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EDITORIAL

Cross-reactivity between aeroallergens and food allergens

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Abstract

In patients with respiratory allergy, cross-reactivity between aeroallergens and foods may induce food allergy, symptoms ranging from oral allergy syndrome to severe anaphylaxis. Clinical entities due to IgE sensitization to cross-reactive aeroallergen and food allergen components are described for many sources of plant origin (pollen-food syndromes and associations, such as birch-apple, cypress-peach and celery-mugwort-spice syndromes, and mugwort-peach, mugwort-chamomile, mugwort-mustard, ragweed-melon-banana, goosefoot-melon associations), fungal origin (*Alternaria*-spinach syndrome), and invertebrate, mammalian or avian origin (mite-shrimp, cat-pork, and bird-egg syndromes). Clinical cases of allergic reactions to ingestion of food products containing pollen grains of specific plants, in patients with respiratory allergy to *Asteraceae* pollen, especially mugwort and ragweed, are also mentioned, for honey, royal jelly and bee polen dietary supplements, along with allergic reactions to foods contaminated with mites or fungi in patients with respiratory allergy to these aeroallergens. Medical history and diagnosis approach may be guided by the knowledge about the diverse cross-reacting allergens involved, and by the understanding of these clinical entities which may vary significantly or may be overlapping. The association between primary IgE sensitization with respiratory symptoms to inhaled allergens and food allergy due to cross-reactive allergen components is important to assess in allergy practice. The use of molecular-based diagnosis improves the understanding of clinically relevant IgE sensitization to cross-reactive allergen components from aeroallergen sources and foods.

Key words: Cross-reactivity syndromes and associations; Aeroallergens; Food allergens

Core tip: Many different syndromes and associations due to cross-reactivity between aeroallergens and food allergens of plant, fungal and animal origin have been described. Significant examples are pollen-food syndromes or associations, along with mite-shrimp, cat-pork, and bird-egg syndromes, but rare or more complex clinical entities must also be discussed. It is important to underline the impact of relevant cross-reactivities between aeroallergens and food allergens and of molecular-based allergy diagnosis in clinical practice.

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INTRODUCTION

Respiratory allergies affect 10%-30% of adults and children worldwide[1,2], while food allergy is estimated to affect more than 1%-2% and less than 10% of the population[3]. Allergic rhinitis, asthma and food allergies have significant detrimental effects on health-related quality of life, family economics, social interactions, school and work attendance[4-7]. There is a high co-occurrence of food allergy with other atopic diseases, including allergic rhinitis and asthma. Evidence of respiratory allergy may indicate an increased risk of IgE-mediated food allergy. Moreover, underlying asthma, regardless of severity, has been associated with increased risk of severe reactions and even death caused by food allergy[3].

This editorial underlines the importance of the IgE sensitization *via* the respiratory route to aeroallergens and food allergy due to cross-reactivities between some allergen components. This phenomenom should be distinguished from the common food allergy without sensitization to cross-reactive aeroallergens, in which heat- and enzyme-resistant class 1 food allergens induce allergic sensitization *via* the digestive tract, typically being responsible for systemic allergic reactions. Class 2 food allergens are more heat-labile and susceptible to digestion and therefore do not cause gastrointestinal sensitization, but instead provoke allergic reactions in already sensitized patients to cross-reactive aeroallergens through the respiratory route. Typically, pollen-food syndromes are produced by class 2 food allergens. In contrast to class 1 food allergy which mainly affects young children, class 2 food allergy is observed especially in adults as a consequence of sensitization to cross-reactive aeroallergens[8-10]. This traditional classification has a more modern changed approach from a molecular allergy point of view. Important allergen components families involved in cross-reactivity between aeroallergens and food allergens are presented in Table 1. The clinical expression for IgE sensitization to PR-10 proteins and profilins is mainly oral allergy syndrome.

Cross-reactivity is an immune-mediated phenomenon of an IgE antibody recognizing, binding, and inducing an immune response to similar allergenic molecules (homologues). IgE cross-reactivity often occurs between allergenic molecules in closely related species or well preserved molecules with similar function present in widely different species, belonging to the same protein family[3,11,12].

The clinical relevance of cross-reactivity seems to be influenced by a number of factors including the host immune response against the allergen, exposure and the allergen itself[13]. Cross-reactivity is important for various reasons, such as its immunologic basis, particularly in relation to the regulation of allergic sensitization, the risk of allergic cross-reactivity to novel foods and the identification of the patterns of cross-reactivity, because they often, but not always, may reflect the pattern of clinical sensitivities. Cross-reactivities involve clustering cross-reactive allergens or family-restricted homologous molecules, panallergens and cross-reactive carbohydrate determinants (CCDs)[14]. Panallergens are cross-reactive allergens, belonging to protein families well preserved throughout many widely different species, able to trigger IgE antibody binding[12]. Panallergens are ubiquitous proteins responsible for IgE cross-reactivity to a wide variety of related and unrelated allergenic sources. IgE cross-reactivity is usually approached from an allergen-perspective, meaning that cross-reactivity is a consequence of structural similarity between homologous proteins, which is translated into conserved sequence regions, three-dimensional folding and function[15]. CCDs are carbohydrate moieties of glycoproteins that induce the production of highly cross-reactive IgE. Many plant and invertebrate allergens are glycoproteins containing carbohydrate moieties called N-glycans that interfere with *in vitro* specific IgE determinations. Anti-CCD IgE biomarker indicate the presence in serum of IgE directed against carbohydrate epitopes. Grass pollen sensitization is the most common cause of CCDs sensitization in food allergic patients, anti-CCD IgE antibodies are highly cross-reactive with CCD monovalent peanut allergens, but does not induce clinical symptoms. CCDs rarely cause allergic reactions, but are an important cause of cross-reactivity for *in vitro* specific IgE assays for CCD-containing allergens from pollen, plant foods, insects and venoms. The use of CCD-free recombinant allergen components may be of utility in such cases[16-20].

In general, the term cross-reactivity should be used to describe defined clinical features revealing the reactivity to a source without previous exposure[13,21]. The comprehensive term co-recognition, including by definition cross-reactivity, could be usefully adopted to define the large majority of the IgE reactivity where co-exposure to a number of sources bearing homologous molecules does not allow the identification of the sensitizer. The CCD-IgE co-recognition of similar carbohydrate structures on unrelated sources may lead to *in vitro* false positive results in diagnostic tests[13]. Despite having high sequence homology in some cases, the ability of cross-reactive allergens to mediate clinical allergic reactions is highly variable, and often depends on the specific allergen sources involved. In addition, cross-reactivity between allergens may cause covariation of sensitization, such as a higher frequency of sensitization to two or more allergens than the expected frequency[3,22]. Immunologically, cross-reactivity is distinct from co-sensitization in which

Table 1 Important allergen components families involved in cross-reactivity between aeroallergens and food allergens[9,11,12,20]

Allergen components families (sensitivity to heat and proteases)	Examples of relevant allergen components involved (allergen sources)
PR-10 proteins, Bet v 1 homologues	Bet v 1, Aln g 1 (tree pollen)
(sensitive to heat and digestion)	Mal d 1, Pru p 1, Api g 1, Gly m4 (fruits, vegetables, legumes)
Profilins, Bet v 2 homologues	Bet v 2, Ole e 2 (tree pollen), Che a 2, Art v 4, Amb a 8 (weed pollen)
(sensitive to heat and digestion)	Api g 4, Dau c 4, Pru p 4, Cuc m 2, Mus xp 1, Sin a 4 (vegetables, fruits, seeds)
Lipid transfer proteins	Pla a 3, Ole e 7, Art v 3, Amb a 6 (tree and weed pollen)
(stable to heat and digestion)	Api g 2, Pru p 3, Cuc m LTP, Mus a 3, Sin a 3 (vegetables, fruits, seeds)
Tropomyosins	Der p 10, Bla g 7 (house dust mites, insects)
(stable to heat and digestion)	Pen m 1, Myt e 1 (crustaceans, mollusks)
Serum albumins	Fel d 2, Can f 3, Equ c 3 (cat, dog and horse serum albumins)
(fairly sensitive to heat and digestion)	Bos d 6, Sus s 6 (bovine and porcine serum albumins)

genuine sensitization to more than one allergen sources is not due to cross-reactivity, being not mediated by shared epitope-specific antibodies[3,12].

Accurate epidemiologic data on the prevalence of clinical cross-reactivities between aeroallergens and food allergens are generally limited by the lack of large, controlled population-based studies, incorporating oral food challenges. In adults, up to 80% of all cases of food allergy are preceded by sensitisation (clinical or subclinical) to aeroallergens, food allergic symptoms being caused in these patients by cross-reactions between ingested food and inhaled allergens[23]. Even in children, it is suggested that cross-sensitization may be found in up to 25% of cases[24].

CROSS-REACTIVITY BETWEEN AEROALLERGENS OF PLANT ORIGIN AND FOOD ALLERGENS

Pollen-food syndromes and associations are food allergies affecting pollen-sensitized individuals, that have become the most prevalent types of food allergy in European adolescents and adults, affecting about 5% of the population in central Europe. In United Kingdom, pollen-food syndrome overall prevalence is about 2%, in South-Eastern England urban practice being slightly over 4%. The symptoms of pollen-food allergy syndromes range from oral allergy syndrome to severe anaphylaxis, and the foods involved are of vegetal origin, mostly fruits and vegetables, eaten raw[9,25,26]. Pollinosis patients often display adverse reactions upon ingestion of plant-derived foods as a result of IgE cross-reactive epitopes shared by pollen and food allergen sources[1].

The role of an allergy specialist in recognizing and assessment of pollen-food syndromes and associations is essential. Many purified native and recombinant allergen components have been obtained in order to use them for a detailed molecular component-resolved diagnosis of the genuine sensitization and cross-reactivities profiles, and for a more accurate prescription of allergy immunotherapy[20,27,28].

Specific IgE antibodies to recombinant and native specific allergen components from trees, grasses and weeds pollen are important to differentiate the true sensitization profile in patients with multiple pollen sensitizations, as described below[20,27-32].

Tree pollen-specific allergen components are mentioned for anemophilous trees/shrubs belonging to the *Betulaceae* family: rBet v 1, a 17 kDa pathogenesis-related protein PR-10 with ribonuclease activity from the pollen of birch *Betula verrucosa*, cross-reactive with other *Betulaceae* pollen PR-10 components with about 70% identity to it (alder *Alnus glutinosa* rAln g 1, hazel *Corylus avellana* rCor a 1); *Oleaceae* family: nOle e 1 and rOle e 1, a 19-20 kDa trypsin inhibitor from the pollen of olive *Olea europaea*; *Platanaceae* family: rPla a 1, a 18 kDa invertase inhibitor, and nPla a 2, a 43 kDa polygalacturonase, from the pollen of plane tree *Platanus acerifolia*; *Cupressaceae* family: nCup a 1, a 43 kDa pectate lyase, from the pollen of cypress *Cupressus arizonica*, cross-reactive with other *Cupressaceae* pollen pectate lyase components (cedar *Criptomeria japonica* nCry j).

Grass pollen-specific rPhl p 1 (27 kDa beta-expansin), rPhl p 5b (32 kDa ribonuclease), and natural timothy grass (*Phleum pratense*) extract are used to identify grass pollen allergy. Specific IgE against rPhl p 1 is a *Poaceae* family-specific biomarker for genuine sensitization to grass pollen, and against rPhl p 2, rPhl p5 and rPhl p 6 are *Pooideae* subfamily-specific biomarkers for true sensitization to temperate grass pollen. Specific IgE antibodies to nCyn d 1 (beta-expansin of Bermuda grass *Cynodon dactylon)*, a warm climate grass-specific native pollen allergen component, represent biomarkers of genuine sensitization to *Chloridoideae* subfamily grass pollen.

Weed pollen-specific allergen components are described for herbaceous plants belonging to the *Asteraceae* (*Compositae*) family: nArt v 1, a 28 kDa defensin from the pollen of mugwort *Artemisia vulgaris* and nAmb a 1, a 38 kDa pectate lyase from the pollen of short ragweed *Ambrosia artemisiifolia* var. *elatior*; *Plantaginaceae* family: rPla l 1, a 17 kDa Ole e 1-like trypsin inhibitor from the pollen of plantain *Plantago lanceolata*; *Urticaceae* family: rPar j 2, a 14 kDa lipid transfer protein (LTP) from the pollen of wall pellitory *Parietaria*

Table 2 Significant syndromes and associations due to cross-reactivity between aeroallergens and food allergens of plant origin[9,11]

Syndrome or association (sensitivity to heat and proteases)	Relevant allergen components involved (allergen sources)
Birch-apple syndrome	Bet v 1 homologue Mal d 1
Cypress-peach syndrome	Pru p 3 non-specific lipid transfer protein (nsLTP)
Celery-mugwort-spice syndrome	Art v 4 profilin, Art v 60 kDa homologue to Api g 5
Mugwort-peach association	Art v 4 profilin, Art v 3 LTP
Mugwort-chamomile association	Art v 1 defensin (possible candidate)
Mugwort-mustard syndrome	Art v 3 LTP, Art v 4 profilin, Art v 60 kDa (possible candidates)
Ragweed-melon-banana association	Amb a 6 LTP, Amb a 8 profilin (possible candidates)
Goosefoot-melon association	Che a 2 profilin (possible candidate)

LTP: Lipid transfer protein.

judaica; *Amaranthaceae/Chenopodiaceae* family: rChe a 1, a 24 kDa trypsin inhibitor from the pollen of goosefoot *Chenopodium album* and nSal k 1, a 43 kDa protein belonging to the pectin methylesterase family from the pollen of saltwort *Salsola kali.* Art v 6 (pectate lyase) plays an important role in mugwort allergy and the cross-reactivity between Art v 6 and Amb a 1 is frequent, bidirectional, and clinically relevant.

Many cross-reactive allergen components are involved in pollen-food syndromes and associations, such as plant panallergen profilins (actin-binding proteins with roles in the dynamic turnover and restructuring of the actin cytoskeleton), PR-10 proteins (Bet v 1 homologues), lipid transfer proteins (LTPs)[9,27,33], as presented in Table 2.

Tree/shrub pollen aeroallergens and food allergens of plant origin

Several cross-reactivities between tree, shrubs and lianas pollen and foods are described in patients with respiratory allergy. Trees and shrubs discussed below as a source of pollen cross-reactive with foods belong to different anemophilous plant families: *Betulaceae* (birch family), *Oleaceae* (olive family), *Platanaceae* (plane-tree family), and *Cupressaceae (cypress family).* The temperate liana, vine *Vitis vinifera*, is also mentioned.

Regarding the birch-fruit-vegetable-syndrome, about 70% of birch pollen-allergic patients develop symptoms of allergy to plant foods, most frequently involved being *Rosaceae* fruits (mainly apple), nuts (especially hazelnut), and vegetables from the *Apiaceae* family (mainly celery and carrot). Pollinosis precedes the symptoms of food allergy, which, in the majority of cases, is limited to the oropharynx as oral allergy syndrome, occuring when eating raw food. The main allergen component involved in more than 90% of patients with birch pollinosis-associated food allergies, is Bet v 1, a pathogenesis-related PR-10 protein, which is cross-reactive with its homologous in these foods. Bet v 1 homologues represent major allergens in pollen of trees and shrubs from the order *Fagales* (including the *Betulaceae* and *Fagaceae* families), but can also be found in many allergenic foods belonging to the botanical families *Rosaceae* (50%-60% identity to Bet v 1 for the *Maleae* tribe PR-10 proteins: apple Mal d 1, pear Pyr c 1, and *Amigdaleae* tribe PR-10 proteins: apricot Pru ar 1, plum Pru c 1, peach Pru p 1, cherry Pru av 1), *Betulaceae* (hazelnut Cor a 1.0101 with 50% identity to Bet v 1), and *Apiaceae* (PR-10 proteins with 40%-50% identity to Bet v 1: carrot Dau c 1, celery Api g 1). Less than 25% of patients with this syndrome are sensitized to the panallergen Bet v 2 (birch profilin), its contribution to symptoms being unclear. Bet v 1 homologues and profilins, incriminated in the birch-plant foods syndrome, are denatured by high temperatures and by gastric enzymes[20,25,34-37].

The birch pollen-hazelnut association is a *Betula* pollen-associated food allergy to hazelnuts, with Cor a 1-reactive T cells and specific IgE cross-reactive to Bet v 1[38]. This type of hazelnut (*Corylus avellana*) allergy occurs in adults with pollinosis to *Betulaceae* trees/shrubs, and manifests mainly as an oral allergy syndrome, due to an extensive cross-reactivity between the labile hazelnut Cor a 1.04 and birch pollen Bet v 1 allergen components. In contrast, children predominantly exhibit sensitisation to hazelnut storage proteins, Cor a 9 and Cor a 11, which is unrelated to birch pollen allergy, and had more severe clinical manifestations on consumption on raw and processed hazelnuts. In the absence of a cure, avoidance remains the key measure of effective management, especially in patients with severe symptoms[39].

The most common tree pollen-fruit cross-reactivity is represented by the birch-apple syndrome[11,40]. IgE antibodies formed against either Bet v 1, the birch pollen PR-10 allergen, or Mal d 1, the apple allergen, cross-react and give rise to sensitivity to both birch and apple. Moreover, patients with oral allergy syndrome to apple have a higher Bet v 1-induced T cell proliferation compared with those monosensitized to birch pollen without food allergy[12,41].

Interestingly, soy allergen component Gly m 4 also belongs to the PR-10 protein family, and in birch pollen-allergic patients, the combination of IgE sensitization to Gly m 4 and intake of large amounts of mildly processed soy, like soy drinks, may induce a severe allergic reaction[12].

The birch-apple-carrot association is another possible cross-reaction in patients with birch pollen and food allergy, in which IgE-mediated systemic allergic reaction to both apple and carrot, in both fresh and cooked form, is reported[42]. The birch-*Apiaceae* syndrome is seen

mainly in central Europe, and the typical clinical picture is oral allergy syndrome, which occurs when raw foods are ingested. This food allergy to *Apiaceae* is secondary to pollinosis and is due to the presence in these foods of Bet v 1 homologues (Api g 1, Dau c 1), and less frequently to profilins[34].

IgE sensitization patterns to different cross-reactive allergen components are variable according to climate and eating habits. In the Western Mediterranean region, allergies to *Rosaceae* fruits are caused by monosensitization to profilin, monosensitization to LTP, or co-sensitization to both these allergen molecules. In Northern and Central Europe, monosensitization to PR-10 and, to a lesser degree, co-sensitization to profilin and PR-10, is dominant. LTP sensitization is present both in pollinosis and non-pollinosis patients, and is associated with peach allergy in particular. The disease pattern for patients sensitized to profilin is characterized by several concomitant allergies, including grass pollen, *Rosaceae* and non-*Rosaceae* fruits. Sensitization to PR-10 is primarily associated to concomitant birch pollen and apple allergy[43]. In a birch endemic area in Western Europe, both mild and anaphylactic apple-allergic patients are sensitized to PR-10 proteins, whereas only a few of the mild local and none of the anaphylactic apple-allergic patients is sensitized to LTP. In contrast, anaphylactic hazelnut-allergic patients display no such clear sensitization pattern: few are sensitized to both PR-10 proteins and hazelnut LTP, and others to only LTP or to only PR-10 proteins, or to neither PR-10 proteins, nor LTP[44]. Bet v 1 sensitization is associated to concomitant birch pollen rhinoconjunctivitis and oral allergy syndrome to *Rosaceae* fruits in patients from the Southeastern-Central Europe, in a sylvosteppe area with low density forests[45]. In East-Central Europe, in patients with birch pollen allergy with associated food allergy, IgE sensitization to Bet v 1 is frequently associated with food allergy to fruits from *Rosaceae* family. Bet v 2 profilin may be involved in cross-reactivity with non-*Rosaceae* plants, such as *Apiaceae*/*Umbelliferae* vegetables[46].

Immune tolerance induction in the birch-apple syndrome was evaluated in several studies. In patients with oral allergy to apple, tolerance can be safely induced with slowly, gradually increasing consumption of apple, but relapse after consumption discounting and absence of immunologic changes suggest it is only transient[47]. Allergy immunotherapy is clearly effective for birch pollen allergy, but its efficacy on apple allergy is still controversial. Some patients treated with subcutaneous or sublingual immunotherapy develop complete tolerance to apple. Pre-treatment evaluation of patients using molecular allergy diagnosis tools and choosing the appropriate immunotherapeutical doses of birch pollen allergen extract is important[40,48]. Although most patients became re-sensitized to apple over time, many of them are still able to tolerate eating apple at a 30-mo follow-up visit[49]. Pollen immunotherapy has also a positive impact on oral allergy syndrome to hazelnut in birch pollen-allergic patients, but the amount of hazelnut tolerated is small, the effect remaining limited[50].

In the cross-reactive olive pollen-fruit syndrome the main fruits involved are peach *Prunus persica*, pear *Pyrus communis*, melon *Cucumis melo* and kiwi fruit *Actinidia deliciosa*. Sensitization to the LTP Ole e 7 is associated with more severe clinical symptoms in patients who had anaphylaxis, while to the profilin Ole e 2 in most oral allergy syndrome cases. Cross-reactivities between profilins (Ole e 2, Pru p 4, Pyr c 4, Cuc m 2, Act d 9) and LTPs (Ole e 7, Pru p 3, Pyr c 3, Cuc m LTP, Act d 10) are involved in the olive pollen–fruit syndrome. The glucanase Ole e 9 is an allergen component candidate for an important role in pollen-latex-fruit syndrome in patients allergic to olive pollen. Beta-glucanases are also present in latex *Hevea brasiliensis* (Hev b 2) and banana (Mus xp 5). Other cross-reactive allergens involved in pollen-latex-fruit syndrome are profilins from olive pollen (Ole e 2), latex (Hev b 8), ananas (Ana c 1), banana (Mus xp 1) and kiwi (Act d 9), and superoxide dismutases from olive pollen (Ole e 5) and latex (Hev b 10)[51].

In the ficus-fruit syndrome, allergic reactions to fresh or dried figs (*Ficus carica*) or other tropical fruits, which may be presented as anaphylaxis, are a consequence of primary sensitization to airborne ornamental *Ficus benjamina* allergens, independent of sensitization to rubber latex allergens. Cross-reactive ficus allergen component ficin (Fic c Ficin) belongs to the family of cystein proteases present also in kiwi fruit *Actinidia deliciosa* (Act d 1), pineapple *Ananas comosus* (Ana c 2), papaya *Carica papaya* (Car p 1). Figs may also be involved in the latex-fruit syndrome[52,53].

The *Platanus* pollen-fruit/vegetables association is a cross-reactivity entity observed among plane tree *Platanus acerifolia* pollen and plant-derived food allergic patients. There is an important cross-reactivity between the pollen of plane tree, hazelnut and banana fruit, and an intermediate cross-reactivity with celery and peanut. Other fruits and vegetables may also be mentioned. The cross-reacting LTPs may be involved, being present in *Platanus acerifolia* pollen (Pla a 3), but also in hazelnut *Corylus avellana* (Cor a 8), banana *Musa acuminata* (Mus a 3) fruit, peach (Pru p 3), celery *Apium graveolans* (Api g 2), peanut *Arachis hypogaea* (Ara h 9). It appears that neither profilin Pla a 8, nor the two major allergens invertase inhibitor Pla a 1 and polygalacturonase Pla a 2 can be the cause for the strong cross-reactivity[54-57].

In the cypress-peach syndrome, allergic crossreactions between cypress pollen and peach have been reported, including oral allergy syndrome. Profilins (Cup s 8, Pru p 4) or thaumatins (Cup s 3, Pru p 2) could not explain the observed clinical association between cypress pollen and peach. Pru p 3-like non-specific LTPs are involved in the syndrome[11,58].

Other rarer cross-reactive associations are those between date-palm (*Phoenix dactylifera*) pollen and vegetal foods manifested as oral allergy syndrome[59] and between *Vitis vinifera* vine pollen eliciting seasonal

rhinoconjunctivitis and asthma with subsequent food allergy to grapes[60], in both the cross-reacting proteins are still not well established.

Grass pollen aeroallergens and food allergens of plant origin

Profilins are highly cross-reactive allergen components which bind IgE antibodies of almost 20% of plant-allergic patients. Grass pollen is cross-reactive with some foods in patients with oral allergy syndrome. The Bermuda grass *Cynodon dactylon* pollen profilin (Cyn d 12) has substantial cross-reactivity with profilins from tomato *Solanum lycopersicum* (Sola l 1) and cantaloupe *Cucumis melo* (Cuc m 2)[3,61].

Although several patients with oral allergy syndrome, urticaria, angioedema, gastrointestinal or anaphylaxis symptoms after ingestion of products containing wheat or maize flour were reported in patients suffering from respiratory allergy to grass pollens, cross-reactivity among cereal grains and grass pollen is generally considered clinically insignificant. Beta-expansin 11 (EXPB11), a homologue of the major allergen of timothy grass pollen, Phl p 1, may bear a high cross-reactive potential in patients who suffer from both food allergy and pollinosis[62,63].

Hypersensitivity reactions to Navajo ceremonial use of oral corn pollen in native Americans were previously described[64], and recently a case of corn silk (*Stigma maydis*) infusion (traditional herbal medicinal product) and *Poaceae* pollen allergy was reported[65].

Weed pollen aeroallergens and food allergens of plant origin

Allergenic weeds with pollen involved in respiratory sensitization followed by food allergy due to cross-reactive allergen components can be found in the plant families of *Asteraceae/Compositae* (mugwort *Artemisia vulgaris*, ragweed *Ambrosia artemisiifolia* var. *elatior*), *Urticaceae* (pellitory *Parietaria officinalis*), *Amaranthaceae/Chenopodiaceae* (goosefoot *Chenopodium album),* *Plantaginaceae* (plantain *Plantago lanceolata*), and *Cannabaceae* (hop *Humulus japonicus*)[9,66].

In the celery-birch-mugwort-spices syndrome, patients IgE-sensitized to *Betula* and *Artemisia* spp pollen present food allergy to celery, other vegetables and spices, due to several cross-reactive allergen components, including Bet v 1 homologs, profilins and high molecular weight allergens of 40-60 kDa. The Bet v 1 homologs, Api g 1 (celery) and Dau c 1 (carrot), are responsible for the association between birch pollinosis and *Apiaceae* allergy, as no Bet v 1-homologous proteins are found in mugwort pollen. Thus, the celery-birch association only involves species from the *Apiaceae* family, whereas the celery-birch-mugwort syndrome comprises additional botanical families. Associated allergy to *Amaryllidaceae* family foods and spices is rare[9,34].

The well-known celery-mugwort-spice syndrome consists of respiratory sensitization to mugwort *Artemisia vulgaris* and IgE cross-reactive reactions to foods belonging to *Apiaceae/Umbelliferae* family: celery (*Apium graveolans*), carrot (*Daucus carota*), parsley (*Petroselinum crispum*), caraway seeds (*Carum carvi*), fennel seeds (*Foeniculum vulgare*), coriander seeds (*Corinadrum sativum*), aniseed (*Pimpinella anisum*); *Amaryllidaceae* family: garlic (*Allium sativum*), onion (*Allium cepa*), leek (*Allium porrum*); *Solanaceae* family: paprika (*Capsicum annuum*); and *Piperaceae* family: pepper (*Piper* sp). The number of allergen sources involved, the nature of the allergen components, and influencing factors, such as climate and dietary habits, make the celery-birch-mugwort-spice syndrome a clinical entity of high complexity[9]. Complicated cases may associate curry spice allergy with pollen-food allergy syndrome and latex fruit-syndrome[67]. Cross-reactivity between profilins of mugwort pollen (Art v 4) and *Apiaceae* foods, such as celery (Api g 4), carrot (Dau c 4) and spices, are involved in the pathogenesis of this celery-mugwort-spice syndrome[9]. Moreover, the mugwort-fennel-allergy-syndrome is associated with sensitization to an allergen homologous to Api g 5, a high molecular weight glycoprotein flavoprotein, Foe v 5, with function of flavin adenine dinucleotide-linked oxidoreductase. An Api g 5-like protein was also identified in carrot. This 60 kDa fennel allergen, highly homologous to Api g 5, may be involved in the mugwort-celery-spice syndrome, being cross-reactive with Art v 60 kDa allergen component from mugwort pollen[68,69].

The mugwort-mustard allergy syndrome describes the association of mugwort pollinosis with several botanically unrelated plant-derived foods allergy from the *Brassicaceae/Cruciferae* family: white mustard (*Sinapis alba*), Indian mustard (*Brassica juncea*), cabbage (*Brassica oleracea* var. *capitata*), broccoli (*Brassica oleracea* var. *italica*), cauliflower (*Brassica oleracea* var. *botrytis*), and possibly from the *Fabaceae/Leguminosae* family: peanut (*Arachis hypogaea*), and *Rosaceae* family: almond (*Prunus dulcis*). Mustard is sometimes a masked allergen in processed foods, and food allergy symptoms vary from oral allergy syndrome to anaphylaxis. Although the causative cross-reactive allergen components have not yet been clearly identified, the possible candidates are LTPs (Art v 3, Sin a 3), profilins (Art v 4, Sin a 4) and high molecular weight allergens, such as Art v 60 kDa[9].

In the mugwort-peach association, the cross-reactive allergen components involved are LTPs (Art v 3, Pru p 3) and profilins (Art v 4, Pru p 4)[9]. This cross-reactivity association appears in a limited group of patients from Southern Europe, in which Art v 3 behaves as the primary sensitizing allergen, although Pru p 3-associated peach allergy is a food allergy driven by primary sensitization to peach in the Mediterranean region. The *Rosaceae* fruits allergens cross-react with mugwort allergens in the mugwort-peach association[70]. A similar group of patients was reported recently in Northern China, in which the food peach LTP allergy originates

from primary sensitization to cross-reactive pollen allergen component Art v 3. The pattern of geographical distribution of this mugwort-peach association may be explained by the dominant role of mugwort pollen exposure in some regions, which is similar to the importance of birch pollen exposure in Northern Europe[71].

An *Asteraceae*-lychee association was also reported in patients diagnosed with respiratory allergy to *Artemisia vulgaris* pollen and food allergy to sunflower seeds, who have subsequently presented anaphylaxis after the first ingestion of lychee fruit. *Litchi chinensis* is a tropical fruit belonging to the *Sapindaceae* family, in which Lit c 1 profilin, a 16 kDa allergen cross-reactive with Art v 4 profilin, was identified. Another allergen component of 70 kDa identified in lychee, and also present in mugwort pollen, is a possible new candidate for the cross-reactive mechanism in this clinical association[72].

In mugwort-chamomile association, respiratory IgE sensitization to mugwort *Artemisia vulgaris* is a primary risk factor for allergy symptoms up to anaphylaxis to ingestion of chamomile infusions. Some patients present positive conjunctival provocation tests with chamomile extract. German Chamomile (*Matricaria chamomilla* var. *recutita*) is a Southern European plant of the *Asteraceae* family, used frequently as herbal tea medical remedy. There is a high degree cross-reactivity between *Matricaria chamomilla* and *Artemisia vulgaris* pollen[73]. The candidate cross-reactive component proposed in mugwort-chamomile association is the Art v 1 defensin[11]. Bet v 1 homologues (Mat c 1) and high molecular weight allergens may also play a role, but not profilins. Patients sensitised to mugwort pollen sometimes present allergic reactions to chamomile, while most subjects allergic to chamomile are sensitized to mugwort. In clinical practice, the incidence and risks of this mugwort-chamomile association may be underestimated[74,75].

In mugwort-sunflower association, the food allergy was reported either manifested as anaphylaxis to consumption of sunflower-pollen contaminated commercial peeled sunflower seeds in a patient sensitized to *Artemisia* pollen, or as oral allergy syndrome after eating sunflower seeds in a patient with airborne allergy to particles of these seeds used as pet food for small animals, such as birds. Moreover, allergy to sunflower seeds may be associated with respiratory allergy to mugwort pollen[76]. Sunflower (*Helianthus annuus*) belongs to the family of *Asteraceae*. Its pollen allergen component Hel a 4 is an Art v 1-like allergen, while Hel a 3 LTP and Hel a 2S albumin are present in seeds[77-79].

Clinical cases of severe allergic reactions, mostly anaphylaxis, to ingestion of bee products, containing pollen grains of *Compositae* plants, in patients with respiratory allergy to *Asteraceae* pollen, especially mugwort and ragweed pollen, were published, for honey, royal jelly and bee polen dietary supplements[80-83]. Cross-reactivity between the pollen of wind-pollinated weeds and other *Asteraceae* insect-pollinated plants is a major mechanism of bee product-induced allergic reactions, likely attributable to several contained pollen allergen components, including profilins, polcalcins, and LTPs. Bee products may contain not only pollen from insect-pollinated plants, but also from wind-pollinated trees or herbaceous plants that grow in the same area, resulting in systemic allergic reactions after accidental ingestion of these airborne pollen grains[81].

The ragweed-melon-banana association is present in patients with respiratory allergy to ragweed *Ambrosia artemisiifolia* experiencing food allergy, usually oral symptoms, when eating various members of the *Cucurbitaceae* family: watermelon (*Citrullus lanatus* subsp. *vulgaris*), netted muskmelon/cantaloupe (*Cucumis melo* var. *cantalupo*), honeydew melon (*Cucumis melo* var. *inodorus*), zucchini (*Cucurbita pepo*), cucumber (*Cucumis sativus*); and *Musaceae* family: banana (*Musa* x *paradisiaca*) fruit. The possible cross-reactive allergen candidates involved in ragweed-melon-banana association are profilins (Amb a 8, Cit la 2, Cuc m 2, Cuc p 2, Cuc s 2, Mus xp 1) and LTPs (Amb a 6, Cuc m LTP)[9,84]. Another possible cross-reactivity between *Ambrosia* pollen and other plants from the *Asteraceae* family recommends not to administer *Echinacea* botanical supplements in patients allergic to ragweeed[85].

In the pellittory-pistachio association, several cross-reacting proteins were suggested using *in vitro* methods. IgE sensitization to pistachio (*Pistacia vera*) is common in *Parietaria* weed pollen allergy. Pistachio nuts, belonging to the family of *Anacardiaceae*, are widely used to produce ice creams, cakes, and mortadella, or are simply eaten roasted. Oral allergy syndrome to pistachio was reported in adult and child patients with *Parietaria* pollinosis. Minor injuries of the oral mucosa due to pistachio shells may enhance local allergic responses[9,86]. Furthermore, different members of the *Anacardiaceae* family (pistachio, mango, and cashew) have been mentioned to share common allergens[87].

The plantain-melon association represents the clustering of allergy to melon *Cucumis melo* and plantain *Plantago lanceolata*, respiratory sensitization to plantain pollen being important in Australia and Mediterranean countries. Several distinct proteins of 14 and 31 kDa, and a spectrum of proteins migrating between 40 and 70 kDa were discussed as cross-reactive allergens[9]. Moreover, the seeds of *Plantago ovata* (psyllium, ispaghula) used in the manufacture of bulk laxatives may cause occupational respiratory allergy in health care and pharmaceutical workers. Cases of anaphylaxis were reported after ingestion of laxatives or breakfast cereals containing *Plantago ovata* seeds, in most of those subjects sensitization occurring previously by inhalation of seed dust. In addition, immunologic cross-reactivity between *Plantago ovata* seed and *Plantago lanceolata* pollen is possible[88].

The goosefoot-melon association or the goosefoot-fruit association was revealed in several cases of patients with pollen allergy to *Chenopodium album*

Table 3 Examples of syndromes due to cross-reactivity between aeroallergens of animal and fungal origin and food allergens[9,11]

Syndrome or association	Relevant allergen components involved
Alternaria-spinach syndrome	Al t a 1
Mite-shrimp syndrome	Der p 10 tropomyosin
Cat-pork syndrome	Fel d 2 cat serum albumin
Bird-egg syndrome	Gal d 5 alpha-livetin (chicken serum albumin)

(allergenic weed of the *Amaranthaceae/Chenopodiaceae* family), who displayed oral allergy syndrome after eating fresh fruits, such as melon, banana and peach. The panallergen profilins (Che a 2, Mus xp 1, Pru p 4) might play a role in goosefoot IgE cross-reactivity[9]. The risk for Russian thistle-saffron association is due to the possible cross-reactivity between *Salsola* and saffron, keeping in mind the use of saffron as a *Crocus sativus* flower-derived spice and the reported flower sensitization in saffron workers[9].

Finally, a hop-celery association is mentioned for Japanese hop (*Humulus japonicus*) pollinosis with allergy to another representative of the *Cannabaceae* family, the common hop (*Humulus lupulus*), and to the unrelated celery (*Apium graveolans*), with no significant associations with ragweed or mugwort pollen[9,89].

CROSS-REACTIVITY BETWEEN AEROALLERGENS OF FUNGAL ORIGIN AND FOOD ALLERGENS

Respiratory allergy to environmental molds is relatively common, fungi representing a prominent source of aeroallergens[90]. *Alternaria alternata* is one of the most common molds associated with allergic diseases, and 80% of *Alternaria*-sensitive patients produce IgE antibodies to Alt a 1, a major allergen with an unique, dimeric beta-barrel structure. Alt a 1 and homologous proteins are characteristic for the *Dothideomycetes* class of ascomycetes[91].

The *Alternaria*-spinach syndrome, in which Alt a 1 is mentioned as an involved allergen component (Table 3), was recently recognized[11]. This cross-reactivity between aeroallergens from fungi imperfecti and allergens from spinach and mushroom *Agaricus bisporus* as foods is mentioned. In the first report of anaphylaxis to spinach and concomitant oral allergy syndrome to mushrooms, cross-reactivity was suggested to be due to common epitopes[92]. A further study identified the cross-reactive 30 kDa protein, probably the Alt a 1 allergen component, present both in spinach and mushroom extracts[93]. This syndrome is different from another possible association between IgE sensitization to mannitol, naturally present in cultivated mushrooms and pomegranate, and anaphylaxis to this sugar alcohol as a drug excipient[94].

In addition, non-fatal anaphylaxis was reported after mycoprotein burger eating, in a young female patient with respiratory IgE-allergy to *Alternaria alternata*, the edible mycoprotein being produced from the fungus *Fusarium venenatum*. Cross-reactivity studies revealed that it shares allergenic determinants with *Alternaria alternata* and *Cladosporium herbarum*[95]. Sensitization to mold allergens *via* the respiratory tract and subsequent oral ingestion of cross-reactive fungal proteins may lead to severe food-allergic reactions, such as those caused by *Fusarium venenatum* acidic ribosomal protein P2 allergen[96]. An unusual case of fatal anaphylaxis was also reported due to heavy mold contamination of a pancake mix with *Fusarium, Penicillium*, *Mucor*, and *Aspergillus* spp, in a teenager allergic to molds[97]. It is also possible that bee products, such as bee pollen supplements, to be contaminated with fungi such as *Aspergillus* and *Cladosporium* spp, and may cause severe allergic reactions in patients sensitized to these molds[81].

Moreover, yeasts should be considered as possible ingestive allergens in mold-allergic patients. A patient with a clustered respiratory IgE sensitization to fungi (*Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Penicillium notatum*) and baker's yeast (*Saccharomyces cerevisiae*), developed multiple anaphylactic reactions after ingesting pasta yeast sauces containing cross-reacting fungal allergens[98].

CROSS-REACTIVITY BETWEEN AEROALLERGENS OF ANIMAL ORIGIN AND FOOD ALLERGENS

Aeroallergens of animal origin, such as those from domestic arthropods (house dust mites, cockroaches) and pets are usual indoor allergens involved in allergic rhinitis and asthma, along with indoor fungal aeroallergens from certain molds. Spending more time in areas inside buildings (homes, workplaces, schools, and indoor public spaces) creates conditions for more exposure to multiple indoor aeroallergens[99]. Examples of syndromes due to cross-reactivity between inhaled allergens of animal origin and food allergens are presented in Table 3. Other data from case reports defining rare or distinct associations are also discussed below, but are not simplistic put in the table as general rule for clinical practice.

Aeroallergens and food allergens of invertebrate animal origin

Dust mites are the most common indoor environmental cause of respiratory allergies. The main sources of allergens in house dust worldwide are the mite species belonging to the phylum of *Arthropoda*, class *Arachnida*, subclass *Acari*), order *Astigmata*. The most important house dust mites are those from the *Pyroglyphidae* family, especially *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. Pyroglyphid mites are highly cross-reactive, but have limited cross-reactivity with *Blomia tropicalis*, mite species from *Echimyopodidae*

family significant for tropical/subtropical regions, or with other storage mites from *Acaridae* and *Glycyphagidae* families[100,101].

Patients sensitized to house dust mites can be classified according to their pattern of sensitization into those sensitized only to the major allergens from group 1 and group 2 allergens of pyroglyphid mites, and those with a broader profile of sensitization, including highly cross-reactive allergens, the most important being tropomyosin, belonging to the group 10 allergens[102].

Allergic reactions to edible invertebrates can generate a variety of clinical manifestations ranging from mild oral allergy syndrome, urticaria and/or angioedema, to severe anaphylaxis. Although cross-reactivity between dust mites and invertebrates consumed as food is demonstrated, sometimes there is a poor correlation of IgE reactivity and clinical symptoms[103].

Edible invertebrates are represented mostly by shellfish (culinary term for exoskeleton-bearing aquatic invertebrates, such as crustaceans and mollusks) and less by edible insects (in some parts of the world). Although most kinds of shellfish are aquatic invertebrate animals from saltwater environments (seafood), some are harvested from freshwater, and, in addition, few species of land snails and crabs are also edible invertebrates. Crustaceans are classified among arthropods, together with arachnids (including house dust mites) and insects, whereas mollusks include bivalves, cephalopods and gastropods. Shellfish is one of the leading causes of food allergy in adults and is a common cause of food-induced anaphylaxis. Most frequent causative types of shellfish are shrimp, crab, lobster, clam, oyster and mussel. Specific invertebrate seafood allergy can reflect regional consumption of particular species. It is also important to differentiate shellfish toxic syndromes frequently masquerading as an allergic reaction[104].

The house dust mites-crustaceans-mollusks syndrome is a relatively rare variant of food allergy in which the house dust mites are the primary IgE sensitising agents, while shellfish can induce food allergy, up to anaphylaxis, even at first ingestion[23]. In the more usual mite-shrimp syndrome, the typical allergen component mentioned is tropomyosin Der p 10[11]. Allergenic molecules involved in shellfish allergy are cross-reactive with allergen components from house dust mites, especially certain proteins with a role in muscular contraction. Cross-reactivity with species that are not closely related is common in shellfish-allergic patients, some seafood allergens being widely distributed invertebrate panallergens[105]. Tropomyosin was the first identified allergen involved in cross-reactivity between *Dermatophagoides pteronyssinus* mite, shrimp and insects[106] and it is still considered a major shellfish allergen frequently responsible for clinical cross-reactivity with inhaled house dust mites[107]. Besides been assumed to be a major cause of cross-reactivity between astigmatid mites and other invertebrates, tropomyosin may be a major cause of covariation of sensitization between house dust mites, crustaceans, and some species of insects and mollusks[22]. Allergenic tropomyosins are highly conserved muscle proteins found in invertebrates, such as arachnids (house dust mites), insects (cockroaches), crustaceans (shrimp, prawn, lobster, crawfish, crab), and mollusks (mussel, oyster, squid, cuttlefish, octopus, abalone, limpet, snail), therefore being considered panallergens. In contrast to invertebrate tropomyosin, vertebrate tropomyosins, such as those from beef, pork, rabbit or chicken, are not allergenic[104,108].

Tropomyosins are a large family of alpha-helical proteins that form a coiled-coil structure of two parallel helices containing two sets of seven alternating actin-binding sites, playing a critical role in regulating the function of actin filaments. Tropomyosins are present in all eukaryotic cells, associated with the thin filament in muscle and microfilament in many nonmuscle cells, being involved in the contractile activity of these cells, and also in helping regulation of cell morphology and motility. As panallergens, these are resistant to heat, low gastric pH and gastroenteric peptidase, therefore their allergenicity is maintained in cooked and digested foods, causing allergic systemic reactions up to anaphylaxis. Natural tropomyosin has an average molecular weight of 37 kDa. House dust mite group 10 allergens are composed of 284 amino acids. Sequence identity within the house dust mite tropomyosins is higher than any other mite allergen. The Der p 10 tropomyosin shares more than 65% identical residues with other invertebrate tropomyosins[22,109-111]. Regions adjacent to the positions 133-135 and 201 of the invertebrate tropomyosins present lower probability of alpha helix folding than those of vertebrates, and are candidates responsible for allergenicity[112]. There is a high cross-reactivity between house dust mite tropomyosins: *Dermatophagoides pteronyssinus* (Der p 10), *Dermatophagoides farinae* (Der f 10) and *Blomia tropicalis* (Blo t 10)[22].

The prevalence of sensitization to tropomyosin among house dust mite-allergic patients, assessed using recombinant group 10 mite allergen components, varies with geographical area[22,113]. In many European countries, this sensitization prevalence to rDer p 10 varies between 9%-18%[114]. Other studies revealed that sensitization rates to tropomyosin are found in higher rates (30%-55%) in subtropical or tropical regions, such as Australia or Central Africa. This variability can be explained by various exposure to sensitizing invertebrate allergens in different parts of the world[113]. The resulting IgE antibodies are able to cross-react with different tropomyosins, even with those which did not induce their production. For example, IgE antibody reactivity to a major food allergen, the cross-reactive brown shrimp tropomyosin, can occur in unexposed subjects (Orthodox Jews, with Kosher dietary laws that prohibit eating shellfish) with clinically significant allergy to house dust mites and/or cockroaches[21]. Another study revealed that half of the house dust mite-allergic

European patients with IgE sensitization to tropomyosin (Der p 10) have a history of clinically relevant cross-reactivity reactions to eating seafood, the other half having no allergic reactions when consuming such edible invertebrates[107].

Cross-reactivity of tropomyosin allergens from house dust mites with crustaceans (subphylum *Crustacea*) is significant, mentioning decapods (order *Decapoda*) from the *Penaeidae* family: brown shrimp *Farfantepenaeus/Penaeus aztecus* (Pen a 1), black tiger shrimp *Penaeus monodon* (Pen m 1), Indian prawn *Fenneropenaeus/Penaeus indicus* (Pen i 1), whiteleg shrimp *Litopenaeus vannamei* (Lit v 1), sand shrimp *Metapenaeus ensis* (Met e 1); *Crangonidae* family: common shrimp *Crangon crangon* (Cra c 1); *Pandalidae* family: Northern shrimp *Pandalus borealis* (Pan b 1); *Nephropidae* family: European lobster *Homarus gammarus* (Hom g 1), American lobster *Homarus americanus* (Hom a 1); *Palinuridae* family: Chinese spiny lobster *Panulirus stimpsoni* (Pan s 1); *Portunidae* family: coral crab *Charybdis feriata* (Cha f 1), and *Cambaridae* family: red swamp crayfish *Procambarus clarkii (*Pro cl 1)[22,104,115]. Cross-reactivity of tropomyosin allergens from house dust mites with mollusks (phylum *Mollusca*) is also reported, mentioning *Bivalvia* class mussels (*Mytilidae* family): blue mussel *Mytilus edulis* (Myt e 1), Mediterranean mussel Mytilus galloprovincialis (Myt g 1), Asian green mussel Perna viridis (Per v 1), oysters (Osteridae family): Pacific oyster *Crassostrea gigas* (Cra g 1), scallops (*Pectinidae* family): scallop *Mimachlamys nobilis* (Mim n 1), razor clams (*Solecurtidae* family): constricted tagelus *Sinonovacula constricta* (Sin c 1); *Gastropoda* class abalones (*Haliotidae* family): disk abalone *Haliotis discus hannai* (Hal di 1), Japanese abalone *Haliotis diversicolor* (Hal d 1), turban snails (*Turbinidae* family): horned turban *Turbo cornutus* (Tur c 1), land snails (*Helicidae* family): brown garden snail *Helix aspersa* (Hel as 1); *Cephalopoda* class decapod arrow squids (*Ommastrephidae* family): Japanese flying squid *Todarodes pacificus* (Tod p 1), cuttlefish (*Sepiidae* family): golden cuttlefish *Sepia esculenta* (Sep e 1), and octopods (*Octopodidae* family): common octopus *Octopus vulgaris* (Oct v 1)[22,104,115,116]. In addition to tropomyosin, other muscle protein crustacean allergens involved in shellfish allergy and cross-reactivity with other invertebrates are arginine kinase and myosin light chain[117].

Arginine kinase, a 40-kDa enzyme involved in the storage of excess energy as arginine phosphate, is a potential new class of invertebrate panallergens, identified mainly in crustaceans, such as black tiger shrimp *Penaeus monodon* (Pen m 2), common shrimp *Crangon crangon* (Cra c 2), whiteleg shrimp *Litopenaeus vannamei* (Lit v 2), Chinese shrimp *Fenneropenaeus chinensis* (Fen c 2), snow crab *Chionoecetes opilio* (Chi o 2), mangrove mud crab *Scylla serrata* (Scy s 2), Atlantic Horseshoe Crab *Limulus polyphemus* (Lim p 2), but also in mollusks: common octopus *Octopus vulgaris* (Oct v 2), ocellated octopus *Octopus fangsiao* (Oct f 2). These are cross-reactive with arginin kinase allergens from house dust mites (Der p 20, Der f 20, Blo t 20), cockroaches (Bla g 9, Per a 9) and moths, such as Indian-meal moth *Plodia interpunctella* (Plo i 1) and silk moth/silkworm larvae *Bombyx mori* (Bomb m 1)[104,118-121].

Myosin light chain is a 20 kDa crustacean allergen identified in common shrimp *Crangon crangon* (Cra c 5), brine shrimp *Artemia franciscana* (Art fr 5), black tiger shrimp *Penaeus monodon* (Pen m 3), whiteleg shrimp *Litopenaeus vannamei* (Lit v 3), American lobster *Homarus americanus* (Hom a 3), with potential cross-reactivity with aeroallergens from dust mite *Dermatophagoides farinae* (Der f 26) and German cockroach (Bla g 8)[104,120,122,123].

Paramyosin is a 103 kDa cross-rective muscle protein described in diverse invertebrates. Molluskan paramyosin is responsible for the "catch" mechanism that enables sustained contraction of muscles with very little energy expenditure. House dust mite allergen Der p 11 (paramyosin with 89% identity with Der f 11) presents significant homology with the paramyosin of mollusks: Mediterranean black Mussel *Mytilus galloprovincialis* (Myt g PM), Japanese Abalone *Haliotis discus* (Hal di PM), Horned Turban *Turbo cornutus* (Tur c PM), common Octopus *Octopus vulgaris* (Oct v PM)[116,120,124,125].

Amylase and haemocyanin are other allergens found in mollusks and are possibly involved in cross-reactivity with house-dust mite aeroallergens. Alpha-amylase Der p 4 may be involved in *Dermatophagoides pteronyssinus* cross-reactivity in gastropod allergy[22,116,126].

It is important to differentiate primary sensitization to pyroglyphid mite aeroallergens, with subsequent food allergy to edible invertebrates, from allergy to shellfish in patients not allergic to house dust mites. There is a profile of sensitization to shellfish in which tropomyosin is involved as a panallergen, with patients not tolerating several crustaceans and/or mollusks, selective sensitization to only one type of seafood being uncommon. Another profile has been also described in cases with house dust mites as primary sensitizing agents and selective allergy to mollusks or crustaceans, described for common European limpet (*Patella vulgata*), terrestrial green garden snail (*Helix* spp) and Mediterranean spiny lobster (*Palinurus elephas*)[126,127]. The role of tropomyosin as a clear cause of cross-reactivity is a matter of debate in some circumstances. Clinical cases of shrimp allergy without snail allergy in relation to house dust mites sensitization, and of allergy to snails without shrimp allergy in context of respiratory mite allergies, were reported, with the observation that in shrimp allergy the symptoms are mainly urticaria or angioedema, while in snail allergy the clinical picture is usually dominated by severe asthma[128].

Moreover, there seems to exist differences in mite-shellfish cross-reactivity depending on climate. A recent study designed to identify which of the shrimp allergen molecules (tropomyosin, arginine kinase, sarcoplasmic

calcium-binding protein, actinins, aldolase, ubiquitin) are involved in mite-seafood cross-reactivity in two different climate populations, revealed that tropomyosin and ubiquitin are responsible for mite-seafood cross-reactivity from both continental dry and humid climates, while alpha-actinin and arginine kinase are involved in dry- and humid-climate groups, respectively. Mites are the primary sensitizer in humid-climate, while shrimps in the continental dry-climate population[129]. Patients sensitized to tropomyosin Der p 10 usually are sensitized to several other house dust mite allergen components besides the major allergens (Der p 1, Der p 2), whereas Der p 10-negative patients are primarily sensitized to Der p 1 and/or Der p 2. Therefore, Der p 10 may be a diagnostic biomarker for mite-allergic patients with additional sensitization to allergens other than Der p 1 and Der p 2, such patients requiring more attention when immunotherapy with allergen extracts is considered[130].

Because allergy immunotherapy with house dust mites extracts is an effective method of treating respiratory allergy, and most of the currently available extracts for subcutaneous or sublingual route of administration contain high concentrations of group 1 and 2 allergens, but may also contain lower concentrations of other sensitizing molecules, including group 10 allergens, it is still unclear whether this type of treatment may induce clinically relevant sensitization to tropomyosin[113,131]. Some studies suggested that food allergy to shrimp or snail can worsen in some patients treated with subcutaneous immunotherapy. However, many patients already had mild allergic reactions to tropomyosin-containing foods before starting immunotherapy, and a new sensitization was confirmed in only one patient[132,133]. Other studies revealed a lack of induction of new sensitization to tropomyosin during house dust mite injection or sublingual immunotherapy[131,134]. Additional studies suggested that, apart from not inducing new sensitization to tropomyosin, house mite subcutaneous immunotherapy could have possible beneficial effects in patients with snail, squid or shrimp allergy[113,135]. Moreover, a recently published report presented a shrimp allergy case improved from anaphylactic symptoms observed before, to mild oral allergy syndrome after one year of sublingual mite immunotherapy with a known and relatively high dosage of tropomyosin[136]. Therefore, induction of clinically relevant sensitization to tropomyosin is an unlikely consequence of house dust mite immunotherapy, but since the risk of adverse allergic reactions to seafood needs to be closely monitored, levels of serum specific IgE to tropomyosins Der p 10 and Pen a 1 may be useful biomarkers[113].

From another point of view, there is a significant prevalence of occupational asthma in shellfish-processing workers, and airborne shellfish exposure not only can cause symptoms in highly allergic subjects, but can also cause *de novo* sensitization. Symptoms may be limited to respiratory tract or may systemic, as in anaphylaxis[104,137]. Moreover, respiratory allergy to aquarium fish food (aquarium syndrome) is due to exposure to aeroallergens (either at work or as a hobby) from a variety of dried arthropod species, including common water fleas (*Daphnia* spp, crustaceans of the *Daphniidae* family), freshwater shrimps (*Gammarus* spp, crustaceans of the *Gammaridae* family), red midge larvae (*Chironomus thummi*, insect of the *Chironomidae* family), mosquito black larvae (*Culex* spp, insect of the *Culicidae* family), and segmented earthworms (*Tubifex tubifex*, annelid of the *Naididae* family). Variable degree of cross-reactivity between these arthropods with house dust mites, cockroaches and edible shrimps, was reported[137,138].

Oral mite anaphylaxis is a new syndrome characterized by severe allergic symptoms occurring immediately after eating mite-contaminated foods, in patients with a previous history of house dust mite-allergic rhinitis and/or asthma. This type of food allergy to mite ingestion was reported in various countries, including the United States, Japan, Taiwan, Venezuela, Brazil and in Southern Europe, being more prevalent in tropical/subtropical environments. Different mite species involved are house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), and storage mites (*Tyrophagus putrescentiae*, *Lepidoglyphus destructor*, *Blomia tropicalis etc.*). Allergenic cross-reactivity between different domestic and storage mite species could explain why patients sensitized to house dust mites may present systemic reactions when exposed to storage mites by oral route. Mite-contaminated foods are usually prepared with wheat and/or corn flour, including pancakes, sponge cakes, pizza, pasta, bread, white sauce, beignets, cornmeal cakes, and polenta. Because exposure to low temperatures inhibits mite proliferation, it is recommended to store the flour in sealed containers in the refrigerator. Other foods that can be contaminated with mites when stored for long periods at ambient temperature are cheese, ham, chorizo, and salami[139]. In Japan, cases involving ingested okonomiyaki or takoyaki prepared at home were reported, due to mite-contaminated flavored flour, the okonomiyaki-mix or takoyaki-mix being previously opened and stored for months at room temperature[140]. It is suggested that thermoresistant mite allergens are involved in pathogenesis, because many cooked mite-contaminated foodstuffs are able to induce symptoms. A variety of this syndrome is the mite ingestion-associated exercise-induced anaphylaxis[141]. Patients with oral mite anaphylaxis present also an increased prevalence of nonsteroidal anti-inflammatory drugs (NSAIDs) hypersensitivity. Even no salicylates were detected in mite-contaminated wheat flour, the opisthonotal gland secretion from *pyroglyphid* mites contains salicylaldehyde analog 2-formyl-3-hydrobenzyl formate[142]. Moreover, intake of NSAIDs sometimes enhance immediate reactions in food-dependent exercise-induced anaphylaxis[143], and salicylate hypersensitivity with reactions to salicylate food additives may occur in patients with cross-reactive NSAIDs hypersensitivity[144].

Domestic cockroaches, especially *Blattella germanica* (German cockroach), are the most important urban indoor inhalant insect allergen sources. Major German cockroach allergens, Bla g 1 and Bla g 2, are cross-reactive with similar American cockroach *Periplaneta americana* allergen components Per a 1 and Per a 2, respectively[145]. Molecular mimicry between cockroach Bla g 5 and helminth glutathione S-transferases promotes cross-reactivity and cross-sensitization[146]. Cockroaches also contain cross-reactive tropomyosin (Bla g 7), which indicates a risk for allergic reactions to shellfish or snail, which can be severe[12,103]. German cockroach allergen molecule Bla g 7 has cross-reactivity with tropomyosins from other cockroaches, such as American cockroach *Periplaneta americana* (Per a 7), but also from dust mites *Dermatophagoides pteronyssinus* (Der p 10), *Dermatophagoides farinae* (Der f 10), and ascarid nematodes *Anisakis simplex* (Ani s 3), *Ascaris lumbricoides* (Asc l 3)[22,147]. Recombinant Bla g 7 sensitization rate in German cockroach-allergic Korean patients is 16.2%[148]. Besides tropomyosin (Bla g 7), myosin light chain (Bla g 8) and arginine kinase (Bla g 9), hemocyanin is another cockroach aeroallergen (Bla g 3) cross-reactive with shellfish allergens, such as the one identified in giant keyhole limpet *Megathura crenulata* (Meg c Hemocyanin)[120,149,150].

An association between sensitization to arthropod aeroallergens and food allergy to edible insects is also possibile. The silkworm *Bombyx mori* is an important insect in the textile industry and its pupa are used in Chinese cuisine, being the most commonly eaten insect in China. The silk, urine and dander of silkworms are often the cause of allergies in sericulture workers, and silkworm pupa is known to be allergenic. Silkworm moth-sensitized patients with rhinoconjunctivitis and asthma from Southern China are frequently concomitantly sensitized to other aeroallergens from relevant mites and cockroaches (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, *Blattella germanica*, *Periplaneta americana*). The silk moth allergen component Bomb m 1 is the significant cross-reactive arginine kinase, similar to house dust mites and cockroaches allergenic molecules, the tropomyosin Bomb b 7 being probable less important[151-153].

Caterpillars are commonly eaten insects in Africa, ingested Mopane worm *Imbrasia belina* being reported as a cause of allergic anaphylaxis in a Zimbabwean adolescent with IgE sensitization to house dust mites and cockroaches (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blattella germanica*), suggesting cross-reactivity due to glutathione transferases (Der p 8, Der f 8, Bla g 5) or tropomyosin[154].

Infestation of food with insects is a different type of allergy described in Spain, lentil pest *Bruchus lentis* proteins being a cause of IgE-mediated rhinoconjunctivitis and asthma in patients eating or inhaling infested legume particles[155].

Cochineal red/carmine is a natural red color, used as food additive (E120, FDA 73.100) or pharmaceutical excipient, and obtained from the dried bodies of the female scale insect *Dactylopius coccus*, which contain dye protein residues attributed to IgE-mediated sensitization, food allergy, including anaphylaxis, and occupational asthma and rhinoconjunctivitis. Insect-derived proteins possibly complexed with carminic acid may be responsible for carmine allergy, and a 38 kDa major allergen in cochineal extract was described as an insect phospholipase or related enzyme. Carmine insect allergens can act both *via* inhalation and digestion, inducing both respiratory allergy and alimentary allergy[156-159].

Aeroallergens and food allergens of vertebrate animal origin

Syndromes and associations related to clinical cross-reactivity bewteen aeroallergens and food allergens of mammalian and avian origin are described below.

Domestic mammals with fur kept as pets induce respiratory symptoms in allergic patients. The popularity of cats and dogs as pets put them among the most important sources of indoor allergens. In Europe and United States of America, at least one person in four is exposed every day to aeroallergens of mammalian origin, and almost everyone is occasionally exposed to inhalant allergens from pets or domesticated animals[160]. Specific *Carnivora* order pet allergen components are described for cat (*Felis catus* syn. *Felis domesticus*): Fel d 1, Fel d 4, and dog (*Canis lupus familiaris* syn. *Canis familiaris*): Can f 1, Can f 2, Can f 5[18,161,162].

Cross-reactive serum albumins (66-69 kDa) from mammals kept as pets or domestic animals are described as allergen components: cat *Felis domesticus* Fel d 2, dog *Canis domesticus* Can f 3, horse *Equus caballus* Equ c 3, cattle *Bos domesticus* Bos d 6, pork *Sus scrofa domestica* Sus s 6, rabbit *Oryctolagus cuniculus* Ory c 6. Allergic sensitization to serum albumins can occur by inhalation as well as ingestion. These proteins are a major component in the circulatory system of mammals, contributing to colloid osmotic blood pressure and the transport of many ligands. As important allergen components, they are present in body fluids, including saliva, in meat, and on dander. IgE cross-reactivity between inhaled (aeroallergens from pets or occupational settings) and ingested or systemically administered serum albumins must be considered in clinical practice[160,163-165].

The cat-pork syndrome consists primarily of IgE-mediated respiratory symptoms following exposure to cat dander, and secondarily of food allergy symptoms after the ingestion of pork meat[166]. The first report on cat-allergic patients experiencing anaphylaxis to pork meat suggested cross-reactivity due to a 67 kDa protein[167], later on the sensitization to cat serum albumin being considered an useful biomarker of possible cross-sensitization not only to porcine serum albumin, but also to other mammalian serum albumins[168]. Despite being a dominant protein in dander, Fel d 2 is a 67-kDa serum albumin regarded as a minor cat

allergen, about 15%-35% of cat allergic patients being sensitized to it. Only 1%-3% of cat-allergic patients seem to be at risk for food allergy to pork meat, under the circumstances that about a third of the subjects sensitized to porcine serum albumin are likely to present allergic reactions to pork consumption[160,165,168].

Although the term cat-pork syndrome seems to be appropriate because the sensitization to cat serum albumin represents the primary event in this cross-reactivity entity, it is also frequently named pork-cat syndrome. Clinical picture varies from oral itching to anaphylaxis. Because albumin is a heat-labile protein, fresh meat or dried and smoked pork are more consistent triggers than well-cooked meat. Pork grilled meat, sausages, ham and pork ribs, hamburger or barbecue were mentioned as causative factors. Small amount of pork meat in a strip of bacon or cooked pork meat may be tolerated without severe reactions, as well as seasoned pork products, such as salami. Fatal anaphylaxis after eating wild boar meat was reported in a patient with pork-cat syndrome. Symptoms usually occur within 30-45 min after eating pork meat, and does not appear to be related to tick bites. In general, patients with pork-cat syndrome, neither react to beef, nor have serum evidence of sensitization. These aspects are helpful in differentiating from delayed food allergy to red meat, due to IgE antibodies to alpha-gal (galactose-alpha-1,3-galactose, a nonprimate mammalian oligosaccharide epitope), in patients with recent tick bite/bites (1-4 wk). These alpha-gal allergic patients present delayed anaphylaxis, angioedema or urticaria, 3-6 h after eating red meat (beef, pork, lamb), but not chicken, turkey, or fish. Both cross-reactivity syndromes do not appear early in life, most reported patients are older than age of five years, with the majority being adults or adolescents[168-171].

Pig allergy was reported from the point of view of food sensitization, but also as occupational allergy. An unusual case of occupational asthma resulting from pork-cat syndrome was also recently described in a female patient having respiratory allergy with sensitization to cat dander, working at a grocery store selling cured meats (having the duty to cut pork bones), and presenting symptoms caused by inhalation. In this case cat dander was the primary sensitizer and sensitization to galactose-α-1,3-galactose, a source of cross-reactivity between meat and dander was ruled out[172]. Pig hair and dander are also important inducers of occupational allergies in farmers exposed in swine production. Moreover, popular uncommon pets include small pigs, mini-pigs, or teapot pigs[163].

Several other cross-reactivity associations between mammalian inhalant allergies with subsequent food allergy were also reported. A case of confirmed occupational respiratory allergy due to pork was followed by food allergy to pork, and later by food allergy to chicken. Porcine and chicken hemoglobin were found to be cross-reactive allergens. Although IgE cross-reactivity is most frequent between mammalian albumins, cross-reactions may also occur between cat and chicken albumins, which share 46% identical amino acids. Cross-reactivity between porcine and chicken serum albumins was possibly linked to a prior sensitization to cat serum albumin[173]. A case of occupational asthma induced by the inhalation of bovine serum albumin powder in a laboratory researcher, was followed by symptoms of food allergy after drinking milk, without symptoms on ingesting beef, pork, or chicken meat[174]. It is important to mention that milk allergic children sensitized to the allergen component Bos d 6 (bovine serum albumin) may also have concomitant beef allergy[175]. Another patient diagnosed with initial sensitization to inhaled rabbit products (such as epithelium, urine, serum) in childhood presented anaphylaxis with severe bronchospasm secondary to ingestion of rabbit meat in adolescence, the allergen involved being the 60-kDa albumin, responsible for cross-reactivity between rabbit epithelium and rabbit meat[176].

Airborne exposure to pet birds antigens may cause allergic rhinitis and/or asthma in IgE sensitized patients or hypersensitivity pneumonitis/extrinsic allergic alveolitis in others.

The bird-egg syndrome consists of primary IgE-mediated sensitization with respiratory symptoms to exposure to bird aeroallergens, and secondarily of allergy symptoms after the ingestion of eggs. This syndrome is due to cross-reactivity between egg yolk and bird allergens (feathers, serum, droppings, and meat). Its pathomechanism is different from hypersensitivity pneumonitis induced by bird antigens, such as pigeon fancier's lung. There are also differences between the bird-egg syndrome and the common allergy without sensitization to bird proteins. Patients with bird-egg syndrome are typical adults, with allergic rhinoconjunctivitis and/or asthma due to repeated exposure to household pet birds, such as budgerigars, canaries, parrots or lovebirds, and the symptoms associated with egg ingestion are usually gastrointestinal, but also cutaneous or respiratory. Food-dependent, exercise-induced anaphylaxis to egg has also been reported. While ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3) and lysozyme (Gal d 4) are involved in common hen's egg white allergy, alpha-livetin found in egg yolk also known as chicken serum albumin (Gal d 5) is the allergen component involved in both respiratory and food-allergy symptoms in the bird-egg syndrome. Gal d 5 is a water-soluble, partially heat-labile, 70 kDa allergen present in egg yolk and avian meat and serum, and induce cross-reactivity to bird allergens, egg yolk, and chicken meat. A minority of patients with egg allergy are reactive to chicken meat. The role in food allergy of several other allergens identified in egg yolk, including apovitellenin I (Gal d Apo I) and apovitellenin VI (Gal d Apo VI), is still unclear[163,177-180]. Two similar cross-reactivity syndromes must also be mentioned. While the bird-egg syndrome is described in patients primarily sensitized to bird antigens, the egg-bird syndrome was reported

in patients in which egg allergy started in infancy and the primary sensitization was to egg yolk. The egg-egg syndrome is an occupational respiratory allergy to airborne egg proteins with subsequent nutritive egg allergy, in bakery and confectionery industry workers[181].

CONCLUSION

The knowledge of significant syndromes and associations related to cross-reactive allergen components and the impact of relevant cross-reactivities between aeroallergens and food allergens are of great importance for the allergy specialist. Allergen cross-reactivity may be an underestimated problem in clinical practice[13,182]. Moreover, molecular-based allergy diagnosis is essential for an accurate allergy evaluation of cross-reactions, sometimes with impact on the therapeutic strategy[12]. Patients allergic to certain food allergens and inhaled allergens should be carefully instructed about cross-reactions to other food allergens[183]. Dietary avoidance of foods that are related and have potentially cross-reactive proteins should be individualized according to the risk of clinical cross-reactivity[3].

Very recently, a trustable expert system was developed to support the interpretation of molecular tests for allergy based on microarrays. Allergen microarrays facilitate the simultaneous testing of more than 100 allergen components, represent the state-of-the-art technology for allergy diagnosis in poly-sensitized patients, and have an important role in the accurate diagnosis of syndromes and associations related to the IgE sensitization to cross-reactive allergens components. A section termed "post molecular anamnesis" suggests any clinical supplemental questions that should arise from the microarray interpretation[11,184-186].

Because the era of the characterization of molecular features of food allergens has begun, new data started to bring useful information about cross-reactivity between different sources of food allergens and aeroallergens in order to help the clinicians to provide appropriate prophylaxis approach, and to estimate the types and severity of allergic reactions[187].

Component-resolved diagnosis is a research method that explains on molecular level allergen cross-reactivity, and allows to distinguish cross-reactions occurring after ingestion of food in patients with IgE sensitization primarily to aeroallergens from the coexistence of inhaled and food allergies. Due to the geographic diversity resulting in different exposure to airborne allergens and dietary factors, studies on allergen components in populations living in different climatic zones give different results. This suggests that the diagnostic and prognostic assessment based on the component-resolved diagnosis results is limited and should always be considered in clinical context[188].

Medical history and diagnosis approach may be guided by the knowledge about the diverse cross-reacting allergens involved, and by the understanding of these clinical entities which may vary significantly or may be overlapping. The use of molecular-based allergy diagnosis improves the understanding of clinically relevant cross-reactive allergen components from aero-allergen sources and foods.

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