheep, cow, ewe, buffalo, and goat milks [107], but not to camel's milk [108]. Oral challenge studies showed goat's milk to be unsafe for patients with CMA since 92% of 26 CMA patients reacted to goat's milk [109]. Mares' milk appears comparatively safe as only 4% of 25 children with CMA reacted to it [110].

For practical purposes, it is important to note that most milk-allergic patients will tolerate beef and that cooking the meat well may improve tolerability, but that some highly milk-allergic individuals do experience reactions. Overall, individualization is usually warranted. It may be less important to try to identify a mammalian milk for those with CMA since cross-reactivity is very high and suitable alternatives (soy milk, rice milk) are available. Cross-sensitization is more common within than between avian and mammalian meats, but clinical correlation with sensitization is generally under 50%, so individualization is also warranted [111].

Fruit, pollens, and latex

Oral allergy syndrome

Oral allergy syndrome (pollen–food allergy syndrome) is described elsewhere (Chapter 11) and the focus here will be on cross-reactions within families of fruits. Several studies have selected patients based on particular fruit allergies, rather

than pollen allergies, and evaluated for reactions to related fruits. Rodriguez and colleagues [112] evaluated 34 adults in Madrid with reported allergy to Rosaceae foods (peach, apple, apricot, almond, plum, pear, and strawberry). Eighty-two percent had positive PSTs and/or RASTs to at least one of the foods with a median of five positive foods per patient. Clinical reactivity determined by DBPCFCs was less than 10% for those positive to pear and up to 90% for peach (overall, 35% with a positive skin test reacted to a given food). Multiple fruit allergy was common in the 22 who reacted to at least one fruit (46%). Peach was the dominant allergenic fruit; 46% reactive to peach reacted to another Rosaceae fruit. Pastorello and colleagues [113] studied patients selected for a history of reactions to peach confirmed through open oral food challenges; among the 19 patients evaluated, 63% reacted to at least one other fruit among cherry, apricot, and plum. Of 19 patients with melon allergy confirmed by DBPCFC (of 54 patients suspected), 94% reacted to at least one of the following related fruits: watermelon, avocado, kiwi, chestnut, banana, peach [114].

Severity of reactions to these foods is an important issue. Pollen-related fruit allergy is usually mild (oral allergy syndrome) and yet in one study, 8.7% experienced associated systemic symptoms outside of the gastrointestinal tract [115], 3% at some time experienced systemic symptoms without oral symptoms, and 1.7% experienced anaphylactic shock. It is becoming clear why some patients are more likely to experience severe reactions. There is evidence that when fruit allergy develops in the absence of pollen allergy, reactions are directed not only to Bet v 1 or profilins, but also to lipid transfer proteins (LTP). Reactions involving fruits with homologous LTPs are more likely to be severe [116,117]. Fernandez-Rivas and colleagues [118] compared patients with Rosaceae fruit allergy with and without pollenosis and found that systemic reactions occurred in 82% without pollenosis compared to 45% with pollenosis. Anaphylactic shock was also more common in the former (36% versus 9%, respectively). A similar theme was noted for hazelnut, where patients without pollenosis experienced severe reactions and had IgE binding to hazelnut proteins that were heat-stable [119]. Asero [120] found that individuals with positive skin tests to commercial Rosaceae food extracts were more likely to experience systemic reactions than those only positive to fresh extracts, (64% versus 6%, $p < 0.001$). This observation is presumably explained by the likelihood that more stable allergens are present in the commercial extract compared to fresh fruit proteins, which include labile proteins that are more likely to induce only symptoms of oral allergy. Crespo *et al.* [121] evaluated 65 adults diagnosed with clinical allergy to one or more fruits for allergy to other related foods. Thirty-four of those tested (52%) were found to be clinically allergic to more than one fruit. Food challenges with potential cross-reactive foods uncovered 18 further reactions in 14 (22%) out of 65. Only 8% (18/223) of positive results for allergy

tests to potential cross-reactive foods investigated were clinically relevant. Therefore, elimination of related fruits without oral challenge testing, that is based on skin test or RAST results, could have resulted in unnecessary restriction of 205 foods in the 65 people studied. However, it was worrisome that 18 food reactions in one-fifth (14/65) of patients could have been missed if oral challenges/evaluations were not pursued. The clinical lesson is that once a patient experiences more than oral symptoms to a fruit, a careful search by history and/or challenge may be warranted to prove the safety of related fruits. Furthermore, positive skin tests to commercial extracts and a lack of pollen allergy may indicate a higher risk of significant reactions.

Latex–food syndrome

Commonly reported latex cross-reactive foods include banana, avocado, kiwi, chestnut, potato, and papaya, and numerous latex allergens cross-react with food and pollen proteins [122,123]. In a study of 136 latex-allergic patients evaluated by RAST to 12 foods reported to be involved in latex–food reactions, 69% were positive to at least one food and 49% were positive to more than one [124]. Challenges were not performed, but only one-third of the 42% of patients who reported reactions to the particular fruit had a positive RAST. In another study of 47 latex-allergic patients, 100 of 376 food skin tests were positive but only 27 (7.2%) were associated with clinical reactions [125]. In evaluating the converse situation of fruit-allergic patients (excluded if there was a well-known risk factor for latex allergy) for sensitization to latex, 86% of 57 patients had serum latex-specific IgE antibody, and 11% experienced clinical reactions to latex [126].

Evaluation of natural rubber latex–food cross-reactivity is complicated by cross-reacting pollens, foods, and co-allergy to various substances with potential allergenic relationships. There may be clinical value in differentiating individuals with isolated food, pollen, or latex sensitization [127]. Levy and colleagues [128] evaluated adults with latex allergy with ($n = 24$) and without ($n = 20$) pollenosis and a group without latex allergy and with pollenosis ($n = 25$) for allergies to 12 foods (by convincing history) classically associated with latex and pollen allergy. In those with isolated latex allergy, reactions were reported to banana (4), avocado (4), kiwi (2), melon and peach (1 each) while those with pollenosis were more likely to react to Rosaceae foods and celery. In the pollen-allergic groups, positive skin tests to the foods were found in 45%, but for isolated latex allergy, only 24% were positive. The numbers of reactions among those with positive tests were generally less than 25%, except for reactions to banana, avocado, and kiwi, which approached 50% in those with isolated latex allergy. Overall, caution is warranted and individualization is necessary, but for patients with allergy to latex, banana, avocado, or kiwi, it may be prudent to consider potential reactions to the related foods.

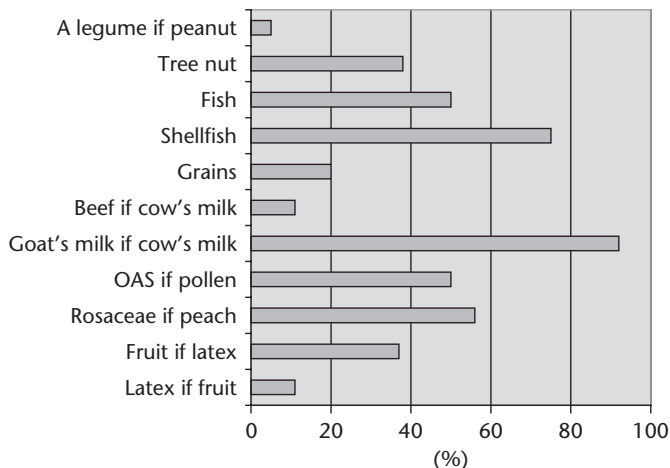


Figure 25.1 The approximate rate of clinical reactivity to at least one other related food. The probability of reacting to related foods varies, depending on numerous factors (data reviewed in Sicherer [51]). OAS, oral allergy syndrome/pollen-food syndrome.

Summary and management

As outlined in preceding sections, there is a high likelihood of sensitization to foods that bear homologous allergens, but clinical reactivity correlates poorly. It is therefore necessary to consider a variety of issues when evaluating a patient for the possibility of multiple food hypersensitivities on the basis of possible cross-reactions. Among these are *a priori* reasoning about likelihood of reactions (Fig. 25.1), severity of reactions, social and nutritional importance of the food, and the (poor) predictive value of tests for IgE antibody in this setting. However, for most foods and for most patients, multiple food allergies are relatively uncommon and the extra effort to prove which foods are or are not tolerated is worthwhile.

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