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Clinical implications of cross-reactive food allergens

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As a consequence of the general increase in allergic sensitization, the prevalence of hypersensitivity reactions to multiple foods that share homologous proteins has become a significant clinical problem. A variety of these allergens conserved among plants (eg, profilin and lipid transfer proteins) and animals (eg, tropomyosin and caseins) have been characterized. Although studies with molecular biologic techniques have elucidated the nature of these ubiquitous allergens, clinical studies have lagged behind. The physician is called on to determine the risk of reaction to related foods among legumes, tree nuts, fish, shellfish, cereal grains, mammalian and avian food products, and a variety of other plant-derived foods that may share proteins with pollens, latex, and each other. Clinical evaluations require a careful history, laboratory evaluation, and in some cases oral food challenges. The pitfalls in the evaluation of food allergy–unreliable histories and limitations in laboratory assessment primarily caused by false-positive skin prick test responses/RAST results are magnified when dealing with cross-reactive proteins. This review focuses on the clinical data regarding cross-reacting food allergens with the goal of providing a background for improved risk assessment and a framework on which to approach these difficult clinical questions. (J Allergy Clin Immunol 2001;108:881-90.)

Key words: *Food allergy, cross-reactivity*

Abbreviations used
CMA: Cow's milk allergy
DBPCFC: Double-blind, placebo-controlled, oral food challenge
IT: Allergen-specific immunotherapy
LTP: Lipid transfer protein
OAS: Oral allergy syndrome
SPT: Skin prick test

The diagnosis of clinical hypersensitivity to a particular food allergen is attained through careful history, physical examination, a priori reasoning concerning clinical and epidemiologic features of food allergy, and judicious selection and interpretation of tests, including skin tests, RASTs, elimination diets, and oral food challenges.[1,2] Allergists are painfully familiar with the pitfalls of these evaluations, some of which are related to the limitations of tests for food-specific IgE antibody. Compounding the clinical challenge of identifying particular causal food allergens is the phenomenon of cross-reactivity among various plant and animal proteins. Exposure to homologous proteins can trigger reactions or may be clinically silent while provoking positive test responses for food-specific IgE antibody. Is the patient with peanut, fish, or apple allergy likely to react to related foods? The molecular basis of cross-reactivity was recently reviewed[3,4] and will not be highlighted in this article. Rather, this review will focus on the clinical data regarding cross-reacting food allergens with the goal of providing a framework on which to approach these difficult clinical questions.

GENERAL CONCEPTS

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,[4] whereas homologous animal proteins include muscle proteins, enzymes, and various serum proteins. The conservation of these proteins across biologic substances affects cross-reactivity in several ways. Certain foods (eg, peanut) are able to sensitize and elicit reactions after oral exposure (type 1 allergy) and could trigger responses that generalize to related foods (legumes). Other foods (eg, apple) with labile proteins are not strong oral sensitizers. In this latter group of foods, however, sensitization to homologous proteins encountered through respiratory exposure (eg, birch pollen) may mediate reactions to cross-reacting proteins in the food (type 2 allergy) with generally mild clinical manifestations.

Factors that determine the clinical appearance of allergy in the face of sensitization are complex and relate to the host (immune response and target-organ hyperreactivity) and the allergen (lability and digestibility).[5] Similar factors determine the clinical relevance of cross-reacting food proteins (Table I). Over 70% identity in primary

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TABLE I. Features that affect clinical relevance in cross-reactions

Immune responses	Protein characteristics	Exposure
Affinity of IgE antibody	Homology	Concentration
Degree of response (concentration of IgE)	Solubility	Route (oral and respiratory)
	Stability-digestibility	Cofactors (exercise and ethanol)

sequence is generally needed for cross-reactivity.[3] Poorly soluble proteins are less likely to elicit reactions unless cofactors, such as exercise or ethanol ingestion, increase absorption (eg, food-dependent, exercise-induced anaphylaxis to wheat gamma-gliadin[6]). Resistance to digestive enzymes is associated with an increased risk of systemic reactions and oral sensitization.[7,8] Additional factors influencing clinical correlation are allergen concentration, differential expression of allergens during ripening,[9] and cooking.[10] Host immune responses are also important: the risk of reaction rises with increasing concentration of serum food-specific IgE antibody,[11] and antibody affinity is also likely to be influential.[3]

CROSS-REACTIONS AMONG VARIOUS FOODS

Legumes

It is common to find positive test responses for IgE antibody to several beans in individuals who are clinically reactive to one type. Using RASTs, Barnett et al[12] screened sera from 40 patients with peanut allergy against 10 other legumes and demonstrated IgE binding to multiple legumes for 38% of patients. Bernhisel-Broadbent and Sampson[13] studied 62 children with allergy to at least 1 legume and found that 79% had serologic evidence of IgE binding to more than 1 legume, and 37% bound all 6 legumes.

Despite the high rate of cross-sensitization, clinical cross-reactions are uncommon, as demonstrated by studies of allergenic legumes, such as peanut and soy. Among 113 children with atopic dermatitis evaluated with double-blind, placebo-controlled, oral food challenges (DBPCFCs), only 1 (0.8%) had clinical allergy to both foods, despite 19% reacting to peanut and 5% to soy.[14] Bock and Atkins[15] studied 32 children with peanut allergy confirmed by DBPCFCs and found that 10 (31%) had a positive skin test response to soy, but only 1 (3% of those with peanut allergy) had a clinical reaction to soy. In recent reviews of children with peanut allergy in which DBPCFCs were not routinely performed, higher estimates of reactions are reported: 14% of 102[16] and 15% of 223 children.[17]

In considering a wider variety of legumes, only 3 (1.8%) of 165 children with atopic dermatitis evaluated with DBPCFCs reacted to more than 1 legume, despite 19% reacting to at least 1 legume.[18] Bernhisel-Broadbent and Sampson[13] specifically addressed the issue of legume cross-reactivity by performing open tests or DBPCFCs in 69 highly atopic children, with at least 1 positive skin test response to a legume. Oral challenges to the 5 legumes (peanut, soybean, pea, lima bean, and green bean) resulted in 43 reactions in 41 patients (59%). Only 2 (5%) of 41 with any 1 positive challenge reacted to more than 1 legume. The authors concluded that elimination of all legumes in individuals with clinical reactions to 1 legume was unwarranted, despite the high prevalence of patients with multiple legume-positive skin prick test (SPT) responses.

These studies did not include large batteries of legumes, and it may be that particular types are more allergenic or cross-reactive.[19-21] In an evaluation of children with peanut allergy in France,[21] 11 (44%) of 24 had positive skin test responses to lupine, and of 8 subjects who underwent DBPCFCs (6 children) or labial challenges (2 children) to lupine, 7 reacted. In vitro studies showed the potential causal protein to be an allergen (43 kd) common to both legumes but not a major peanut allergen. Regional dietary habits and pollen exposure may influence the epidemiology of legume allergy. In Spain, for example, allergy to lentil was more common than allergy to peanut,[22] and of 22 children with lentil allergy evaluated for reactions to other legumes,[23] 6 had a history of reacting to chickpea, 2 to pea, and 1 to green bean. These findings raise suspicion for multiple legume allergy on those reacting to lentil, lupine, and chickpea, but more studies in a variety of geographic settings are needed to quantify the risks.

Tree nuts

Assessment of cross-reactivity among tree nuts is complicated by shared allergens among the nuts and between nuts and other plant-derived foods and pollens. Clinical reactions to tree nuts can be severe,[24] potentially fatal, and can occur from a first exposure to a nut in patients allergic to other nuts.[25] Serologic studies have indicated a high degree of IgE binding to multiple tree nuts.[16,26,27] In our studies of children with tree nut allergy,[16] 92% of 111 patients with peanut allergy, tree nut allergy, or both had IgE antibody to more than 1 tree nut, and 37% of 54 had experienced convincing reactions and had specific IgE antibody to more than 1 nut.

Because of the frequency of severe reactions, there are no comprehensive studies on cross-reactivity to tree nuts. Bock and Atkins[15] performed challenges to 1 or more nuts in 14 children, and at least 2 reacted to multiple nuts (as many as 5 types). Similar to our studies,[16] Ewan[24] has reported coallergy to multiple tree nuts in over a third of 34 patients evaluated for tree nut allergy. 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 suggested.[16,28] These recommendations are potentially overrestrictive. Some nut allergens may be homologous and cause reactions (eg, in pistacchio-cashew[29]), whereas others may be homologous but rarely elicit clinical cross-reactivity (eg, proteins in coconut and walnut[30]).

Legumes, tree nuts, and seeds

Cosensitization to allergenic foods, such as peanut, tree nuts, and seeds (sesame, poppy, and mustard) is common. In a study of 731 subjects in the United Kingdom, 59% sensitized to peanut were also sensitized to hazelnut, Brazil nut, or both.[26] Although clinically significant cross-reacting proteins have not yet been described, coallergy to peanut and tree nut has been reported between 23% and 50% in referral populations of atopic patients.[16,24,31,32] The rate of coallergy is much lower in unselected populations (2.5%).[33] The clinician must consider the age of the patient, history, and perhaps sensitization in considering categoric elimination of these allergenic foods.[34] Reactions to seeds, such as sesame, mustard, and poppy, are reported,[27,35,36] and cross-reactivity with foods (hazel, kiwi, and other seeds) and pollens is potentially important, but the full clinical implications are far from established.

Fish

Several reports demonstrate that isolated allergy to a single species of fish (eg, tropical sole[37] and swordfish[38]) occurs and usually does so in the relative absence of IgE antibody to common fish allergens (Gad c 1). However, positive skin test responses to multiple fish in subjects with fish allergy is almost the rule,[39-41] and clinical cross-reactivity is also common. In 61 children with a history of fish allergy exposed to 2 to 8 species, 34 (56%) reacted to all, and 27 (44%) tolerated some types.[41] In a study of 20 Italian children with codfish allergy,[42] a high frequency of positive skin test responses (from 5% to 100% per each of 9 species tested) was documented. For those who ingested the fish to which antibody was detected, the clinical reaction rate per fish on the basis of history was 25% to 100%. In these children with cod allergy, 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 et al[43] from Spain evaluated the relevance of cross-reactivity among 6 regionally important species in 79 children with fish allergy in whom codfish is not a common food. Although all subjects had positive skin test responses to multiple species, only 31 (39%) of 79 had clinical reactions; hake and whiff had the highest and albacore the lowest reaction rate.

A few studies have used challenges to evaluate fish allergy. In 10 US children evaluated with DBPCFCs to 4 to 6 species of fish and in whom reactions were confirmed to at least 1 species, 3 reacted to more than 1 type.[39] Hansen et al[44] evaluated 8 adults with codfish allergy proven by DBPCFC results. 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 result to at least 1 of 3 fish (catfish, codfish, and snapper) and challenged to at least 2 types, 4 reacted to more than 1 species.[40] In summary, a patient with fish allergy is at high risk for reactions to other fish but may tolerate some fish species and may deserve further evaluation with supervised oral challenges if desirous of ingesting other fish. The fact that fish allergy can be severe and that cooking-canning and other processing can alter allergenicity must be considered during these evaluations.[10]

Shellfish

Invertebrate tropomyosin is a panallergen with significant sequence homology identified in Crustacea, such as shrimp,[45] crab,[46] and lobster[47]; mollusks, such as oyster, scallop, and squid[48]; parasites, such as anisakis[49]; and insects, such as cockroach, grasshopper, and dust mite,[48,50,51] with less homology to vertebrate tropomyosin.[52] Although the clinical impression is that reactions to multiple crustaceans are fairly common, there are few clinical studies addressing this issue. In 16 atopic patients with shrimp allergy, greater than 80% had positive SPT responses to crab, crayfish, and lobster.[53] In 11 patients with immediate reactions to shrimp ingestion, the reaction rate to lobster, crab, and crayfish was 50% to 100% per species.[54] On the other end of the spectrum is a report of several individuals with reactions to only particular species of shrimp.[55] Overall, Crustaceae represent an increased risk of cross-reactivity, with a potential for severe reactions.

Even less well defined is the risk for mollusk allergy for individuals with allergy to Crustaceae or mollusk. Lehrer and McCants[56] reported a study of 6 oyster-sensitive, 7 oyster- and Crustacea-sensitive, 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. Although oyster-specific IgE antibody did not correlate with clinical reactions to oyster, 9 of 19 Crustacea-sensitive subjects had positive RASTs to oyster, indicating cross-reactive proteins. In another study evaluating 9 patients with shrimp anaphylaxis, binding to tropomyosin of 13 crustaceans and mollusks was universal.[48] These studies lacked systematic clinical evaluations, and therefore, the risk of mollusk reactivity is unclear (although the overall impression is that it is not common).

Tropomyosin is found in several common aeroallergens, which raises the possibility of sensitization by the respiratory route. Interestingly, there is a case report of a seafood-restaurant worker who had IgE to tropomyosin and occupational asthma to both mollusk (scallop) and crustacean (shrimp).[57] In a report of asthma induced by snail consumption in 28 patients, RAST inhibition studies indicated that house dust mite sensitization was the likely initial sensitizing event.[51] There are several reports linking allergen immunotherapy (IT) with *Der-*

matophagoides pteronyssinus to development of severe reactions to mollusks and Crustacea. Five of 6 patients from the Canary Islands with anaphylaxis to limpet, a mollusk, had received IT with dust mite.[58] In a prospective study, 2 of 17 patients receiving dust mite IT had cross-reactive IgE antibodies to tropomyosin and oral symptoms to shrimp.[59]

It appears that there is a high, but not absolute, clinically relevant cross-reactivity among crustaceans, and reactions can be severe. Allergy to mollusks is less well established and appears less common. Allergy to and IT with dust mite may be an additional risk factor, but determination of the precise risks requires further investigation.

Cereal grains

Cereal grains (eg, wheat, rye, barley, and oat) share homologous proteins with grass pollens and each other.[60,61] This may account for the high rate of cosensitization to these foods,[60] but among 145 children with positive SPT responses to cereal grains, only 21% exhibited clinical reactivity during challenges. In addition, among those with reactions to 1 grain, 80% were tolerant of all other grains. Caution is warranted, but clinical reactivity to multiple grains appears uncommon.

Mammalian and avian food products

Cross-sensitization is more common within than between avian and mammalian meats, but clinical correlation with sensitization is generally under 50%.[52] For avian foods, sensitization has been described to α-livetin found in feathers, egg, and meat and associated with reactions to chicken meat in 22% to 32%.[62,63] Although avian meat allergy is uncommon,[64] when chicken meat allergy is present without egg allergy, the risk of reaction to multiple species of avian meats (turkey, pheasant, and quail) may be increased.[65,66] Cross-reactive proteins among various avian eggs is also common,[67] but the clinical implications have not been systematically studied. Reactions to duck and goose egg in the absence of hen's egg allergy has been described.[68]

Homologous proteins influence reactions to mammalian meats and milks. A study with oral challenges showed that 9.7% of 62 children with cow's milk allergy (CMA) reacted to beef.[69] Heating and other cooking processes can reduce the allergenicity of beef,[70] and therefore, well-cooked beef is less likely to cause a problem for those with CMA. The allergic relevance of cross-reactivity among a variety of mammalian milks has recently been beautifully elucidated. In vitro studies showed extensive cross-reactivity among sheep's, cow's, and goat's milk[71] and among cow's, ewe's, goat's, and buffalo's milk, with no significant binding to camel's milk.[72] Oral challenge studies of goat's milk unequivocally showed this to be unsafe for patients with CMA: 92% of 26 patients reacted.[73] However, only 4% of 25 children with CMA allergy reacted to mare's milk.[74] Unfortunately, most of the readily available animal milks are problematic for those with CMA.

FRUIT, POLLENS, AND LATEX

Pollen-food allergy syndrome (oral allergy syndrome)

Oral allergy syndrome (OAS) is classically described as isolated oral symptoms caused by labile proteins in fresh fruits and vegetables that share homology with proteins in pollens (the initial source of sensitization[75,76]). Several clinical associations have been described (eg, birch pollen with Rosaceae fruits, ragweed with melons, and mugwort with celery). The number of foods reported to be involved in the syndrome is ever expanding,[77-79] and the molecular basis for the reactions is continually being elaborated.[4] Cooked forms of the foods (eg, apple sauce) are typically tolerated. The epidemiology varies by the exposure to pollens. Among those with allergic rhinitis, 23% to 76% experience OAS to at least 1 food.[80-82] Among those with OAS, upward of 70% react to more than 2 foods.[83] Considering the almost doubling of sensitization to aeroallergens over the past 2 decades in the United States,[84] an epidemic is brewing.

Several studies have selected patients on the basis of particular fruit allergies rather than pollen allergies and evaluated for reactions to related fruits. Rodriguez et al[85] evaluated 34 adults in Madrid with reported allergy to Rosaceae foods (peach, apple, apricot, almond, plum, pear, and strawberry). Eighty-two percent had positive SPT responses, RAST results, or both to at least 1 of the foods with a median of 5 positive foods per patient. Clinical reactivity determined by DBPCFCs was less than 10% for pear and up to 90% for peach (overall, 35% with a positive skin test response reacted to a given food). Multiple fruit allergy was common in the 22 (46%) who reacted to at least 1 fruit. Peach was the dominant allergenic fruit; 46% reactive to peach reacted to another Rosaceae fruit. Pastorello et al[86] studied patients selected for a history of reactions to peach confirmed through open oral food challenges; among 19 evaluated, 63% reacted to at least 1 other fruit among cherry, apricot, and plum. Worse, of 19 patients with melon allergy confirmed by DBPCFC (of 54 patients suspected), 94% reacted to at least 1 of the following related fruits: watermelon, avocado, kiwi, chestnut, banana, and peach.[87]

Severity of reactions to these foods is an important issue. In a review of several studies with a total of 1,361 patients allergic to food pollen with OAS,[88] 8.7% experienced associated systemic symptoms outside of the gastrointestinal tract, 3% at some time experienced systemic symptoms without oral symptoms, and 1.7% experienced anaphylactic shock. Hence the term *pollen-food syndrome* may be more appropriate than *OAS*. What distinguishes those at risk for 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 (LTPs). Reactions involving fruits with homologous LTPs are more likely to be severe.[89,90] Fernández-Rivas et al[91] compared patients with Rosaceae fruit allergy with and without pollinosis

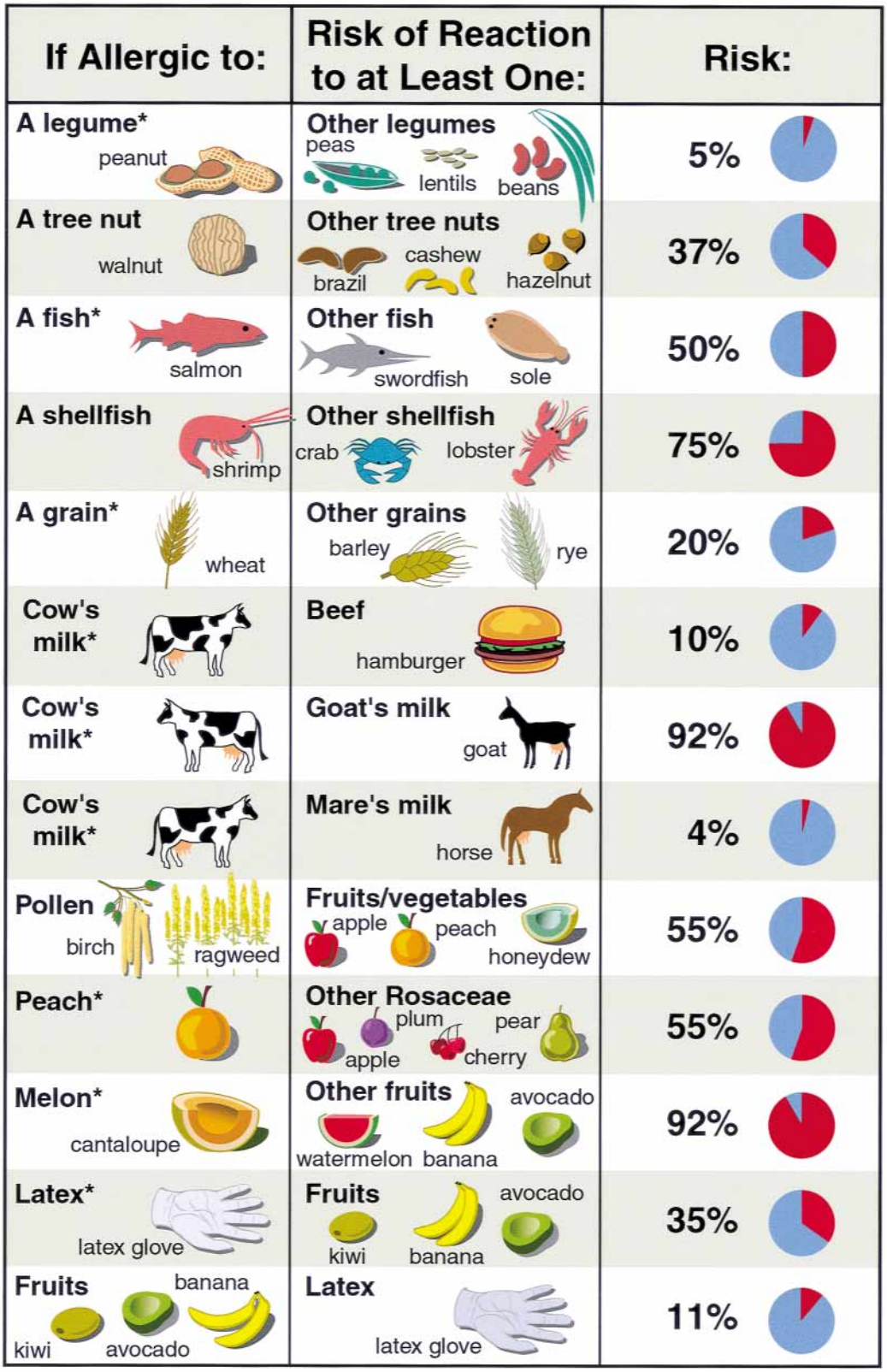

FIG 1. Approximate rate of clinical reactivity to at least 1 other related food. The probability of reacting to related foods varies, depending on numerous factors (see text). *Data derived from studies with DBPCFCs.

and found that systemic reactions occurred in 82% without compared with 45% with pollinosis. Anaphylactic shock was also more common in the former (36% vs 9%, respectively). A similar theme was noted for hazelnut, in which patients without pollinosis experienced severe reactions and had IgE binding to hazelnut proteins that were heat stable.[92] Asero[93] found that individuals with positive skin test responses to commercial Rosaceae food extracts (presumably enriched for stable allergens) were more likely to experience systemic reactions than those with responses positive only to fresh extracts (64% vs 6%, $P < .001$).

Latex-food syndrome

Evaluation of natural rubber latex-food cross-reactivity is complicated by cross-reacting pollens and foods and coallergy to various substances with potential allergenic relationships. Commonly reported cross-reactive foods include banana, avocado, kiwi, chestnut, potato, and papaya, and numerous latex allergens cross-react with food and pollen proteins.[94,95] In a study of 136 patients with latex allergy evaluated by means of RAST to 12 foods reported to be involved in latex-food reactions, 69% of responses were positive to at least 1 food, and 49% were positive to more than 1 food.[96] Challenges were not performed, but only one third of the 42% of patients who reported reactions to the particular fruit had a positive RAST result. In another study of 47 patients with latex allergy, 100 of 376 food skin test responses were positive, but only 27 (7.2%) were associated with clinical reactions.[97] In evaluating the converse situation of patients with fruit allergy (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.[98]

There may be clinical value in differentiating individuals with isolated food, pollen, or latex sensitization. Levy et al[99] evaluated adults with latex allergy with (n = 24) and without (n = 20) pollinosis and a group without latex allergy and with pollinosis (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 (n = 4), avocado (n = 4), kiwi (n = 2), and melon and peach (n = 1 each), whereas those with pollinosis were more likely to react to Rosaceae foods and celery. In the groups with pollen allergy, positive skin test responses to the foods were found in 45%, but for isolated latex allergy, only 24% of responses were positive. The numbers of reactions among those with positive test responses were generally less than 25%, except for reactions to banana, avocado, and kiwi, which approached 50% in those with isolated latex allergy.

DIAGNOSIS AND MANAGEMENT

The typical diagnostic routine for classical food allergy has recently been reviewed.[1,2] The limitations and difficulties of the food allergy evaluation are compounded when dealing with issues of cross-reactive proteins-panallergens. Evaluation of food-specific IgE antibody is particularly confusing because the risk of false-positive test results is great. Performing batteries of tests for screening is likely to result in confusion. Still, a negative test response is valuable to conclude that clinical reactivity is unlikely. For many of the cross-reactive proteins, lability of proteins in commercial extracts is an issue. SPTs with the prick-prick method with fresh fruits and vegetables may increase sensitivity when evaluating these labile allergens[100]; however, they carry additional concerns about reproducibility, triggering systemic reactions, and increased false-positive results.

The oral food challenge remains the only modality to identify true clinical reactions. Unfortunately, the clinician could be facing an enormous number of oral challenges with potentially severe reactions. In practical terms many patients will not undergo oral challenges but may maintain diets arrived at through their clinical history, reasoning on the basis of the available literature, and the results of tests for specific IgE antibodies. The importance of obtaining a definitive diagnosis to allow the broadest diet depends on nutritional needs, food preferences, social issues, and other factors. It is easy to develop a pattern of unnecessarily avoiding multiple related foods. As outlined above, the rather low rate of clinical allergy within some food families (legumes and grains) begs for more thorough evaluations. As a guide, the epidemiologic likelihood of reacting to a related food is depicted in Fig 1. The clinical history of tolerance should be paid attention to because it is essentially a free oral food challenge indicating that the food is safe (at least for that point in time). Except perhaps for fish and shellfish allergy (with an appropriately suspicious history and positive skin test response), all of the studies indicate that oral challenges confirm nonreactivity for a majority of specific foods tested. This encouraging feature should be emphasized.

A number of considerations come into play once a decision to perform oral food challenges is made. Risk assessments are based on the history, food involved, and test results to determine the rate and quantity of administration and precautions (eg, office vs hospital setting). Because many of the cross-reactive foods have labile proteins (fruits, vegetables, meat, and fish), additional care is needed in preparing food for blinded challenges. Freeze-drying, heating, and other processing methods could reduce allergenicity, leading to a false-negative result.[10,87,101] When evaluating pollen-related allergy, additional problems arise. Ripening[102] and localization of allergen (peel of Rosaceae fruits[103]) may influence challenge results. An open challenge with the food in its natural form should always follow a negative blinded challenge result.

Some of the salient features derived from the literature that may be helpful in these assessments are summarized in Table II. Unfortunately, there are no certainties. Uncertainty increases when a potentially cross-reactive food has never been ingested (anaphylaxis can occur on a first ingestion of a food with cross-reactive proteins[104]) or

TABLE II. Special risk factors

Food family-relationship	Severity*	Special considerations
Legumes	High, peanut; variable, others	Allergy to lentil, lupine, or chickpea may represent a higher likelihood for legume cross-reactions. Established allergy to more than 1 indicates higher risk for multiple allergies
Tree nuts	High	High rate of coallergy, cosensitization, severity, and difficulty in avoiding particular nuts may warrant class restriction. Some patients may have pollen-associated reactions
Fish	High	Canned fish are less allergenic. High rate of cross-reactivity may warrant class restriction; importance of food may warrant individualized challenges. Isolated species allergy has been reported.
Crustaceae	High	Risk of multiple reactions may warrant class restriction, but importance of food may warrant individualized challenges. Allergy to isolated species is reported. Sensitization or immunotherapy with dust mite may increase risks.
Mollusks	Variable	No comprehensive studies, but risk appears lower between Crustaceae and mollusk than within Crustaceae. Sensitization or immunotherapy with dust mite may increase risks.
Grains	Variable	Importance of food group and low risk of clinical cross-reactivity warrants individualization.
Pollen-related food allergy	Low-Variable	Finite but low risk of systemic reactions. Risks increased if history of systemic reactions to 1 of the related foods, reactions to cooked forms, or positive commercial SPT results. Variations by type of pollen exposure. Allergy to related foods without sensitization to related pollen or pollens may indicate increased severity and cross-reactions within food family.
Rosaceae family foods	Variable	Established allergy to any one Rosaceae family food increases risks. Some members are less problematic (eg, pear), and others are more problematic (eg, peach); also as above for pollen-related foods.
Melon allergy	Variable	Established allergy carries high risk of reaction to other gourds.
Latex allergy	Variable	If isolated latex allergy, then primary foods involved include banana, kiwi, avocado, and chestnut, but associated pollen allergy broadens scope.
Meats	Variable	Rare allergy but potential for avian-avian and mammalian-mammalian cross-reactions is greater than between types. Chicken allergy without egg increases likelihood of reacting to multiple avian meats.
Milks	Variable	Except perhaps for mare and camel, mammalian milks cause cross-reactions.

In most cases oral food challenges prove that most related foods are tolerated, even when SPT responses, RAST results, or both are positive.
*General impression.

when an individual is presenting a history of reacting to increasing numbers of related foods.[19] A question arises also for those with food-pollen syndrome: Should they avoid the food or food family if they do not mind the mild oral symptoms? There are no definitive answers, but the results mentioned above caution that there is a finite risk for reactions beyond the mouth and even anaphylaxis, which can occur even to previously tolerated or unsuspected foods.[87,90,91] The natural progression of these allergies has not been elucidated. Clearly, an open discussion with the patient is mandatory in deciding on an approach, and consideration for prescribing self-injectable epinephrine should be made with each evaluation.

More specific in vitro diagnostic methods may be on the horizon because the causal cross-reacting allergens are being characterized.[3,105] Testing directed to panallergens, such as tropomyosin or LTPs, may prove helpful, but more studies with DBPCFCs in a variety of settings will be needed. In addition to numerous novel therapeutic approaches being investigated in allergy, the approach to treating pollen-related food allergy with pollen IT has had some success.[106-109] Future therapies with anti IgE, specific panallergen IT, and others may prove helpful for these panallergic patients.

SUMMARY

The prevalence and magnitude of clinical allergy caused by cross-reacting proteins and panallergens appears to be increasing and reflects an increase in atopy and allergen sensitization. The limitations that have plagued the evaluation of classical food allergens (egg, milk, wheat, soy, peanut, and seafood), such as the high false-positive rate of SPTs and RASTs, failure of oral challenges to confirm most clinical suspicions of reactivity, and inconsistent reaction rates to related foods, are

magnified when dealing with cross-reactive proteins. Future studies are needed to address the clinical relevance, diagnosis, management, natural history, and treatment of these allergies. Such information can only be obtained from careful clinical studies that use blinded oral challenges.

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