Food allergies resulting from immunological cross-reactivity with inhalant allergens

Guidelines from the German Society for Allergology and Clinical Immunology (DGAKI), the German Dermatology Society (DDG), the Association of German Allergologists (AeDA) and the Society for Pediatric Allergology and Environmental Medicine (GPA)

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Summary

A large proportion of immunoglobulin E (IgE)-mediated food allergies in older children, adolescents and adults are caused by cross-reactive allergenic structures. Primary sensitization is most commonly to inhalant allergens (e.g. Bet v 1, the major birch pollen allergen). IgE can be activated by various cross-reactive allergens and lead to a variety of clinical manifestations. In general, local and mild – in rare cases also severe and systemic – reactions occur directly after consumption of the food containing the cross-reactive allergen (e.g. plant-derived foods containing proteins of the Bet v 1 family). In clinical practice, sensitization to the primary responsible inhalant and/or food allergen can be detected by skin prick tests and/or in vitro detection of specific IgE. Component-based diagnostic methods can support clinical diagnosis. For individual allergens, these methods may be helpful to estimate the risk of systemic reactions. Confirmation of sensitization by oral provocation testing is important particulary in the case of unclear case history. New, as yet unrecognized allergens can also cause cross-reactions.

The therapeutic potential of specific immunotherapy (SIT) with inhalant allergens and their effect on pollen-associated food allergies is currently unclear: results vary and placebo-controlled trials will be necessary in the future. Pollen allergies are very common. Altogether allergic sensitization to pollen and cross-reactive food allergens are very common in our latitudes. The actual relevance has to be assessed on an individual basis using the clinical information.

Cite this as Worm M, Jappe U, Kleine-Tebbe J, Schäfer C, Reese I, Saloga J, Treudler R, Zuberbier T, Wassmann A, Fuchs T, Dölle S, Raithel M, Ballmer-Weber B, Niggemann B, Werfel T. Food allergies resulting from immunological cross-reactivity with inhalant allergens. Allergo J Int 2014; 23: 1–16
DOI 10.1007/s40629-014-0004-6

Level of development
S1

AWMF-guideline-register-number
061/019

Finalised
August 27, 2013

Valid until
Oktober 31, 2018

Check
Oktober 30, 2016

ICD-10-numbers
T78.1, T78.0, L27.2, T78.2

German version
www.springer-medizin.de/allergo-journal

Introduction

The nationally adapted guidelines presented here were created on the basis of the current European Academy of Allergology and Clinical Immunology (EAACI) guideline "Food allergy due to immunological cross-reactions with common inhalant allergens" which involved several authors of the present article.

The importance of food as a trigger of allergic reactions has increased over recent decades. Up to 60 % of food allergies seen in older children, adolescents and adults are associated with an inhalant allergy. In case of type 1 food allergies – including reactions to food allergens such as milk protein or chicken egg albumin – the primary sensitization occurs via the gastrointestinal tract. In the case of pollen-associated food allergies (type 2), primary sensitization occurs via inhalation. The allergic reactions are mediated by cross-reactivity resulting from the related molecular structures of aeroallergens and food-derived allergens (**Table 1**).

This increased incidence of pollen allergies will probably lead to a further increase in pollen-associated food allergies in the next years [1, 2].

Immunoglobulin E (IgE) antibody cross-reactivity results from the existence of homologous allergen structures that share linear or conformational epitopes. Such structures may be conserved across protein families, where they may have similar functions [3, 4]. While the primary sensitizing allergen is known for some cross-reactions (e. g. Bet v 1 homologues), there are others for which it is unclear how the cross-reactivity has arisen [e. g. thaumatin-like proteins (TLP)].

Classic examples of protein families with allergenic epitopes include the panallergenic pathogenesis-related protein family 10 (PR-10) proteins, glucanases and tropomyosins [5]. Cross-reactivity with the carbohydrate side chains of plant glycoproteins (cross-reactive carbohydrate determinants [CCD]) has also been described. However, specific IgE (sIgE) directed against these carbohydrate side chains is generally not clinically significant. Such sensitizations have been identified by detection of sIgE against horseradish peroxidase, bromelain or MUXF 3 (the carbohydrate epitope of bromelain lacking the peptide entity) [6].

The majority of pollen-associated food allergies are complex and cannot, in general, be traced back to individual sensitizations with specific aeroallergens. Most patients are sensitized to pollen and other inhalant allergens, so that the profile of potentially possible cross-reactions can be very broad. Furthermore, geographical variations and different nutritional habits can also be of relevance.

These guidelines represent recommendations for the diagnosis and treatment in the main focus of pollen-associated food allergies. Although cross-reactions can also be observed in the case of primary food allergies (e. g. to hazelnuts; peanuts and other legumes; cow's and goat's milk; cod and other species of fish), these are not discussed in the present recommendations.

Abbreviations

AD	Atopic dermatitis
CCD	Cross-reactive carbohydrate determinants
EAACI	European Academy of Allergy and Clinical Immunology
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
IgE	Immunoglobulin E
IgG	Immunoglobulin G
LFS	Latex–fruit syndrome
LTP	Lipid transfer protein
NSAID	Nonsteroidal anti-inflammatory drug
PR-10	Pathogenesis-related protein family 10
SCORAD	Scoring atopic dermatitis
sIgE	Specific immunoglobulin E
SIT	Specific immunotherapy
TLP	Thaumatin-like proteins (PR-5)
VCin	Inspiratory vital capacity

Symptoms of food allergies due to cross-reactivity

The symptoms of a food allergy resulting from a cross-reaction generally appear within a few minutes to 2 h after intake of the food and can affect various organ systems. These include the oral mucosa, the skin, the gastrointestinal tract, the respiratory tract and the cardiovascular system.

Contact urticaria of the oral mucosa

Contact urticaria of the oral mucosa (previously also named oral allergy syndrome) is the most common clinical manifestation of a food allergy in adult patients [7]. Symptoms usually appear immediately after contact with the allergenic food; although less commonly symptoms may take up to 2 h to develop following allergen intake (itchiness of the lips, tongue, gums, ears and throat). The symptoms may be associated with mucosal swelling. In a subgroup of patients, erythema or small vesicles within the oral mucosa (particularly on the lips) may develop. These symptoms generally stop progressing within a few minutes; however, patients may subsequently

Table 1

Food allergen sensitizations due to cross-reactivity

Inhalant allergen	Food allergen
Common	
Tree pollen	Apple, hazelnut, carrot, cherry, green kiwi, nectarine, peach, apricot, plum, celery, soya, fig
Less common	
Mugwort pollen	Spices, carrot, mango, celery, sunflower seeds
Natural latex	Avocado, banana, kiwi, tomato, chestnuts, peach, mango, papaya, acerola cherry, celery
Rare	
Ficus benjamina (weeping fig/ficus–fruit syndrome)	(Dried) figs, kiwi, banana, papaya [87, 116], pineapple and avocado [88], possibly also breadfruit and jackfruit
Bird feathers	Egg, poultry, offal
House dust mites	Crustaceans and mollusks
Animal epithelia	Meat
Unconfirmed	
Ragweed (ambrosia) pollen	Melon, zucchini, cucumber, banana
Grass and cereal pollen*	Flour, bran, tomato, legumes

**Considering the high frequency with which grass and cereal allergies occur, cross-reactions with food allergens are very rare*

also develop systemic reactions. The oropharyngeal symptoms can be caused by any food. However, they are particularly common among pollen allergy patients, where fresh fruit and nuts are the most frequent triggers [8–10].

Aside from the oral mucosa, the skin is the organ most frequently affected by systemic allergic reactions caused by food allergy [11, 12]. Acute generalized urticaria (hives) is particularly common; angioedemas are less frequent. A further possible skin reaction is flushing, which may be associated with itchiness. Within a subgroup of patients with atopic dermatitis (AD) and pollen sensitization, oral provocation with cross-reactive food allergens may result in a temporary worsening of eczema [13, 14].

Respiratory, gastrointestinal and cardiovascular symptoms can also appear as a consequence of a pollen-associated food allergy. Compared to local and respiratory symptoms, gastrointestinal and cardiovascular symptoms are rare and generally are not the only clinical manifestation. The frequency of severe allergic reactions (anaphylactic reactions) attributed to pollen-associated food allergies is increasing [15, 16, 17, 18, 19]. Why the local symptoms are compounded by systemic reactions in these patients is unclear. It is likely that the quantity of the allergen consumed but also simultaneously consumed food components (matrix effect) play an additional role. Furthermore, the degree of sensitization to the primary allergen and additional patient- or lifestyle related factors (augmentation factors) may have an influence.

Contact urticaria of the oral mucosa (previously named oral allergy syndrome) is the most common symptom of a food allergy due to crossreactions. Although rare, respiratory and severe cardiovascular reactions (anaphylaxis) can occur.

Diagnosis of food allergies due to crossreactivity

Diagnosis of food allergies due to crossreactivity is based on the classical criteria of allergy diagnostics:

- Patient history
- Evidence of a sensitization (skin and/or IgE test)
- Oral provocation testing [20]

In the case of food allergy due to crossreactivity the sensitization profile to inhalant allergens should be defined. This can be done using skin prick tests [21] and/or by testing for allergen-specific IgE antibodies. A nutrition and symptom diary log may be helpful. The individual diagnostic process can vary according to the patient's case history, particularly with regard to allergic symptoms. Examples of possible clinical presentations and the corresponding recommended diagnostic procedures are given in **Table 2**.

Specific aspects of skin testing

When food allergy is suspected to result from crossreactions, skin testing should be performed (depending on age) with inhalant allergens and – depending on the symptoms and age of the patient – with the associated sources of food allergens. Not all relevant

sources of food allergens are available as licensed allergen extracts. Furthermore, most commercially available food allergen extracts are not biologically standardized and maybe unreliable in terms of certain allergens (e. g. minor and instable allergens). These extracts are manufactured from natural sources and the results obtained may differ from extract to extract. Due to production processes, relevant allergen components might not sufficiently be present in the test extracts available for skin prick testing (e. g. Bet v 1 homologues). In case of plant-derived food allergens, commercial skin test extracts have a low sensitivity, which can lead to a high rate of false-negative results. Reasons are the potentially low levels of the relevant allergenic components in the food and/or the instability of the allergens toward endogenous enzymatic processes that may occur in the food allergen extracts. It is thus preferable to perform skin testing with native food material. Native food can be tested in different forms (raw or heated). The prick-to-prick test using native material from fresh fruit and vegetables has a higher sensitivity; however, this results in reduced comparability between tests due to potential differences in allergenic raw material in terms of type and ripeness of the fruit/vegetable, as well as differences in storage conditions [22–25]. Due to the lack of available standardized allergen extracts, testing with raw material is often the only diagnostic option.

Aspects relating to the suitability of foods for native testing are described in more detail by the guideline relating to skin testing for food allergies [21].

The limitations of native prick-to-prick testing arise from the low specificity due to possible irritative components in the food – which can lead to false-positive results – and the question of whether the corresponding food is even available in its fresh form [26, 27]. Testing with raw materials involves application of nonstandardized allergen extracts or allergen concentrations. Before performing skin testing for a food allergy, all contraindications must be considered [21, 28].

In vitro testing in clinical practice

Testing in search of allergen-specific IgE is appropriate in cases where a food allergy is suspected. The following situations, primary in vitro diagnosis is indicated:

- Suspicion of a food allergy with an unclear case history
- Suspicion of a food allergy with unclear skin prick test results
- Suspicion of a food allergy to a food which is not suitable for skin testing
- Suspicion of a food allergy in patients with severe allergic reactions
- Suspicion of food allergy in situations where the possibilities for performing and interpreting the results of a skin prick test are limited [29, 30]

Furthermore, in vitro analysis enables the determination of sIgE to individual components.

IgE antibodies against carbohydrate side chains (cross-reactive carbohydrate determinants, CCD) of glycoproteins, e. g. in vegetables, are detectable in

Table 2

Clinical procedures for food allergies resulting from cross-reactivity with inhalant allergens

Clinic	Recommended diagnostic procedure	Management
Clinically relevant allergy to pollen and local reactions after intake of the corresponding cross-reactive food	Depending on case history, confirmation of sensitization to pollen by skin prick or specific serum IgE testing	Recommendation to avoid eating the food or opt for alternative methods of preparation as soon as local reactions develop; inform patient of factors with a potential influence, particularly during the pollen season
Clinically relevant allergy to inhalant allergens and systemic allergic reactions after intake of the corresponding cross-reactive food*	Depending on the case history, confirmation of sensitization to pollen and food by skin prick and/or in vitro IgE testing	Recommendation to avoid eating the food; inform patient of factors with a potential influence, particularly during the pollen season
Unclear symptomatic response to inhalant allergens and a systemic allergic reaction after intake of a cross-reactive food*	Depending on case history and the nutrition and symptoms log, skin prick and/or in vitro IgE testing with inhalant allergens and foods; followed by oral provocation testing under clinical observation	Recommendation to avoid eating the food if there was a positive provocation reaction; inform patient of factors with a potential influence, particularly during the pollen season

*e. g. birch – carrot, mugwort – celery, house dust mites – shrimps, latex – banana

10 %–20 % of patients with a pollen allergy [31, 32]. They exhibit strong cross-reactivity with many types of vegetables, but are generally not of clinical relevance [33]. However, there are individual cases where reactions to foods have been reported to be caused by CCD from vegetables such as celery [34], kaki fruit [35] and tomato [36].

Testing for food-specific IgG or IgG4 is not useful for the diagnosis of food allergy [37, 38] and is not recommended.

Differences between immunological and clinical results

For the interpretation of sensitization to cross-reactive allergens, it is important to distinguish a clinically relevant cross-reaction from a cross-reaction without associated clinical symptoms. The identification of multiple sensitizations to cross-reactive allergens in skin and/or in vitro testing is not rare. However, these need not necessarily be associated with clinical symptoms. Currently available diagnostic methods do not provide a simple explanation why patients with cross-reactions to proteins occurring in different food only react with clinically relevant symptoms in response to certain foods (**Table 3**). Skin and sIgE test results have only a limited predictive value for the outcome of oral provocation testing or the severity of a clinical reaction. The hypothesis that only patients with severe pollen allergies also develop pollen-associated food allergies has not be confirmed to date. There are patients who only develop food allergy symptoms long after initial onset of their pollen allergy. On the other hand, there are also cases where the pollen allergy does not cause any symptoms and only the cross-reactive food is clinically relevant [13]. Various serological and food-specific factors (**Table 4**) are likely to promote the occurrence of clinically relevant cross-reactions.

Table 3

Allergens available for component-based diagnosis of cross-sensitivities

Food	Allergen	Protein family	Symptoms	Allergen available for component-based diagnostics
Peach	Pru p 1	Bet v 1 homolog	oral	Pru p 1[a,b] Bet v 1[a,b,c,d,e]
	Pru p 4	Profilin	usually oral	Pru p 4[a,b] Bet v 2[a,b,c,d,e]
	Pru p 3	Lipid transfer protein	oral and/or systemic	Pru p 3[a,b,c]
Melon	Cuc m 1	Cucumisin	oral and/or systemic	N/A
	Cuc m 2	Profilin	oral	Bet v 2[a,b,c,d,e]
	Cuc m 3	PR-1	oral and/or systemic	not available
Peanut	Ara h 1	Cupin superfamily: vicilin	systemic	Ara h 1[a,b]
	Ara h 2	Prolamin: 2S albumin	systemic	Ara h 2[a,b,d]
	Ara h 3	Cupin superfamily: legumin	systemic	Ara h 3[a,b]
	Ara h 5	Profilin	usually oral	Bet v 2
	Ara h 8	Bet v 1 homolog	oral	Ara h 8[a,b] Bet v 1[a,b,c,d,e]
	Ara h 9	Prolamin superfamily Lipid transfer protein	oral and/or systemic	Ara h 9[a,b], Pru p 3[a,b,c]
	Ara h 10	Oleosin	systemic	nicht verfügbar
Hazelnut	Cor a 1	Bet-v-1 homolog	oral and/or systemic	Cor a 1[a,b,d] Bet v 1[a,b,c,d,e]
	Cor a 8	Prolamin superfamily lipid transfer protein	systemic	Cor a 8[a,b]
Kiwi	Act d 8	Bet v 1 homolog	oral and/or systemic (typically mild reactions)	Act d 8[a,b], Bet v 1[a,b,c,d,e]
Celery	Api g 1.01	Bet v 1 homolog	oral and/or systemic (typically mild reactions)	Api g 1[a,b] Bet v 1[a,b,c,d,e]
Soy	Gly m 4	Bet v 1 homolog	oral or systemic (sometimes severe)	Gly m 4[a,b], Bet v 1[a,b,c,d,e]
Shrimps	Pen a 1	Tropomyosin	systemic	Pen a/m 1[a,b,c,e] Der p 10[a,b]

[a]ImmunoCAP® singleplex determinations; [b]ImmunoCAP® ISAC microarray (Thermo Fisher); [c]Immulite® (Siemens-Healthcare); [d]Allerg-O-Liq (Dr. Fooke Laboratories); [e]Allergozyme® (Omega)

Oral provocation testing

In instances where the case history – including nutrition and symptom records – is unclear, the oral provocation test is the only instrument that can differentiate between a clinically relevant food allergy and a silent sensitization [39, 40].

The provocation test procedure is described in detail in the guidelines for oral provocation testing upon suspicion of food allergy [20].

In addition, the following aspects must be considered when performing oral provocation testing for a suspected inhalant allergy associated food allergy (see also **Table 5**):

- During the pollen season, a generally slight increase in serological and clinical reactivity [39, 41] [42] may be observed.
- Intervals of low symptom levels are preferred.
- The native test material should be freshly prepared due to the instability of certain allergens [26, 27, 43].
- Depending on the expected severity of the reaction, a mucosal provocation can be performed initially, followed by systemic provocation with gradually increasing amounts [16, 26, 44] (**Table 6**).
- In asthma patients, lung function should be tested before and in certain cases after provocation (at least spirometry including forced expiratory volume in one second [FEV1] and forced vital capacity [FVC], or inspiratory vital capacity [VCin]).
- In the case of AD and suspicion of eczema worsening after intake of the aeroallergen-associated food, the oral provocation test should be repeated on two consecutive days with careful standardized evaluation of the skin [45].
- Augmentation factors (physical exertion) and other potential parameters may also require consideration (**Table 7**).

Table 4

Factors promoting the onset of clinically relevant cross-reactions

Influence of the individual IgE repertoire	Influence of the specific food
High proportion of cross-reactive antibodies	(Orally) consumed quantity
Adequate binding strength (avidity) of the cross-reactive antibody	Proportion of the cross-reactive allergen in the food
Cross-reactive antibody-mediated recognition of multiple epitopes	Similarity, number and stability of cross-reactive epitopes

IgE, immunoglobulin E

Table 5

Food allergies resulting from cross-reactivity with inhalant allergens:

Recommendations for clinical practice
Sensitizations to various inhalant allergens are responsible for a broad spectrum of sensitizations to foods
Demonstration of a sensitization by skin or in vitro testing does not constitute proof of clinical relevance. Positive case history is of greater importance than a confirmed sensitization
General dietary recommendations should not be made on the basis of a proven cross-reactivity between inhalant and food allergens
Potential augmentation factors should be considered
For some food allergies, the prick-to-prick test using fresh material is better than prick testing with commercially available food extracts for determining sensitizations
In vitro testing of individual allergens (component-based diagnosis) can be helpful for individual determination of sensitization to plants. Testing of individual allergens can also be helpful for assessing the individual risk of systemic reaction profile
In the case of unclear case history, it may be useful to implement and analyze a nutrition and symptom diary
Avoidence or re-exposure and/or oral provocation testing with the presumed reactive food is necessary before performance of a therapeutic elimination diet
Specific immunotherapy with cross-reactive inhalant allergens for treatment of a food allergy alone is not recommended; indications should be the respiratory symptoms

The oral provocation test is the only instrument (particularly where case history is unclear) that can differentiate between a clinically relevant food allergy (and the required quantity) and a sensitization. Factors influencing the individual pattern of reactions elicited by food allergies caused by a primary sensitization to inhalant allergens (e. g. mites, pollen) must be considered when planning and performing the test.

Therapeutic consequences of a proven clinically relevant cross-reaction

Therapeutic approaches

The safest food allergy therapy is currently allergen avoidence. However, absolute elimination should not always be recommended, but rather the therapeutic recommendations should consider the individual context (e. g. the food may be consumed outside the pollen season) and, where applicable, augmentation factors (avoidance of the food prior to physical exercise). Tolerance toward pollen-associated foods may vary throughout the year depending on the pollen season and may also change upon the influence of augmentation factors. In case of food allergies resulting from primary sensitization to inhalant allergens, specific elimination of a food should only be recommended when the patient exhibits clinically relevant reactions.

General dietary avoidence protocols for pollen sensitization are not justified. Upon demonstration of multiple clinically relevant cross-reactions, attention should be paid to an adequate nutritional balance.

The therapy of symptoms is based on recommendations for treatment of food allergy [46].

Some patients with pollen-associated food allergy may benefit from specific immunotherapy (SIT). Several studies have shown that immunotherapy with pollen led to relief of mucosal symptoms [47, 48, 49, 50, 51]. However, the current literature on this topic is inconsistent [52, 53]. SIT using pollen extracts should only be conducted if the patient also has symptoms in the sense of a clinically relevant pollen allergy. Based on the results of investigations performed to date, SIT of oral allergy symptoms without pollen allergy-induced respiratory symptoms is not indicated [54].

Further studies in the future are necessary to demonstrate the efficacy of SIT with e. g. pollen extracts for pollen-associated food allergies.

Allergen avoidence is the safest therapy of pollen-asociated food allergy.

In the case of pollen allergies to heat-labile allergens, the therapeutic diet can be adapted (e.g. patients with birch pollen-associated cross-reactions to hazelnuts might tolerate ufficiently heat-treated food containing hazelnut).

Patients who have experienced a severe reaction require detailed information and emergency medication for self treatment.

Specific immunotherapy (SIT) should only be considered when symptoms of a preexisting rhinoconjunctivitis are dominating.

Specific aspects of relevant inhalant allergens that cause pollen-associated food allergies due to cross-reactivities

Birch

Tree pollen-associated food allergies are the most frequently occurring pollen-associated food allergies in Germany. Birch pollen-associated food allergies are normally characterized by the appearance of predominantly oropharyngeal symptoms. However, the literature contains numerous case studies describing severe reactions caused by Bet v 1 cross-reactivity [15, 26, 27, 55, 56]. Common foods that typically lead to

Table 6

Procedure for double-blind placebo-controlled food provocation tests with cross-reactive food according to Bindslev-Jensen [40]

Procedure	Observation
Preparation	Documentation of initial condition
Step 1: Mucosal provocation	
Retain increasing quantities (e.g. 5, 10, 20, 40 ml) of allergen drink in mouth for 1 min; spit out; wait for 15 min	Oropharyngeal symptoms (irritation and swelling of mouth and throat) or clinical allergy symptoms
Retain increasing quantities (e.g. 5, 10, 20, 40 ml) of placebo drink in mouth for 1 min; spit out; wait for 15 min	No symptoms
Interpretation: result positive if localized oropharyngeal symptoms are observed three times or upon real positive symptoms following allergen provocation with a negative placebo reaction	
Step 2: Systemic provocation	
Swallow increasing quantities (e.g. 10, 20, 40, 80 ml) of allergen drink; increase dose every 15 min	Oropharyngeal symptoms, rhinoconjunctivitis, urticaria, angioedema, vomiting, diarrhea, dyspnea, reduced blood pressure
Swallow increasing quantities (e.g. 10, 20, 40, 80 ml) of placebo drink; increase dose every 15 min	No symptoms
Interpretation: result positive if symptoms are observed upon allergen provocation three times and the placebo reaction is negative	The order of the verum and placebo administrations set in a blinded manner. Allergen dosage and the number of administrations depend on the patient's case history. Where case history reveals that symptoms do not develop in the mouth or throat, step 1 can be omitted

Table 7

Factors potentially influencing aeroallergen-mediated cross-reactions with foods

Individual pollen sensitization profile	
Cumulative effect of high pollen count	
Physical exercise	
Bronchial asthma (severity or medication)	
Simultaneous gastrointestinal disease	
Meal size and composition (matrix effect)	
Quantity of allergen and cumulative effect of cross-reactive food consumption	
Simultaneous intake of:	– Medication with an influence on allergen stability (e.g. proton pump inhibitors) – Medication that may influence allergic events (beta-blocker, NSAID) – Alcohol

NSAID, nonsteroidal anti-inflammatory drugs

severe reactions on the basis of Bet v 1 cross-reactivity are hazelnuts, carrots and soy, as well as rarer consumed food such as persimmon.

The allergenic structures in most pollen-associated foods are highly heat-labile and the majority of patients tolerate these foods after heating (by boiling, baking or cooking). However, there are data in the literature indicating that small quantities of pollen-associated allergens, for example from roasted hazelnuts or boiled celery, can still cause symptoms in highly sensitized patients [16, 43, 57]. Even cooked, birch pollen-associated foodstuffs can lead to worsening of eczema in a subgroup of sensitized AD patients [58].

In Germany, numerous well-characterized cross-reactive allergens from pollen, vegetables and fruits are derivatives of birch pollen allergens. In contrast, only a proportion of the species-specific cross-reactive allergens from mugwort and grass pollen could be identified until now. The major birch pollen allergen, Bet v 1, is recognized by over 95 % of patients allergic to birch pollen. Bet v 1 belongs to the PR-10 protein family, members of which can be found in many plant-based foods. These proteins are the dominant allergens for pollen-associated food allergies (**Table 8**) [59].

Bet v 1 homologues allergens are underrepresented in most allergen extracts. For example, the Bet v 1 homologue allergen Gly m 4 is not detected in total soy extract. In the case of suspicion of a soy allergy resulting from a primary Bet v 1 sensitization, Gly m 4 should be tested as a recombinant allergen. For other extracts (such as hazelnut or apple), sensitivity was improved by supplementing the allergen extracts with recombinant major allergens from the corresponding family.

Minor allergens are recognized by 10 %–32 % of patients allergic to birch pollen. In addition to Bet v 1, four other birch pollen allergens namely Bet v 2 (profilin, major allergen in melon), Bet v 6 (isoflavone reductase), Bet v 7 (cyclophilin) and Bet v 8 (pectin methylesterase) can cause cross-reactions with

Tabelle 8

Selected Bet v 1 homolog allergens in foods (adapted from Vieths [117])

Birch pollen allergen	Homologous food allergen	Corresponding food	Botanical family	Selected reference
	Mal d 1	Apple (*Malus domestica*)	Rosaceae	Vanek-Krebitz et al. 1995 [118]
	Cor a 1.04	Hazelnut (*Corylus avellana*)	Corylaceae	Breiteneder et al. 1993 [119]
	Api g 1	Celery (*Apium graveolens*)	Apiaceae	Breiteneder et al. 1995 [120]
	Dau c 1	Carrot (*Daucus carota*)	Apiaceae	Hoffmann-Sommergruber et al. 1999 [121]
Bet v 1 (PR-10)	Pru av 1	Cherry (*Prunus avium*)	Rosaceae	Scheurer et al. 1997 [122]
	Pyr c 1	Pear (*Pyrus communis*)	Rosaceae	Karamloo et al. 2001 [123]
	Act d 8	Green kiwi (*Actinidia deliciosa*)	Actinidiaceae	Oberhuber et al. 2008 [124]
	Act c 8	Yellow kiwi (*Actinidia chinensis*)	Actinidiaceae	Oberhuber et al. 2008 [124]
	Gly m 4	Soy bean (*Glycine maxima*)	Fabaceae	Kleine-Tebbe et al. 2002 [15]
	Ara h 8	Peanut (*Arachis hypogaea*)	Fabaceae	Mittag et al. 2004 [125]
	Vig r 1	Mung bean (*Vigna radiata*)	Fabaceae	Mittag et al. 2005 [126]

PR-10, pathogenesis-related protein family 10

plant-derived foods. Cross-reactions between Bet v 1, Bet v 2 or Bet v 6 and structurally related allergens in exotic fruits can cause severe allergic reactions; possibly even upon the first consumption of the food (e. g. kiwi, litchi) [60].

Mugwort

Mugwort pollen (**Table 9**) are the main cause of rhinoconjunctivitis symptoms in late summer. Severe anaphylactic reactions to celery have been reported in patients with a monosensitization to mugwort pollen. Also in Germany, celery is one of the most common trigger of severe food-induced anaphylaxis in adults [11]. The primary mugwort allergen (*Artemisia vulgaris*) is the glycoprotein Art v 1 (a defensin). More than 95 % of patients are sensitized to this allergen [61, 62]. Unfortunately, the literature contains no data relating to the frequency of food allergies among patients with an isolated mugwort allergy. Application of the Art v 1 and Art v 4 (profilin) allergens for sIgE analyses using component-based diagnostic methods led to positive results in 91 % of mugwort allergy patients [63].

There are currently no data that adequately explain the cross-reactivity of individual mugwort allergens with plant-derived foods.

Grass pollen

Grass pollen are the most important inhalant allergens worldwide. Cross-reactive carbohydrate-specific IgE antibodies have been described in connection with grass pollen sensitizations. These antibodies can cross-react with glycan structures from other allergen sources, in particular with plant-derived food allergens. However, cross-reactive IgE antibodies directed against carbohydrate determinants of glycoproteins identified in grass pollen-sensitized patients have only a low biological activity [33, 64].

Another group of proteins that can cause strong cross-reactivity in patients with a grass pollen sensitization are the profilins. Profilins are highly conserved proteins [65]. However, the majority of sensitized patients with antibodies to profilin do not react in provocation tests. In terms of clinical presentation, patients with profilin sensitization report oropharyngeal symptoms after eating melon, banana, mango, zucchini and many other fruits and vegetables. It was recently shown that IgE against grass pollen profilin was detectable in patients with occupational asthma and associated food and pollen allergies [66]. Interestingly, patients with an isolated wheat allergy show a marked in vitro cross-reactivity with other cereals, but only a very low level of cross-reactivity with taxonomically more closely related grass pollens. In contrast, patients with grass pollen allergies often exhibit a marked in vitro cross-reactivity with cereals and other grass pollen allergens.

In summary, the relevance of grass pollen-associated food allergies in patients allergic to grass pollen must be considered critical.

Table 9

Mugwort-associated food allergies

Syndrome	Food allergies	Reference
Celery–birch–mugwort–spice syndrome*	Celery and/or other vegetables and spices of the umbelliferous plant family (e.g. carrots, parsley; caraway, fennel, coriander and anise seeds)	Wüthrich and Dietschi 1985 [127]
Celery–birch–spice syndrome	Plants of the Umbelliferae, Solanaceae (paprika), Piperaceae (pepper), Sumach (mango) and Liliaceae (garlic, onion) families	Egger et al. 2006 [61]
Mugwort–mustard allergy syndrome	Mustard, cruciferous vegetables other than mustard (e.g. broccoli, cabbage and cauliflower), nuts, pulses, fruits of Rosaceae, cereals	Figueroa et al. 2005 [128]
Mugwort-peach syndrome	Peach (allergy triggered by LTP Art v 3 and Pru p 3)	Pastorello et al. 2002 [129]

LTP, Lipid transfer protein
**Frequently observed in birch pollen allergy patients; rarer among mugwort allergy patients*

Ragweed

Allergens from ragweed pollen can cross-react with allergens from plant-derived foods. This was first described 40 years ago, when the simultaneous occurrence of an allergy to melons and bananas was reported in a ragweed pollen rhinitis patient [67]. This observation was subsequently confirmed [68]. These studies reported that the serum of up to 50 % of ragweed-reactive patients reacted with food from the squash family (melon, watermelon, zucchini and cucumber) or banana. In both studies, the patients' case histories included reports of hypersensitivity reactions manifesting as oral allergy symptoms after consuming the aforementioned foods.

More recent studies show that melon allergy patients react with a series of taxonomically unrelated plant-derived foods such as peach, figs and kiwi as well as also having latex sensitization [69]. The plant panallergen profilin was identified as the major melon allergen [70]. In ragweed allergy patients, this profilin sensitization was confirmed by Bet v 2 reactivity.

Despite the case studies mentioned above, it is still unclear whether or not ragweed-specific allergens – aside from profilin-mediated cross-reactions – can cause a clinically relevant sensitization to cross-reactive foods. Unpublished data from more than 137 patients with ragweed pollen monosensitization revealed no evidence of a pollen-associated food allergy [71].

Plane

An association between plane pollen rhinitis and a pollen-associated food allergy has been described in the literature [72, 73]. However, the cross-reactive allergens have not yet been convincingly characterized.

To date, four plane pollen allergens have been identified: Pla a 1 (invertase inhibitor) and Pla a 2 (polygalacturonase, a CCD-bearing protein) are the major plane pollen allergens and are responsible for up to 79 % of IgE reactivity [74]. Profilin-specific IgE was described for 47 % of patients with plane pollen sensitization. There are currently no data providing definite evidence of cross-reactivity between plane pollen and pollen-associated food allergies [75].

Pla a 3 [the plane lipid transferase protein (LTP)] has been described as a minor allergen in up to 27 % of plane pollen allergic patients. However, none of these patients had food allergy. These data stand in contrast to those from patients with both peach and plane pollen allergy: in this group of patients, sensitization to Pla a 3 could be identified in up to 64 % [76]. In light of this, it is currently unclear whether Pla a 3 or the peach LTP is the primary source of sensitization in the latter patients.

Latex

The incidence of allergies to natural latex rose during the later 1980's due to increased exposure to latex in both working and home environment. The milky fluid from the rubber tree Hevea brasiliensis that gives rise to natural latex contains numerous proteins, more than 60 of which are IgE-binding structures [77, 78, 79, 80]. Following introduction of legal regulations governing the latex protein content of rubber gloves and other products, the frequency of latex allergies has been reduced in recent decades [81]. To date, 17 natural latex allergens and isoforms with molecular weights ranging between 4.7 and 60 kDa (Hev b 1–14) have been documented (www.allergen.org) (**Table 10**). Approximately 30 %–40 % of latex allergic patients have cross-reactive sensitizations to foods such as carrots, potatoes, tomatoes, celery, zucchini, apple, pear, melon, kiwi, papaya, fig, passion fruit, banana, avocado, acerola or chestnuts (latex–fruit syndrome, LFS) [82], although only a proportion of these are clinically relevant. The literature contains recently published case reports describing isolated instances of cross-reactivity between latex and cassava [83] and latex and curry spice [84].

Tabelle 10

Latex allergens

Clinical aspects	Individual allergens	References
Major allergens (e. g. medical personnel)	Hev b 5, Hev b 6.01 and Hev b 6.02	Mari et al. 2007 [130]
Major allergens (patients undergoing frequent surgery, e. g. spina bifida)	Hev b 1 and Hev b 3	Raulf-Heimsoth et al. 2007 [131], Wagner and Breiteneder 2005 [81]
Cross-reactive allergen in latex-fruit syndrome	Hev b 2, Hev b 6.01, Hev b 6.02, Hev b 6.03, Hev b 7, Hev b 8 and Hev b 11, Hev b 12	Wagner and Breiteneder 2005 [81]
No or low clinical relevance	Cross-reactive carbohydrate determinant (CCD)	Raulf-Heimsoth et al. 2007 [131]

The frequency of latex-associated food allergies is associated with eating habits [85]. Among 137 patients with latex allergy, fruit-specific IgE was detected in 69 % and allergic symptoms after intake of particular food were observed in 42 % [85]. In contrast, sIgE antibodies against total-latex extract was identified in 86 % of patients with fruit allergy but no risk factors for latex sensitization, although clinically significant symptoms after latex provocation were observed in only 11 %. A latex sensitization should always be considered for its clinical significance, since a sensitization to total-latex extract can be attributed to CCD or other panallergens such as profilin in an above average number of instances [77].

In summary, a clinically relevant natural latex sensitization is characterized by positive IgE against the major latex allergens Hev b 1, Hev b 3, Hev b 5 and Hev b 6.01.

Sensitization to the minor natural latex allergens Hev b 8 and Hev b 11 is seldom associated with a clinically relevant latex allergy.

Testing for anti-CCD IgE antibodies is helpful

- when pollen or insect venom allergic patients test positive for sIgE to latex extract, but do not develop clinical symptoms upon contact with latex products.
- when sensitisations to plant-derived food stuff are detected in the absence clinical symptoms of the LFS in cases of a plant-derived food sensitization in the absence of clinical LFS symptoms [6, 86].

In cases of LSF relevant cross-reactions may occurr based on sensitizations to Hev b 2, 5, 6.01/02, 7, 11 or 12.

Ficus benjamina (weeping fig)

This plant is very often found in homes or public buildings. The allergens are airborne and sensitization is possible by inhalation.

Reactions to figs are most strongly associated with Ficus benjamina allergy, although severe systemic reactions after intake of dried figs have also been reported [87, 88]. Almost 90 % of patients with allergic reactions to fruit – past or present – had a weeping fig in their home. The sensitization appeared to be clinically relevant in approximately half of the patients examined. In most cases, however, the sensitization remained latent, since many of the patients never ate figs. Other fruits that may be relevant here include the breadfruit (although this is not eaten raw) and the jackfruit.

Cysteine proteases are the major allergens for ficus-associated allergies. Cysteine proteases are also found in pineapple (bromelain, Ana c 2) and kiwi (actinidin, Act d 1) – fruits that are associated with ficus-fruit syndrome.

Contact urticaria following consumption of fresh figs has been described in pollen allergy patients who are not sensitized to Ficus benjamina or natural latex [89]. Dried figs contain no significant quantities of Bet v 1 epitopes, possibly due to the progressive proteolysis of PR-10 proteins by fig ficine [90].

In summary, upon suspicion of a fig allergy, a distinction should be made between clinical reactions to fresh or dried figs. Prick-to-prick tests may be helpful: IgE directed against Bet v 1 may indicate a possible primary sensitization to birch pollen with associated fig cross-reactions.

Olives

Olive tree (Olea europaea) pollen are important aeroallergens in southern Europe and the Mediterranean region. Reports of olive pollen allergy in relation with food allergy are rare. There are no reports of patients with a monosensitization to olive pollen developing food allergy. Allergens that could potentially lead to cross-reactivity are profilin, LTP and glucanase [91, 92]. Peach, apple, pear, kiwi, melon and nuts have been described as the cause of oral allergy syndrome in patients with olive pollen allergy [91]. The severity of pollen-associated food allergy depends on the particular sensitization: LTP sensitization tends to lead to increased, and profilin sensitization to less severe reactions.

Of 134 Spanish patients allergic to Olea europaea pollen, 40 had sensitization to plant-derived foods. Among these 40 patients, allergic reactions to fresh

fruit or nuts were either clear from their case history or anaphylactic response, or the symptoms of oral allergy syndrome were confirmed by positive results in double-blind placebo-controlled oral provocation tests with fruit [93]. The fruits that most frequently tested positive were peach, pear, melon, kiwi and nuts. Of the individual olive pollen allergens, Ole e 7 (LTP) was most often associated with severe clinical symptoms. In 90 % of patients exhibiting oral allergy syndrome, sIgE antibodies directed against the profilin Ole e 2 could be detected. In contrast, the prevalence of Ole e 2-specific IgE antibodies in patients with fruit anaphylaxis was significantly lower than in a control group of pollen allergy patients without food allergy [93].

Relationship to latex–fruit syndrome: The major olive pollen allergen, Ole e 9, is a β-1,3-glucanase belonging to the PR-2 protein family [94]. Latex Hev b 2 is also a β-1,3-glucanase and is cross-reactive with Ole e 9. Ole e 10 also appears to share IgE B cell epitopes with various plant proteins and cause cross-reactivity with latex, tomato, kiwi, potato and peach. Similar to Hev b 10, Ole e 5 is a manganese superoxide dismutase [95] and thus another potentially cross-reactive allergen in pollen-latex-fruit syndrome.

Summary and recommendations: Upon suspicion of an olive pollen-associated food allergy, prick-to-prick testing using the possible triggers is recommended. Analysis of IgE to known cross-reactive components (e. g. profilin, LTP) can help to clarify cross-reactions.

House dust mites

Crustaceans and mollusks can cause severe allergic reactions. The major allergen is the muscle protein tropomyosin. Tropomyosins are not only found in crustaceans (shrimps, lobster, crabs, crayfish) and mollusks (squid, snails, mussels), but also in arachnids and insects. In contrast to the tropomyosins of invertebrates, the tropomyosins of vertebrates do not appear to be allergens. [96]. Der p 10 and Der f 10 of house dust mite tropomyosin show a marked homology to the tropomyosins of crustaceans and mollusks [97]. Similar amino acid sequences and epitopes explain the in vitro cross-reactivity of invertebrate species [98].

Allergic reactions to shrimps have been described in patients with house dust mite allergy. The causative cross-reactive allergen sensitization is usually to tropomyosin. It has been shown by inhibition assays that sometimes the house dust mites and sometimes the shrimps themselves were the source of the sensitization [97, 99]. Snails are the main cause of a clinically relevant cross-reaction to house dust mites. Inhibition experiments have demonstrated that the house dust mite is mostly the primary source of sensitizing allergen [97, 99].

Animal epithelia

Inhalant allergies to animal epithelia are not rare. Reports of food allergies resulting from primary sensitization to animal allergens are very rare.

The term pork-cat syndrome is used to describe patients who have an inhalant allergy to cat epithelia and who develop allergic reactions after eating pork [100]. The triggering protein is albumin. Since albumin is also present in other epithelia and animals, a broader IgE reactivity can arise [108, 109]. The development of generalized symptoms varies from case-to-case (probably depending on the albumin content of the meat that was eaten), although a death from anaphylaxis has also been reported [109]. Adults are primarily affected. Primary inhalant sensitization is also possible to the serum albumin of other animals with fur (dog, Can f 3 and hamster). Furthermore, cross-reactions to other types of meat are also possible [108, 110]. Overall, however, the cross-reactions of Fel d 2 and Can f 3 with bovine serum albumin seem to be much weaker than those with porcine serum albumin or may even be completely absent [111]. Depending on the study, IgE to serum albumin (Fel d 2) was found in 14 %–23 % of cat allergy patients [111, 112]. The clinical relevance of this IgE is lower: it is assumed that 1 %–4 % of all patients allergic to cats could have clinically manifest pork allergy [113].

Poultry meat allergies in the context of bird-egg syndrome are based on a primary sensitization to inhaled bird serum albumin as a consequence of exposure to excretion and feathers from pet birds and/or poultry [102]. Adults are more often affected. The cross-reactivity is usually between bird serum albumin (ca. 66 kDa) and the chicken serum albumin present in egg yolk (α-livetin, Gal d 5) [101, 103, 104]. Following the consumption of eggs, correspondingly sensitized patients develop oral symptoms and in some cases also gastrointestinal complaints, urticaria, angioedema and asthma [101, 105, 106, 107].

Summary: The cross-reactive allergenic components underlying pork-cat (Fel d 2) and bird egg (Gal d 5) syndromes are available for IgE detection tests. These can be supplemented by skin tests to support the diagnosis.

Clinical implications

Food allergies resulting from cross-reactivity with primary inhalant allergens are frequent and probably on the increase. An important aspect of these is the broad spectrum of IgE reactivity, since sensitization is predominantly to proteins that can be found in numerous plant- and also animal-derived foods. Nowadays, molecular diagnositic tests allow to determine individual sensitization profiles. However, the allergological relevance of a sensitization profile must al-

ways be reflected on the basis of the case history or to be proven by oral provocation testing.

In most cases, food allergies resulting from cross-reactions cause mild allergic symptoms; however, they also have the potential to cause severe systemic allergic reactions, particularly if large quantities of protein are consumed. Patients must be informed about the distribution of the allergen, its characteristics (thermal and pH stability) and the potential threat that it represents (**Table 5**). In line with the guideline for the treatment of food allergies [46], patients developing severe allergic reactions should always be equipped with an emergency aid kit.

The only currently available therapy for food allergies resulting from sensitization to an inhalant allergen is avoidence. This is accomplished by adherence to an individualized elimination diet which should be supported by therapists with allergological nutritional expertise. The literature contains evidence to indicate that SIT directed to the primary allergen can also result in clinical improvement of a pollen-associated food allergy [114], although sufficient data from controlled clinical trials are currently not available [115].

Contributing societies

- German Society of Allergy and Clinical Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie, DGAKI; primary responsibility; passed; May 28, 2013)
- German Dermatology Society (Deutsche Dermatologische Gesellschaft, DDG; passed: June 27, 2013)
- Association of German Allergologists (Ärzteverband Deutscher Allergologen, AeDA; passed: August 8, 2013)
- Society for Pediatric Allergology and Environmental Medicine (Gesellschaft für Pädiatrische Allergologie und Umweltmedizin, GPA; passed: June 27, 2013)

Methodology of guideline development

Literature reviews and expert consensus (February 20, 2013)

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Cite this as Worm M, Jappe U, Kleine-Tebbe J, Schäfer C, Reese I, Saloga J, Treudler R, Zuberbier T, Wassmann A, Fuchs T, Dölle S, Raithel M, Ballmer-Weber B, Niggemann B, Werfel T. Food allergies resulting from immunological cross-reactivity with inhalant allergens. Allergo J Int 2014; 23: 1–16
DOI 10.1007/s40629-014-0004-6

Conflict of interests
The authors state that there are no conflicts of interest.

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