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Received: 1 November 2020 | Revised: 29 January 2021 | Accepted: 24 February 2021

DOI: 10.1111/all.14797

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

REVIEW

The diagnosis and management of allergic reactions in patients sensitized to non-specific lipid transfer proteins

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Abstract

Sensitization to one or more non-specific lipid transfer proteins (nsLTPs), initially thought to exist mainly in southern Europe, is becoming accepted as a cause of allergic reactions to plant foods across Europe and beyond. The peach nsLTP allergen Pru p 3 is a dominant sensitizing allergen and peaches a common food trigger, although multiple foods can be involved. A frequent feature of reactions is the requirement for a cofactor (exercise, alcohol, non-steroidal anti-inflammatory drugs, *Cannabis sativa*) to be present for a food to elicit a reaction. The variability in the food and cofactor triggers makes it essential to include an allergy-focused diet and clinical history in the diagnostic workup. Testing on suspected food triggers should also establish whether sensitization to nsLTP is present, using purified or recombinant nsLTP allergens such as Pru p 3. The avoidance of known trigger foods and advice on cofactors is currently the main management for this condition. Studies on immunotherapy are promising, but it is unknown whether such treatments will be useful in populations where Pru p 3 is not the primary sensitizing allergen. Future research should focus on the mechanisms of cofactors, improving diagnostic accuracy and establishing the efficacy of immunotherapy.

KEYWORDS
cofactors, diagnosis, lipid transfer protein, management

Key Messages

1. Clinical reactions to foods in those sensitized to nsLTP may vary from mild oral symptoms or urticaria to life-threatening anaphylaxis
2. Cofactors are a common feature of reactions, usually exercise, NSAID or alcohol but can include a wide range, with some experiencing food-allergic reactions only when a cofactor is present.
3. The diagnostic pathway should include taking a detailed clinical history, establishing sensitization to the suspected food(s) and testing for sensitization to relevant nsLTP allergens such as Pru p 3 (peach).
4. Oral food challenge (OFC) performed in a clinical setting may be useful for determining whether, in an individual sensitized to nsLTP, all foods that test positive need to be excluded especially if there is no history of reactions to those foods. However, OFC cannot determine whether nsLTP is the definitive cause of a reaction, especially in those with a positive skin prick test or specific IgE test to the whole food.
5. Those sensitized to nsLTP in a given food without reactions to that food may not need to avoid it although this can vary depending on the individual case.
6. The main management for those sensitized and symptomatic is the avoidance of known trigger foods; it is difficult to predict whether more foods are likely to provoke reactions over time, and also whether all forms of the food need to be avoided.
7. Immunotherapy can be effective, but it is not commonly available, and the success of the treatment might depend on the primary sensitizing allergen.

1 | INTRODUCTION

Non-specific lipid transfer proteins (nsLTPs) are ubiquitous in the plant kingdom, and there is a high degree of structural homology between nsLTP allergens, even from plants with a distant taxonomic relationship.[1] These proteins, present in native, cooked or processed foods, are an important cause of IgE-mediated food-allergic reactions to plant-derived foods. Reactions to nsLTP can occur in

combination with or only when cofactors such as exercise and intake of non-steroidal anti-inflammatory drugs (NSAIDs) are present. In its simplest form, nsLTP sensitization may be associated with reactions to one food or more from a single taxonomic group, whereas those with the so-called 'nsLTP syndrome' (Box 1) may react to diverse taxonomically unrelated foods.[2,3] However, sensitization may also exist in apparently non-reactive individuals, and diagnostic assessment is complicated by widespread but clinically irrelevant IgE cross-reactivity. This can lead to misleading positive skin prick tests (SPTs) or *in vitro* tests, and potentially the exclusion of many foods, which might be tolerated, unless a thorough clinical history is undertaken prior to testing. Food challenges are the gold standard for food allergy diagnosis, but validated nsLTP-specific challenge protocols do not yet exist.

Accurate identification of this condition and characterization of the relevant nsLTP triggers is the cornerstone of appropriate management, which should focus on minimizing the risk of further reactions through dietary modification. This condition is conceptually complex, and therefore, patient education is of paramount importance to encourage adherence, minimize anxiety and limit unnecessary dietary restriction. For many, dietary management, together with appropriate use of rescue medication, is the mainstay of treatment. However, sublingual immunotherapy with peach extract has been developed, and immunotherapies to address other forms of nsLTP allergy, including nsLTP syndrome, are currently being researched. The European Academy of Allergy & Clinical Immunology (EAACI) Task Force on nsLTP Allergy across Europe has written two papers. The first of these dealt with the molecular structure and function of nsLTP allergens, routes of sensitization and epidemiology, including the geographical spread of sensitization to nsLTP.[4] This second paper summarizes the current evidence relating to diagnosis and management of individuals with clinically relevant sensitization to nsLTP allergens. Particular areas of uncertainty and future research needs are highlighted. Keywords used in the literature search were as follows: non-specific lipid transfer proteins, nsLTP syndrome, Pru p 3, plant food allergy, pollen food syndrome.

2 | SYMPTOM TYPE AND SEVERITY

One of the most intriguing aspects of nsLTP sensitization is the extreme variability of its clinical presentation, which may range from mild contact urticaria to anaphylaxis.[5–12] However, many patients remain asymptomatic despite nsLTP sensitization; although the reasons for this are still undefined, one explanation could be that cofactors may be needed for the clinical expression of nsLTP sensitization.[7,10,13–16] Patients may also exhibit considerable clinical heterogeneity, with some reacting only to one food (often peaches), whereas others may have nsLTP syndrome, experiencing symptoms to many fruits of the Rosacea family, or react to multiple nsLTPs from allergenic sources that are not taxonomically related and do not follow a defined pattern.[2,7,17,18] Individuals with nsLTP syndrome often experience very severe reactions.[5,19–23]

In Spain and Italy, nsLTP is probably the main cause of peach-induced contact urticaria, which may remain the only clinical sign of LTP sensitization.[5,24] Another frequent clinical expression of nsLTP sensitization is the oral allergy syndrome, that is itching and tingling of the lips, oral mucosa and/or tongue immediately after ingesting the offending food.[8,25] A few studies have shown that isolated gastrointestinal symptoms (vomiting, nausea, abdominal discomfort and/or diarrhoea) may follow the ingestion of LTP-containing foods, especially apples, although in most cases, such symptoms accompany urticaria/angio-oedema.[8,21,25] It should be considered that some patients may have a severe reaction, or no reaction, to the same plant food at different time points.[7,26] Although some studies have demonstrated that those sensitized only to Pru p 3, the nsLTP from peach (*Prunus persica*), may be more likely to experience severe symptoms, paradoxically others have shown that patients sensitized to more than 5 different nsLTPs (from foods or pollens) show a significantly higher propensity to develop severe reactions upon the ingestion of offending foods.[8,25] Whilst the number of sensitizations may be relevant, the level of specific IgE to Pru 3 does not correlate with the severity of reactions.[23] Also, some studies suggest that co-sensitization to PR10 allergens (homologous to the major birch pollen allergen Bet v 1 (*Betula verrucosa*) and profilin allergens may have less severe reactions.[25,27]

BOX 1 Definitions

nsLTP sensitisation—sensitization to one or more nsLTP.

nsLTP allergy—clinically relevant sensitization to one or more nsLTPs.

nsLTP syndrome—multiple plant food allergies attributed to nsLTP sensitization.

3 | FOODS INVOLVED

Historically, peach has been consistently the food most often reported as a trigger food, especially in southern Europe. Sixty-two per cent of Spanish individuals with a confirmed peach allergy had a positive test to Pru p 3.[5] Other foods may also be involved; a similar percentage of Spanish patients in another study reported reactions not only to peach, but also to lettuce and green beans.[7] In northern Spain, peaches are still the dominant food trigger, alongside peanuts and tree nuts.[26] Even when peach is not the initial reported food trigger, it is still often cited by patients as provoking reactions.[17,28] In other parts of Europe, nsLTP sensitization linked to clinical reactions is reported in an increasing number of publications and the food sensitizations are also similar. A study from Belgium found 25% were sensitized to nsLTP in apple, peach, hazelnut and peanut.[10] Austrian subjects with nsLTP sensitization reported not only some similar food triggers to the Spanish studies, but also less common ones such as parsley, raspberry, sauerkraut (cabbage) and juniper berry.[12] A UK

study reported tree nuts, peanuts, apples, stone fruits and tomatoes were the most frequent triggers in nsLTP-sensitized adults, but curry and pizza were also cited.[29] Although vegetables, legumes, cereals and tree nuts, such as walnuts, almonds and hazelnuts, are also important trigger foods, fruits remain the food most likely to provoke reactions.[30] This includes so-called superfoods such as blueberries, goji berries and pomegranate, all of which are reported to have provoked reactions in nsLTP-sensitized individuals.[31–33]

The allergenic potential of individual nsLTP will vary when the food is processed, depending on the stability of individual nsLTP allergens when exposed to heat; also, the food matrix itself can influence the digestion of different allergens.[34–36] The Maillard reaction between proteins and sugars, which occurs during cooking and processing, can alter immunoreactivity towards food proteins and has been shown to protect Mal d 3 (*Malus domestica*) from the denaturing effects of thermal processing.[36–38] Due to the concentration of nsLTP allergens in the peels of fruits, many of those with nsLTP-driven allergy to peaches may tolerate peeled peach.[39,40] However, cooked and/or processed foods, containing the peels and pips of fruits or vegetables, may provoke reactions. The allergenic profile of 40 tomato-allergic patients revealed that the 25% who reacted to cooked tomatoes (*Solanum lycopersicum*) were all sensitized to tomato nsLTP, found to be the only detectable allergen in canned peeled tomatoes, tomato puree and tomato paste.[41] Seeds also contain nsLTP allergens. Martín-Pedraza and colleagues sequenced two nsLTP allergens from tomato seeds, structurally different to the nsLTP from the peel and associated with severe reactions to tomato-allergic patients.[42] Other dried whole food ingredients such as sun-dried tomatoes or raisins/sultanas, or foods where the whole food is fermented, such as red wine, may also be a source of nsLTP in the diet.[43,44]

The nsLTP content of foods can also vary due to varietal differences, vary considerably, with up to a 100-fold difference in the level of Mal d 3 between apple cultivars from Italy and the Netherlands.[45] It is also known that during maturation on the tree, the level of Mal d 3 increases, but decreases during storage, especially under controlled atmosphere conditions.[46] Organic fruits may not be any less allergenic; a study analysing the level of profilin, Bet v 1 homologues and nsLTP allergens in tomatoes from both organic and conventional systems over three consecutive years concluded that organically grown tomatoes are no less allergenic.[47] A list of foods most likely to trigger reactions and foods associated with primary sensitization can be found in Table 1. In addition to ingested nsLTP in foods, inhaled or cutaneous contact with nsLTP allergens may also be important in the aetiology of nsLTP allergy.[4]

4 | COFACTORS

The clinical expression of nsLTP allergy in sensitized individuals following allergen ingestion frequently depends on cofactors,[2,7,48] which may be present in up to one-third of nsLTP food-allergic reactions.[7,9,11] If a cofactor-induced condition is identified, the patient should be able to consume the culprit food in the absence of exercise or other cofactors, and vice versa without symptoms. The World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology (EAACI) guidelines define cofactors as 'patient-related or external circumstances associated with more severe allergic reactions'; they are reported to be relevant in up to 20–30% of anaphylactic episodes.[49-52] The best-documented cofactors are exercise and intake of NSAIDs, although other cofactors may include fasting, alcohol, antacids, temperature, oestrogens, angiotensin-converting enzyme inhibitors, β-blockers, lipid-lowering drugs, stress and tiredness.[51,53–57] The mechanisms of cofactors are not completely understood, but might include increased gastrointestinal permeability, blood flow redistribution, mast cell heterogeneity, increased plasma osmolality leading to basophil histamine release or induction of acidosis and mast cell degranulation.[58,59] It has been demonstrated that NSAIDs can enhance IgE-mediated degranulation of basophils, an effect that can be essential for the occurrence of severe reactions in patients who have a low level of sensitization to certain foods.[60]

In those who have food-dependent exercise-induced anaphylaxis (FDEIA), nsLTPs are the most frequent sensitizer. In an Italian cohort, 78% of patients with FDEIA were sensitized to nsLTP.[16] Although the wheat (*Triticum aestivum*) allergen omega 5 Gliadin (Tri a 19) is the most usual cause of wheat-dependent exercise-induced anaphylaxis (WDEIA), the wheat LTP allergen Tri a 14 has also been shown to elicit WDEIA.[61,62] In a Spanish cohort of nsLTP-allergic patients sensitized to Tri a 14, one-third of the reactions were cofactor-dependent.[7] The spectrum of foods involved in nsLTP food allergy, induced or exacerbated by exercise, is broad, with peach, lettuce, nuts and wheat all being reported trigger foods.[2,7,61] To identify the influence of exercise, the initial evaluation should focus on the type of activity, the intensity of activity, onset of symptoms and food consumption.[63] Another interesting aspect is the frequent association between nsLTP hypersensitivity and adverse reactions to NSAIDs.[7,16,64] Based on the observation by Asero that NSAID hypersensitivity was significantly higher among nsLTP-sensitized patients,[65] Romano hypothesized that a percentage of patients with a clinical history of NSAID hypersensitivity, but negative tests to the culprit drug, could have food allergy induced by NSAID.[66] However, there are no methodologically well-designed studies that address this issue. It has been suggested that selective cyclooxygenase 2 (COX-2) inhibitors may be a safe alternative in patients with NSAID-enhanced nsLTP food allergy.[60] Cannabis (*Cannabis sativa*) may act as a cofactor and a sensitizing allergen, with one in three cannabis-allergic patients reporting cofactor-mediated reactions to plant foods.[67]

5 | DIAGNOSIS

As with any diagnostic workup for food allergy, screening without clinical necessity is absolutely discouraged. A detailed clinical history is therefore critical for selecting the appropriate confirmatory

TABLE 1 Reported reactions to foods where an nsLTP allergen has been determined to be the likely trigger

Trigger food (species)	nsLTP allergen[a,b]	Region	Reference
Fruits			
Apple (*Malus domestica*)	Mal d 3	Belgium, Italy, northern Spain, Austria, the UK	10,12,20,21,26,28
Cherry (*Prunus avium*)	Pru a 3	Italy	11
Peach (*Prunus persica*)	Pru p 3	Italy, Spain, China, Belgium	5-7,10,11,26
Plum (*Prunus domestica*)	Pru d 3	Austria, Italy	1,11,110
Strawberry (*Fragaria ananassa*)	Fra a 3	Italy, Spain	111
Grape (*Vitis vinifera*)	Vit v 1	Italy, Greece	8,43,44,112
Kiwifruit (*Actinidia deliciosa*)	Act d 10	Italy	113,114
Orange (*Citrus sinensis*), Tangerine (*Citrus reticulata*) Lemon (*Citrus limon*)	Cit s 3, Cit r 3	Spain, Belgium	115,116
Banana (*Musa acuminata*)	Mus a 3	Spain (children)	117
Goji Berry (*Lycium barbarum*)	#	Spain	31,118
Blueberry (*Vaccinium myrtillus*)	#	Germany	33
Pomegranate (*Punica granatum*)	#	Spain	32
NUTS, legumes and seeds			
Hazelnut (*Corylus avellana*)	Cor a 8	Italy, northern Spain, Austria, the UK, Belgium	10-12,26,29,81,119
Walnut (*Juglans regia*)	Jug r 3	Italy, northern Spain, Austria, the UK	11,12,26,29,81
Almond (*Prunus dulcis*)	Pru du 3	Italy	120
Peanut (*Arachis hypogea*)	Ara h 9	UK, Spain, Belgium	10,29,121,122
Lentil (*Lens culinaris*)	Len c 3	Spain	71,123
Mustard (*Sinapis alba*)	Sin a 3	Spain	28,124
Flaxseed/Linseed (*Linum usitatissimum*)		Spain	125
Vegetables			
Green been (*Phaseolus vulgaris*)	Pha v 3	Spain	17
Cabbage (*Brassica oleracea*)	Bra o 3	Austria, Spain	7,28
Lettuce (*Lactuca sativa*)	Lac s 1	Spain	17,126,127
Tomato (*Solanum lycopersicum*)	Sola l 3	Italy, the UK	29.41,42,47,128,129
Celery (*Apium graveolens*)	Api g 2	Germany, Switzerland, Austria	130
Fennel (*Foeniculum vulgare*)	#	Italy	131
Eggplant (Aubergine) (*Solanum melongena*)		Poland	132
Asparagus (*Asparagus officinalis*)	#	Spain	133
Parsley (*Petroselinum crispum*)	#	Austria	13
Onion (*Allium cepa*) and Garlic (*Allium sativum*)	#	Spain	134
Cereals			
Maize (*Zea mays*)	Zea m 14	Italy, Spain	135,136
Barley (*Hordeum vulgare*)	Hor v 14 Hor v 7 k-LTP	Spain	137
Wheat (*Triticum aestivum*)	Tri a 14	Italy, Belgium	60,61,138

[a]Allergens are listed in the WHO/IUIS allergen nomenclature database.

[b]Allergens are listed in the Allergome database but not currently approved by WHO/IUIS.

diagnostic tests and for differentiating nsLTP-related allergies from other plant food allergies such as pollen-related food syndrome and WDEIA (Table 2).[68] Many individuals might be sensitized but asymptomatic to nsLTP, and thus, undertaking testing in isolation may result in the unnecessary exclusion of foods. The clinical history must include the following: possible causative food(s), time of onset, extent and reproducibility of symptoms, identification of allergic symptoms with other plant food(s), the quantity of ingested food, details of the food preparation (eg raw vs. cooked, peeled vs. unpeeled) and also relevance of cofactors.[63,67,68,69] In

TABLE 2 Clinical characteristics of LTP-related syndrome as compared to other IgE-mediated allergies involving similar foods

Allergic condition	Clinical features	Typical food(s) involved	Cofactor(s)	Marker
Pollen food syndrome (PFS) also known as pollen food allergy syndrome (PFAS) and oral allergy syndrome (OAS) (involves profilin/ PR10/Bet v 1 homologues)	Usually manifests as immediate-onset localized symptoms restricted to the oropharynx, for example itchy mouth, scratchy throat, or swelling of the lips, mouth, tongue, throat and ears[139]	Typically, reactions occur to raw fruits, vegetables and nuts. Roasted nuts may still provoke reactions. The type of fruits and vegetables involved will vary depending on the food habits of the population and the dominant sensitizing pollen. The number of foods involved can be many, but food triggers may include the following[140]: birch—apple, pear, peach, plum, apricot, cherry, kiwi fruit, hazelnut, walnut, almond, carrot, celery, soy, peanut, sunflower seed; profilins—orange, banana, melon, kiwi, carrot, celery, tomato, fennel, aubergine, pepper, squash, peanut, mustard, parsley	Proton pump inhibitors (PPIs)[141] Exercise[142]	Bet v 1/ Bet v 2 (birch, *Betula verrucosa*) Phl p 12 (grass, *Phleum pratense*) Art v 4 (mugwort, *Artemisia vulgaris*) Amba 8 (ragweed, *Ambrosia artemisiifolia*)[143]
LTP sensitization	Clinical symptoms vary and can range from mild localized symptoms, for example oropharyngeal symptoms or contact urticaria to generalized allergic symptoms, including gastrointestinal symptoms, angio-oedema and anaphylaxis, or the whole spectrum of symptoms[7–9]	Reactions occur to both raw cooked and processed plant foods, including fruits, vegetables, legumes, tree nuts and cereals. The foods involved will vary depending on the primary sensitizing allergen and the food norms of the population but may include[8–11,26] Peach, plum, apricot, cherry, apple, melon, raspberry, grape, tomato, lettuce, green beans, cabbage, mustard, hazelnut, peanut, walnut, maize, barley, rice and wheat Non-food triggers: Cannabis(could possibly also be a cofactor)[16,53,61,64,66,67]	NSAID, aspirin, exercise, alcohol	Pru p 3 (peach, *Prunus persica*) Jug r 3 (walnut *Juglans regia*) Pla a 3 (London plane tree *Platanus acerifolia*) Art v 4 (mugwort, *Artemisia vulgaris*)[7-10,27,29,75,76]
Food-dependent exercise-induced anaphylaxis	Clinical symptoms vary between localized symptoms and generalized allergic symptoms including urticaria, angio-oedema and anaphylaxis[144]	Wheat, buckwheat, shellfish, soy, cheese and milk (other foods may also be involved depending on region or country) (NB Hazelnut, tomato, celery and strawberries have also been linked to FDEIA, but early studies might not have considered these reactions could be due to nsLTP allergens in these foods[53,145-147]	Exercise Alcohol NSAID Aspirin Hormonal changes Food Additives[48,144,145]	Omega 5 gliadin (Tri a 19) (wheat, *Triticum aestivum*) or other relevant food allergens[148]

addition to the food and symptom history, information about the presence of allergic rhinitis should be obtained, to understand whether the reactions to plant foods could be caused by cross-reactions between PR10 and profilin allergens in pollen-sensitized individuals.[70,71] If the history is concordant with the likelihood of reactions being due to nsLTP sensitization, tests can be undertaken to confirm this.

The specificity and positive predictive value (PPV) of allergy tests may be low due to poor discrimination between clinically relevant and irrelevant nsLTP sensitizations.[72] Therefore, the food extracts used should be carefully selected depending on the plant foods involved in the allergic reaction. Skin prick tests (SPTs) are a useful first-line test; using the prick-to-prick (PTP) method with fresh whole fruits might add diagnostic value as nsLTPs are more abundant in the peel of plant foods.[19,39,73] However, this method is difficult to standardize as fruits and vegetables may contain varying amounts of nsLTP due to varietal differences and growing, ripening and storage conditions.[45,46] Thus, a positive SPT result only indicates sensitization to a mixture of constituent proteins, without formal proof that it is the nsLTP that has triggered the allergic reaction. The same is true

TABLE 3 Commercially available SPT extracts and sIgE tests to determine LTP sensitization

Commercially available SPT extracts			
Skin prick extracts	**Concentration Pru p 3**	**Company**	**Availability in Europe:**
Peach extract (enriched with Pru p 3)	30 μg/mL	ALK, Denmark	Benelux, Italy, Austria, Portugal, Turkey, Germany, France, the UK, Spain

Commercially available sIgE tests					
		Native		**Recombinant**	
LTP allergen	**Source**	**Single plex**	**Multiplex**	**Single plex**	**Multiplex**
Api g 2 (*Apium graveolens*)	Celery				7
Api g 6 (*Apium graveolens*)	Celery				7
Ara h 9 (*Arachis hypogaea*)	Peanut		5	1,2,3	4,7
Act d 10 (*Actinidia deliciosa*)	Kiwifruit		5,7		
Art v 3 (*Artemisia vulgaris*)	Mugwort	2	4		7
Cor a 8 (*Corylus avellana*)	Hazelnut		5	1,2	4,7
Fra a 3 (*Fragaria ananassa*)	Strawberry			1	
Jug r 3 (*Juglans regia*)	Walnut		4,5	2	4
Mal d 3 (*Malus domestica*)	Apple			1,2	4,6,7
Ole e 7 (*Olea europaea*)	Olive tree		4		
Par j 2 (*Parietaria judaica*)	Wall pellitory		5	2	4,7
Pis s 3 (*Pisum sativum*)	Peas		5		
Pla a 3 (*Platanusacerifolia*)	Plane tree		4		
Pru p 3 (*Prunus persica*)	Peach	6	5	1,2	4,7
Pun g 1 (*Punica granatum*)	Pomegranate		5		
Sola l 6 (*Solanum lycopersicum*)	Tomato		5,7		
Tri a 14 (*Triticum aestivum*)	Wheat			2	4
Vit v 1 (*Vitis vinifera*)	Grape		7		
Zea m 14 (*Zea mays*)	Corn		5		

Note: 1. Allerg-o-liq (Dr. Fooke Laboratorien, Germany), 2. ImmunoCAP (Thermo Fisher Scientific, Sweden), 3. Euroline (Euroimmun, Germany), 4. ImmunoCAP ISAC (Phadia, Thermo Fisher, Sweden), 5. Faber test (Sermolab S.R.L, Italy), 6. Immulite 2000 (Siemens Healthcare, USA) and 7. Allergy Explorer—ALEX (Macro-array DX, Austria).

for standard commercial SPT reagents. However, reagents are now available that contain purified natural and/or recombinant single allergen protein components such as Pru p 3, which can enhance their predictive value and performance.[15,74,75] One such Pru p 3–enriched peach SPT extract (ALK-Abello, Hoersholm, Denmark) has good specificity and sensitivity for diagnosing nsLTP sensitization, due to the lack of PR10/profilin (Pru p 1 and Pru p 4) peach allergens, which would cross-react in Bet v 1 or profilin-sensitized individuals (Table 3).[75] However, a negative test does not exclude nsLTP sensitization since Pru p 3 does not cover the entire nsLTP sensitization profile.[7,72] Also, since this extract contains the peach allergen peamaclein (Pru p 7), a gibberellin-regulated protein, it is unable to discriminate between sensitizations to Pru p 3 and Pru p 7, both of which can provoke systemic reactions after peach ingestion.[77]

Nevertheless, SPT with nsLTP-enriched peach extracts may provide a useful starting point for those who have had clinical symptoms and possible cofactor involvement, but no clear trigger food, or one who is not available for skin prick testing. The next step would be the detection of serum IgE (sIgE) antibodies, but native extract preparations, being mixtures of allergenic and non-allergenic components, are not so effective. However, molecular allergen diagnosis using individual single allergen protein components, also known as component-resolved diagnosis (CRD), has been shown to be more specific compared with sIgE measurement to extracts (Table 3).[49,73,77,78,79] The drawbacks with CRD are similar to those using nsLTP SPT; firstly, most studies have used a recombinant Pru p 3 assay as a biomarker for nsLTP sensitization, which may not identify all patients who might be sensitized to nsLTP from other sources.[10,12,72,80] Palacin and colleagues demonstrated that although Pru p 3 had the highest frequency of recognition in different Spanish regions, only 40% of patients from the region of Ourense recognized this allergen.[81] A study by Morales and colleagues reported that although many foods cross-react with Pru p 3, the use of this allergen may not detect all nsLTP sensitivities.[82] In addition, although CRD enables screening for nsLTP sensitization and to narrow down sensitization profiles, it still fails to discriminate between clinically

relevant sensitization (with symptoms) and irrelevant sensitization (without symptoms).[10,15,83] Therefore, the use of single-component allergens only to foods reported to provoke reactions is the most appropriate diagnostic method, with Pru p 3 used in cases where the trigger allergen is unknown. The basophil activation test (BAT) could also be an option to help to discriminate between clinically relevant and irrelevant food-specific IgE results.[84–87] This test has been shown to be able to predict clinical reactivity to apple in Mal d 3–sensitized patients; however, BAT with Pru p 3 did not show any benefit in predicting the clinical outcome.[86,88] Thus, the BAT may be a useful adjunct to the diagnostic pathway for determining the true cause of reactions in those sensitized to nsLTP, but as it requires specialized laboratory facilities, its use is currently limited.

Oral food challenge (OFC), both open and double-blinded placebo-controlled food challenge (DBPCFC), constitute the reference test to confirm the diagnosis of food allergy and should be performed in a clinical setting.[33,88,89,90] However, the clinical application of DBPCFC for diagnosis of reactions to foods due to nsLTP sensitization encounters some major challenges. These include the lack of threshold doses for plant foods, false-negative challenges due to under-representation or instability of nsLTPs in the tested food, and non-inclusion of cofactors.[91–93] Besides that, and most importantly, a positive OFC demonstrates an individual will experience allergic symptoms on exposure to that food, not the identification of the causative role of nsLTPs. To evaluate the specific role of nsLTPs, challenges would require isolated administration of the suspected purified or recombinant nsLTPs, but even if reliable and/or safe source material (purified or recombinant proteins) were available, regulatory issues would in all probability prevent their use in daily diagnostic practice. Therefore, robust oral food challenges to determine whether reactions to a food are due to nsLTP sensitization are not currently possible. However, given the high degree of cross-reactivity between nsLTP allergens, an oral food challenge might be the only diagnostic test able to provide the patient with a clear picture of which foods may be tolerated, and so avoid unnecessary exclusion of foods. This is especially relevant in the dietary management of the patient, to ensure optimal nutritional intake. However, in keeping with all other types of food-allergic presentations, those with a history of severe or anaphylactic reactions may not be suitable to undergo oral food challenge. A proposed diagnostic algorithm is outlined in Figure 1.

6 | DIETARY MANAGEMENT

Central to the management of any food allergy is the removal of the food trigger(s) and, if required, substitution with other foods to prevent nutritional consequences.[49,94] However, the dietary management of nsLTP allergy can be difficult, not only due to the heterogeneity of patients, but also due to the stability of nsLTP allergens, the variability of nsLTP content of foods and the effect of cofactors. The best recommendation for the management of nsLTP allergy is to provide individualized dietary advice based on reported reactions, the presence of cofactors, foods habitually consumed and taste preferences.[68] The composition of the food is also important, with good evidence that if the skin is removed from peaches, the pulp may be tolerated as the concentration of Pru p 3 in the flesh is low.[40] Although in many cases, the food can be identified and avoided, it is not always possible to identify the culprit food, especially where composite foods or cofactors have been involved in reactions (Figure 1).[7] Given the potential for multiple food triggers, should patients be advised to avoid all foods provoking reactions or just those linked to more severe systemic reactions? One study reported that patients who experience local reactions to foods started

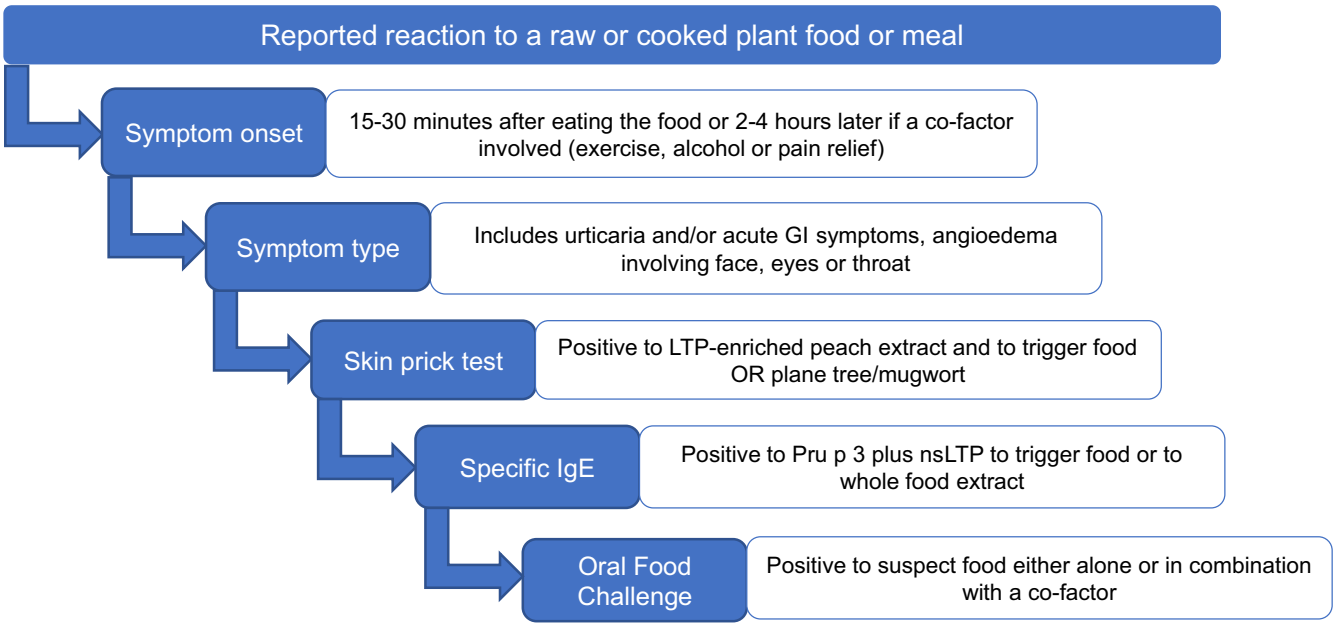


FIGURE 1 Proposed diagnostic pathway for nsLTP allergy

to experience systemic symptoms if they continued to eat the food.[11] Also, sensitization to one nsLTP can result in positive tests to multiple foods, which may in fact be safely consumed. It is probable that foods tolerated will vary; one study reported that carrot, potato, banana and melon may be less likely to provoke reactions.[95]

There are no data on the lowest level of nsLTP allergen that might cause a reaction, but also no reports of those sensitized to nsLTP reacting to trace amounts of the suspect food. Therefore, there is no need for those who react to nsLTP needing to avoid foods with precautionary labels; however, general advice on foods that are more likely to provoke reactions and those that could be relatively safe may be helpful (Table 4). The promotion of certain plant foods as either superfoods or useful energy foods, which fit in with a healthy lifestyle, means that those with nsLTP allergy may be at overt risk of having more severe reactions whilst believing they are consuming foods, which are beneficial for health. Nuts, legumes, dried fruits, fermented fruits or vegetables, fresh juices, smoothies and energy bars all have the potential to contain concentrated amounts of individual or mixed nsLTP allergens.

In addition to dietary modification, management should also include educational and behavioural approaches to allergen avoidance and pharmacological management. This is especially important for those who have experienced reactions to multiple foods, who might be at risk of reacting to new foods, or where cofactors could be playing an important role. Prescription of auto-injectable adrenaline must be considered as per current guidelines, but such patients will also require individualized risk management plans as it might not be possible for them to know when or whether certain foods will trigger an allergic reaction.

7 | IMMUNOTHERAPY

Until recently, the only available intervention for food-allergic individual was avoidance, in conjunction with rescue medication in case of accidental exposure. However, the difficulty in predicting which foods are most likely to provoke reactions and occasional poor adherence to dietary restrictions make avoidance difficult and not always effective. In recent years, sublingual immunotherapy (SLIT) has gained considerable attention for the treatment of respiratory allergies in the form of extract-based drops or tablets. Side effects are reported to be minimal, and efficacy has been demonstrated.[96,97] Sublingual immunotherapy has also been considered to be a safe alternative for treating patients with food allergies, and immunotherapy has become a major treatment in the last few years.[98–103] Given the complexity of management of LTP allergy, it is no surprise that attention has focused on the development of SLIT for the treatment of nsLTP allergy, with Pru p 3 the obvious choice of allergen. A peach peel extract enriched for Pru p 3 was used in a double-blind placebo-controlled SLIT trial to treat peach allergy.[104] After 6 months, actively treated patients tolerated between 3 and 9 times more peach had a 50% reduction in the rate of systemic reactions, a significant decrease in SPT reactivity and a statistically significant increase in the IgG4 responses to Pru p 3. An open study with Pru p 3 SLIT demonstrated an increased tolerance to a significant amount of unpeeled peach in 95% of treated patients compared with the untreated patient group.[105] Most recently, commercial peach juice has also been utilized to desensitize those with a positive skin prick test to peach and a history of anaphylaxis; the authors suggesting this could be used as a short-term management tool.[106]

Most individuals with nsLTP allergy are polysensitized to many LTP allergens.[17] It has been described that nearly 90% of adult patients with peanut (*Arachis hypogaea*) allergy in the Mediterranean area are sensitized to Ara h 9, with Pru p 3 being the primary sensitizer, indicating that Pru p 3 sensitization could be a risk factor for developing peanut allergy.[107,108] The open study mentioned above not only increased tolerance to peach but also reported an increase in the amount of peanut tolerated by nearly 60% of treated individuals after one year of Pru p 3 SLIT.[105,107] Pru p 3 SLIT is safe and well tolerated by patients, with adverse reactions usually only occurring in the build-up phase and consisting mainly of mild oropharyngeal symptoms.

In terms of the mechanisms, oral immunotherapy desensitizes individuals, but usually, there are no cellular changes to the regulatory response, or the development of tolerance. Pru p 3 SLIT shows

TABLE 4 Composite foods that could provoke allergic reactions

Food group	Trigger	Composite foods
Fruits	Apples, raspberries, strawberries, peaches, plums, apricots, cherries, kiwifruit, grapes, figs, oranges, lemons	Jam, dried fruits (raisins, sultanas, apricots, candied peel), sangria (drink), cocktails, fruit tea, wine, cakes, muffins, cookies, snacks, energy bars, breakfast cereals
Nuts	Walnuts, almonds, macadamia nuts, hazelnuts, peanuts, chestnuts	Cookies, cakes, desserts, snacks, breakfast cereals, cheese, chocolates, Chinese or Thai food, curry.
Vegetables	Tomato, cabbage, lettuce, gherkins, spring onion, pepper	Composite salad, pizza, pasta dishes, wraps, kebabs, sandwiches, burgers, sun-dried tomatoes, pickles, sauces
Seeds	Mustard	Sandwiches, burgers
Cereals	Maize, malt (barley), barley, rice	Tortilla chips, malted drinks, beer, malt extract, breakfast biscuits, cornflour, polenta, rice, breakfast cereals or cereal bars containing corn or rice

modulation of allergen-specific effector cells, due to the increase in IL-10–producing allergen-specific T regulatory cells. These cellular changes are orchestrated by the activity of the dendritic cells that changed SLIT, leading to decreased migration and effector activation. This occurred in parallel with a reduction in IgE secreting cells and an increase in IgG4 secreting cells during treatment. Thus, Pru p 3 SLIT has demonstrated a shift towards a regulatory/tolerizing response during the treatment phase.[109] These results show that SLIT with one LTP allergen can increase the tolerance of an nsLTP in different plant foods, which could have major benefits for multiple sensitized and allergic individuals. It is not yet known whether this efficacy is maintained over time after SLIT is stopped or, indeed, whether this treatment with immunotherapy can control cofactors or prevent new sensitizations. Currently, this therapy is only available in Spain, so the results are limited to a very specific population and might not translate to other countries where Pru p 3 may not be the primary sensitizing allergen.

8 | FUTURE RESEARCH NEEDS

Although the importance of cofactors from a clinical point of view is well established, the mechanisms, which make reactions more severe, are still a matter of debate. Studies on the effects of exercise and NSAIDs are particularly challenging, given the variability of nsLTP in foods and threshold of physical activity required for a reaction to occur. Research addressing this issue could combine experimental data on the interaction between nsLTP in foods and the effects of exercise and/or NSAIDs on allergen absorption and availability to the immune system. In addition, epidemiological studies could focus on the identification of other factors affecting the susceptibility of patients to the effects of cofactors and also the natural history of this condition. The other important research focus should be on SLIT with Pru p 3 SLIT; larger and possibly multicentre studies will provide more data on efficacy and safety, therefore making this treatment available in more countries. Evaluating the efficacy of Pru p 3 SLIT in countries where sources of nsLTP are different from peach would be especially helpful, as would the determination of the clinical effectiveness of Pru p 3 SLIT in patients who react to other nsLTPs. Given that clinical symptoms due to sensitization to nsLTP allergens have been demonstrated to exist in northern Europe and further afield, it is also vital that diagnostic and management tools are developed to account for possible differences in the foods involved and the potential relevance of both pollen and food-derived allergenic nsLTPs, which could extend the panel of nsLTPs for CRD in the future. The increasing geographical spread of nsLTP sensitization also highlights the growing impact of this issue and need for prevention strategies, which will be complex due to the variation in the primary sensitizing allergens.

A European registry of nsLTP allergy could collect data on culprit foods, cofactors, risk factors for development and severity and natural history. The registry could exist alone or in collaboration with the European Anaphylaxis Registry, which already may include data on potential nsLTP-driven reactions. However, retrospective data collected using questionnaires might be affected by recall bias, which may be particularly relevant in the case of nsLTP allergy, since culprit foods may vary and sometimes are hard to identify. Quality of life studies would also be very helpful to determine the best way to manage the condition and minimize distress and anxiety. Improvements in the diagnosis of this condition, including the assessment of the diagnostic utility of peach SPT or Pru p 3 in all populations and unified challenge protocols, would help to develop diagnostic accuracy and therefore improve quality of life of this burdensome condition.

ACKNOWLEDGEMENTS

The authors report there are no acknowledgements or funding sources relevant to this publication.

CONFLICT OF INTEREST

Dr. Fernandez-Rivas reports grants from Spanish Government, grants and personal fees from Aimmune Therapeutics, grants and personal fees from Diater, personal fees from DBV, personal fees from Novartis, personal fees from SPRIM, personal fees from GSK, personal fees from HAL Allergy and personal fees from Thermo Fisher Scientific, outside the submitted work. Dr. Barber reports grants from ALK, personal fees from ALK and AIMMUNE and grants from Allero Therapeutics, outside the submitted work. Dr. Hoffmann-Sommergruber reports grants from Government of Lower Austria 'Danube Allergy Research Cluster', and non-financial support from Task Force supported by EAACI, during the conduct of the study. Dr. van Ree reports personal fees from HAL Allergy BV, personal fees from Citeq BV, personal fees from Angany Inc and personal fees from Thermo Fisher Scientific, outside the submitted work. Dr. Skypala, Dr. Bartra, Dr. EBO, Dr. Faber, Dr. GOMEZ, Dr. Till, Dr. Luengo, Dr. Asero, Dr. Cecchi, Dr. Díaz Perales, Dr. Pastorello, Dr. Swoboda, Dr. Konstantinopoulos and Dr. SCALA have nothing to disclose.

AUTHOR CONTRIBUTIONS

I.J. Skypala established the Task Force, set up and chaired the meetings, determined the sections of the manuscript, merged all of the sections from individual contributors, added key points, wrote the abstract, made amendments to the manuscript following both internal and external reviews and submitted the manuscript in its final format. J. Bartra, D. Ebo, M. Faber, M. Fernández-Rivas, F. Gomez, O. Luengo and S.J. Till attended and contributed to the meetings, wrote individual sections of the manuscript, and reviewed it once all the sections had been put together and following internal and external review. R. Asero, D. Barber, L. Cecchi, A. Diaz Perales, K. Hoffmann-Sommergruber, E.A. Pastorello, I. Swoboda, A.P. Konstantinopoulos, R. van Ree and E. Scala attended and contributed to the meetings and reviewed the manuscript following review.

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How to cite this article: Skypala IJ, Bartra J, Ebo DG, et al. The diagnosis and management of allergic reactions in patients sensitized to non-specific lipid transfer proteins. *Allergy.* 2021;00:1–14. https://doi.org/10.1111/all.14797