

## **Clinical management of plant food allergy in patients sensitized to lipid transfer proteins is heterogeneous: identifying the gaps**

**Running title:** LTP sensitization management in Spain

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## Summary

**Background and objective:** Patients sensitized to lipid transfer protein (LTP) present a wide clinical variability. The lack of practical diagnostic and therapeutic guidelines complicate their management. The aim of the study was to describe the clinical approach of Spanish allergists to this pathology using a survey designed by PICO method and subsequent Delphi approach validation.

**Methods:** Designed survey was answered by 224 allergists (75% women; 57.1% with >20 years of professional experience). Homogeneity regarding clinical practice on the main points of LTP allergy diagnosis was observed, except for patients with suspected NSAID hypersensitivity (44.6% frequently include LTP skin testing). Oral food challenges were not frequently performed (63.6% occasionally to never), and they were generally (75.5%) used to confirm tolerance. It was common to recommend fruit skins avoidance (77.2%) and maintaining consumption of foods to which patients are sensitised but tolerant (99.1%).

**Results:** There was heterogeneity on other dietary indications, modifications due to co-factors, or traces avoidance. Peach sublingual immunotherapy (SLIT) was considered very/quite effective by 55.9% of allergists. The majority (79.5%) consider SLIT indicated in <25% of LTP allergic patients, based on severity (95.2%), frequency of reactions (99.4%), allergy to multiple food families (97.4%), and the quality of life/nutrition impairment (91.5%). There was different practice on SLIT prescription based on co-factor involvement.

**Conclusion:** These data suggest that there is a need to increase evidence to reduce the clinical practice heterogeneity in the management of LTP allergy.

**Key words:** Avoidance-diet. Diagnosis. Food allergy. Lipid transfer protein. Management. Peach allergy. Sublingual immunotherapy. Treatment.

## Resumen

**Antecedentes y objetivos:** Los pacientes sensibilizados a la proteína de transferencia de lípidos (LTP) presentan una amplia variabilidad clínica. La falta de guías clínicas prácticas diagnósticas y terapéuticas complica su manejo. El objetivo de este estudio fue describir el abordaje clínico de esta patología por parte de los alergólogos españoles mediante una encuesta diseñada por el método PICO y posterior validación por método Delphi.

**Métodos:** La encuesta diseñada fue respondida por 224 alergólogos (75% mujeres; 57,1% con >20 años de experiencia profesional). Se observó homogeneidad en la práctica clínica en los principales puntos del diagnóstico de alergia a la LTP, excepto en los pacientes con sospecha de hipersensibilidad no inmunológica a AINE (el 44,6% evalúa frecuentemente la sensibilización a LTP en prueba cutánea). Las provocaciones orales a alimentos no se realizaron habitualmente (63,6% de vez en cuando a nunca) y generalmente (75,5%) se utilizaron para confirmar la tolerancia a alimentos. Fue práctica común recomendar la evitación de las pieles de frutas (77,2%) y mantener el consumo de alimentos a los que los pacientes están sensibilizados pero toleran (99,1%).

**Resultados:** Hubo heterogeneidad en otras indicaciones dietéticas, modificaciones debidas a cofactores o evitación de trazas. La inmunoterapia sublingual con melocotón (SLIT) fue considerada muy/bastante eficaz por el 55,9% de los alergólogos. La mayoría (79,5%) considera que la SLIT está indicada en <25% de los pacientes alérgicos a la LTP, según la gravedad (95,2%), la frecuencia de las reacciones (99,4%), la alergia a múltiples familias de alimentos (97,4%), la afectación de la calidad de vida y deterioro nutricional (91,5%). La indicación en la prescripción de SLIT basada en la participación de cofactores fue heterogénea.

**Conclusiones:** Estos datos sugieren la necesidad de aumentar la evidencia en esta patología para reducir la heterogeneidad de la práctica clínica en el manejo de la alergia a la LTP.

**Palabras clave:** Dieta de evitación. Diagnóstico. Alergia alimentaria. LTP. Manejo. Alergia a melocotón. Inmunoterapia sublingual. Tratamiento.

## Summary box

### What do we know about this topic?

Lipid transfer protein (LTP) sensitization can be expressed using different phenotypes. Practical guidelines are missing, evidence scarce and so heterogeneous clinical management of LTP sensitized patients is observed.

### How does this study impact our current understanding and/or clinical management of this topic?

This study described clinical approach of Spanish allergists to LTP sensitization based on a survey and analysing agreements/disagreements. Areas for clinical improvement are identified, knowledge gaps are pointed and recommendations are given based on clinical practice and available evidence.

## Introduction

Lipid transfer proteins (LTPs) are widely distributed panallergens among the plant kingdom. They represent one of the leading causes of food allergy in adults in Southern Europe [1,2], particularly in Spain, although they have also been described as allergens in China [3] and in Northern Europe [4-6]. LTPs are found in a wide variety of foods, with higher concentrations in fruit and vegetable skins [7,8]. Peach LTP, Pru p 3, is the most allergenic LTP in the Mediterranean basin [1,9] and a common primary sensitizing agent [10,11].

Different patterns of sensitization to LTP have been reported regarding: i) clinical presentation, from subclinical sensitization to variable severity reactions; ii) cross-reactivity between foods, as only one food can cause symptoms in a patient, or even a single fraction of the food (e.g. the skin, with tolerance to the pulp), or a multitude of foods can trigger symptoms, resulting in the so-called LTP syndrome [12]; iii) the role of cofactors, whose presence can, in LTP sensitized patients, trigger a reaction in a previously tolerated food (on/off effect) [13] or increase the severity of a pre-existing reaction (for example, a food causing oral allergy syndrome in a resting patient can cause anaphylaxis in the presence of a cofactor) [1,14], and finally; iv) disease progression has been described in around one third of LTP sensitized patients, developing symptoms with previously tolerated foods in long-term follow-up [15,16]. (Figure 1). Recently, the EAACI Task Force published a review on the diagnosis and treatment of food allergy in patients sensitized to LTP [17], which highlights the variability in sensitization

profiles and clinical presentation and the lack of robust evidence in many aspects of this pathology.

The complexity and clinical variability of LTPs sensitized patients, the lack of evidence supporting practical management guidelines as well as usual medical practice variability depending on available resources [18], can lead to heterogeneity in the decision-making amongst allergists. This study aims to describe LTPs sensitized patients clinical practice, regarding both diagnosis and treatment in Spain, a country with high prevalence of sensitization to this proteins [19], and to analyse the degree of agreement in the practices carried out.

## **Methodology**

### *Study design*

This is an observational, exploratory and descriptive study aimed to collect information through an online survey on the usual clinical practice of allergists for LTP sensitized patients. The survey was designed in PICO format [20,21] and each question was validated through a Delphi approach (detail of survey design are available on Supplementary Material). The survey resulted in 51 questions considered relevant by agreement (Table S2) (question selection flow diagram depicted in Figure 2). In a second phase, the survey was distributed to allergists with clinical practice and members of SEAIC. After analysing the results and identifying possible inconsistencies, only one question (question 22 of Table S2) was discarded.

### *Statistical analysis*

Qualitative variables are presented as frequencies (percentages).  $\chi^2$  test (or the Fisher exact test, when needed) was used to compare proportions. Homogeneity was considered when answers achieved above or equal 80% of agreement, using the answer alone or taking together frequent and very frequent or never and rarely. Statistical analysis was performed using Stata/IC 12.0 software. A P-value of less than 0.05 was considered significant.

## **Results**

### *Characteristics of the surveyed allergists.*

Out of the 1056 specialist members of the SEAIC at the time of the survey (November 2021-January 2022), 224 allergists with clinical activity (21.2%) answered it. Seventy-five percent of respondents were women, with wide experience (57.1% over 20 years of experience) and working in a public hospital (92.9%). Most respondents attended both pediatric and adult patients (66.1%) and more than 25 patients sensitized to LTP per month (51%). The majority of surveyed allergist were not part of the SEAIC Food Allergy committee (87.5%).

Table 1 summarizes these data.

### *General survey results*

The proposed survey has shown a high disparity among the surveyed allergists in the management of patients sensitized to LTP, since only one-third of the answered questions (33.3%) showed homogeneity. Table 2 summarizes questions showing agreement.

### *Diagnosis management*

Nearly all specialists conducted a detailed clinical history, systematically questioning about cofactors involvement in reactions (98.7%) and specifically asking about tolerance to other foods related to the LTP syndrome that are not spontaneously reported (99.6%), following the recommendations of guidelines and experts [17,22]. However, they did not use any questionnaire to collect data on tolerance and habitual intake of a list of foods (91.5%), although they considered it would be useful (94.6%).

For food allergy screening, purified LTP or LTP-quantified extract was systematically employed for skin prick testing (SPT) by 96% of the surveyed specialists. Additionally, 48.7% of the respondents reported routinely conducting SPTs on predetermined food panels.

There was great variability in enriched peach extract or purified LTP SPT use in patients with suspected respiratory allergy (57.4%) and in patients with suspected NSAID hypersensitivity (44.6%). Skin testing to LTP in patients with suspected NSAID hypersensitivity was more frequent by the surveyed allergists belonging to the LTP subgroup of the SEAIC food allergy committee ( $P=0.007$ ) and by those who attended a higher proportion of patients sensitized to LTP ( $p=0.024$ ) than by the rest of the respondents. More than a half of the respondents (57.6%) did not modify the management of their patients depending on co-sensitization to profilin and/or PR-10, although data on literature suggest a possible decrease in the risk of reactions in patients sensitized to LTP and profilin or PR-10 [23,25].

Only 36.4% of respondents frequently performed oral food challenges (OFC) in patients with suspected LTP allergy. OFCs were predominantly performed (75.5%) to assess food tolerance as an exclusion diagnosis. Only 42% of respondents sought out to expand the diet by challenging with foods showing sensitization with unknown tolerance, and 50% frequently performed OFCs to foods implicated in the reaction with negative diagnostic tests. More than half of respondents (56.7%) did not recommend free consumption at home of those foods with negative SPTs not consumed recently. The frequency of OFCs was limited by the lack of confidence in real-life reproducibility in only 33.9% of respondents, while 66.1% of the surveyed allergists considered that OFCs limitation was due to the lack of resources, especially among respondents who worked in public settings centres ( $p=0.004$ ). Controlled exposure tests with cofactors were infrequently performed (16.5%).

#### *Reactions treatment management*

There was an absolute homogeneity on adrenaline autoinjector inclusion in the emergency kit of patients with LTP allergy and severe symptoms (100%). Prescribing adrenaline was close to homogeneity in LTP allergic patients with moderate symptoms (77.2%). Interestingly, 9.82% of respondents prescribed adrenaline autoinjector in patients with subclinical sensitization, and this indication was more frequent among respondents working in private healthcare settings compared to public ones ( $p=0.002$ ).

### *Dietary recommendations*

There was a great heterogeneity regarding additional dietary recommendations beyond the avoidance of plant-foods implicated in reactions with demonstrated sensitization. Thus, 64.7% of surveyed allergists also recommended avoiding foods showing sensitization with unknown tolerance. However, a fixed list of foods was not usually indicated to be avoided (97.3%), nor plant-foods showing sensitization with known tolerance (99.1%). Regular consumption of these tolerated foods that showed sensitization was frequently or very frequently recommended by 76.8% of the respondents, avoiding cofactors. Most of the respondents recommend avoiding fruit peel (77.2%), consistent with the higher concentration of LTP in this part of the fruit [8,26]. Recommendations regarding the avoidance of traces were highly heterogeneous, recommending avoidance 31.7% of surveyed specialists frequently or very frequently and never or rarely the 42.9% of surveyed allergists.

It seems that the surveyed allergists were aware of the importance of cofactors in food allergy due to LTP sensitization, since most of them informed the patient about cofactors, only verbally (23.7%) or verbally and by written indications (74.1%). Half of the allergists (50.9%) made different recommendations for avoiding certain foods or parts of them depending on cofactor involvement in the index reaction.

### *Immunomodulatory treatment use*

Peach peel extract enriched with Pru p 3 (ALK-Abelló, Madrid, Spain) sublingual immunotherapy (SLIT-peach) was perceived as very or quite effective only by 55.8% of respondents, although 73.7% of specialists reported experience using it. For three quarters of respondents (75%) this treatment would be indicated in 1 to 25% of LTP-mediated plant food allergic patients. Prescribing criteria were symptoms severity, frequency of reactions, allergy to multiple food-plant families, and quality of life/nutritional impairment, according to more than 90% of the prescribers. Cofactors involvement was important or very important for SLIT-peach prescription for 60% of allergists prescribing it.

The main barrier for SLIT-peach prescription was patient refusal for most of the interviewed (74.5%). In fact, treatment was frequently or very frequently rejected by patients according to 26.6% of the 165 prescribers. Other rejection causes were its cost (58%) and treatment duration (42%). The lack of knowledge about this immunotherapy management was a significant barrier for its prescription in 39.7% of the surveyed allergists.

Moreover, omalizumab use is residual in patients with LTP allergy according to the observed data (Table S2).

## Discussion

This study was designed to assess the degree of agreement in the management of patients with LTP allergy or sensitization, given the complexity of this condition, the lack of evidence and the absence of specific clinical guidelines in practical management. The Task force on patients sensitized to LTP [17] focused mainly on LTP diagnosis allergy, highlighting the problems related to the clinical management of these patients that require increased evidence. Our survey instead, places focus on the clinical management of the patient (33/51; 64.7% of questions in the survey) rather than on diagnosis (16/51; 31.4%).

LTP allergy diagnosis involves identifying an IgE-mediated reaction and LTP sensitization (skin prick test and/or serum IgE). It has been observed that allergy to a specific vegetable attributed for sure to its LTP is limited to certain foods, and a negative test for Pru p 3, the most frequent LTP and often the primary sensitizing agent [1, 10-11, 27], may not exclude a diagnosis of LTP allergy due to the absence of universal cross-reactivity among them [28]. However, the high sensitivity and specificity of IgE to Pru p 3 or skin prick tests with enriched or purified LTP extracts [6, 29, 30] support their use in suspected LTP allergy, and thus it is widely used by the surveyed allergists. Nevertheless, although sensitization to multiple food-groups without an established cross reactivity clinical pattern, and the possible appearance of reactivity to new foods would lead to a high number of OFC to achieve an accurate diagnosis, the use of OFC appears to be limited, according to two-thirds of the surveyed allergists due to a lack of resources. Additionally, even though the lack of evidence on reactive

thresholds and cofactor involvement could be limiting for OFC, lack of real-life reproducibility only seems to be a limiting factor for a third of respondents.

These data suggest that there is little confidence in the absence of reactivity to plant-based foods with negative skin prick tests (SPT) in patients with suspected LTP allergy, since despite occasional use of OFC, half of the respondents reported performing OFC frequently with foods involved in the reaction without sensitization. In addition, introducing at home these foods with negative diagnostic tests without recent evidence of tolerance, was only indicated by less than half of the respondents. In this sense, the Task Force indicates the usefulness of OFC in sensitized LTP patients with positive tests for specific foods [17]. In fact, the indication of OFC for foods with negative SPT tests does not seem to be required since the main problem with diagnostic tests in LTP allergy is the low positive predictive value [6,30]. It is interesting to note that one in ten respondents prescribes adrenaline to LTP sensitized patients without previous reactions. The combination of OFC with foods with negative diagnostic tests and the prescription of adrenaline in sensitization without previous clinical reactions suggest that the surveyed allergists are concerned about this pathology.

Introduction of new foods into the diet in order to achieve less restrictive diets seems to be difficult since more than half of the surveyed allergists did not routinely perform OFCs with foods showing sensitization with unknown tolerance. However, almost all respondent agreed in not forbidding consumption of foods showing sensitization but tolerated in daily life, and the majority of the surveyed allergists encouraged frequent consumption of these foods avoiding cofactors. In

fact, they usually provide information on cofactors verbally and in a written way in most cases, highlighting their importance. On the contrary, more than half of the surveyed allergists did not consider the inclusion of LTP in the screening for suspected NSAID hypersensitivity in a country with a high prevalence of LTP sensitization [19], as has been previously proposed [15].

The EAACI Task Force stated that dietary restriction should be individualized based on experienced reactions, foods habitually consumed and taste preferences [17]. Cofactors are also required to be considered. Nevertheless, robust evidence whether co-factor susceptibility is predetermined and can be ruled out in certain patients is lacking [31]. In this document is also discussed the possibility of avoiding most likely reactive foods and to encourage the relatively safe ones ingestion [17]. Actually, wide restriction to other foods is frequent in Spain since it is advised to avoid foods with sensitization and unknown tolerance, foods from the same taxonomic family assuming high cross-reactivity between them [32] although tolerance can be variable between foods of the same group [33], and the skin of fruits in general [26]. This approach presumably increases safety in an scenario of sensitizations detected with uncertain clinical relevance, limited OFC and the possible risk of future reactions to new foods, as described in one out of three patients [15,16]. However, two questions arise from these studies since data are missing. First, the origin of these new food allergies due to LTP allergy is unknown and it could come from the transformation of subclinical sensitizations into clinical ones or from new clinically relevant sensitizations and the second one, whether the emerging of new symptomatic foods depends on

consumption habits (frequent vs. sporadic). These additional restrictions, systematically carried out, hypothetically would reduce the risk of new reactions at the expense of a quality of life impairment in LTP allergic patients, may be due to unnecessary restrictions. On the other hand, our data suggest that there is conviction that maintaining frequent consumption of foods with subclinical sensitization is the best way to preserve their tolerance, at least avoiding co-factors, although there are no robust scientific data to support it [16,34,35].

Since 2015, a sublingual immunotherapy with peach skin extract enriched in Pru p 3 (ALK-Abelló, Madrid, Spain) has been marketed only in Spain, with reported increase in reaction threshold for peach with peel and other symptomatic foods, reduction in severity of reactions and immunological changes, with good tolerance [36-40]. However, although the evidence is insufficient mainly due to the low number of patients included in its pivotal trial [41], both the latest European guideline on immunotherapy [42] and the European Task Force on LTP allergy [17] mentioned the efficacy reported in the literature, endorsing its use in some patients. In our sample, almost 3 out of 4 surveyed allergists have some experience in the use of SLIT-peach in LTP-allergic patients, although the perception of its effectiveness is not very high (55% of respondents consider it very or quite effective). In any case, a very high percentage of respondent restricts SLIT-peach to a minority of LTP-allergic patients (less than 25% of them), those with greater severity and frequency of reactions and/or a greater number of symptomatic foods, aspects in which efficacy has been demonstrated. In fact SLIT-peach treatment in 6 months reduced systemic reaction rate by 50%

and increased the reaction threshold between 3 to 9 times [36] and in one year, increased tolerance to a significant amount of unpeeled peach in 95% of treated patients, compared to the untreated patient group [37,40]. Its prescription homogeneously seeks to improve these aspects of severity and frequency of reactions, as well as the quality of life of patients, as it has been reported [43] and prevent new allergies in evolution, as suggested [40]. Despite the homogeneity on the importance of cofactors in diagnosis, only 60% of respondents consider its frequency important or very important when prescribing peach SLIT probably because the role of this treatment in controlling them has not been studied.

One potential limitation of this study is the low participation in the survey (21.2% of invited allergists), which could affect the representativeness of the sample due to a possible selection bias of respondents, that could show greater interest in LTP sensitization than non-participating allergists. Another limitation of the study is the closed-ended questions used that do not allow for a detailed analysis of the factors that determine decision-making. Furthermore, it is important to consider that the variability observed in the management of patients with LTP sensitization could be due to the variability of the pathology itself beyond heterogeneity in clinical practice. This is an exploratory study that has aimed to address the current situation, from diagnosis to proactive dietary treatment, as a starting point prior to identifying targets of interest for future research (summarize in box 1).

In conclusion, heterogeneity in the management of patients with LTP sensitization has been observed in two-thirds of the questions presented to allergists in a country with a high prevalence of LTP sensitization. Based on

evidence, areas for improvement emerged, such as the inclusion of LTP SPT in adverse reactions to NSAIDs and optimizing the use of limited resources such as OFCs by conducting them with foods with sensitization instead of those with negative diagnostic tests. There are conflicting practices, especially regarding dietary recommendations, likely due to the lack of robust evidences and the concern about this pathology perceived in this survey. With the available evidence, in patients with food allergy and LTP sensitization, it seems reasonable to recommend avoidance of: i) foods involved in reactions showing sensitization; ii) foods with sensitization and unknown tolerance; and iii) those foods with proven tolerance but not guaranteed frequent consumption neither cofactors avoidance. More evidence on LTP sensitization process, clinical presentation and outcomes after SLIT-peach treatment could help in reducing the heterogeneity in the management of LTP allergy.

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### **Meetings**

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## Conflict of interest

The authors have no conflict of interest to declare in relation with this report.

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Accepted Article

## TABLES

Table 1. Demographic data of the survey participants.

		Surveyed allergists N=224
Experience years (4 years training included) N (%)	<5years	6 (2.68%)
	5-9 years	28 (12.5%)
	10-20 years	62 (27.7%)
Sex N (%) female		168 (75%)
Role in SEAIC		
	LTP subgroup in Food Allergy Committee	14 (6.25%)

	Food Allergy Committee, but not the LTP subgroup.	14 (6.25%)
	Not a member of the SEAIC Food Allergy Committee.	196 (87.5%)
Workplace characteristics. Type of centre:		
	Hospital-based	208 (92.9%)
	Outpatient clinic.	16 (7.14%)
Workplace characteristics. Management modality:		
	Public direct (managed by the health services of each Autonomous Community)	174 (77.7%)
	Public - Other modalities (such as public companies, public foundations, and consortia)	12 (5.36%)
	Private (through external contracting with the private sector)	38 (17.0%)
Origin of the attended population:		
	Rural	2 (0.89%)
	Urban	63 (28.1%)
	Rural and urban	159 (71.0%)
Age range of the assisted population:		
	Pediatric population.	9 (4.02%)
	Adult population.	67 (29.9%)

	Pediatric and adult population.	148 (66.1%)
Approximate number of patients with LTP sensitization visited per month:		
	<25 patients/month	110 (49.3%)
	25-50 patients/month	96 (43.0%)
	>50 patients/month	17 (7.62%)
Available resources		
	Purified LTP or quantified LTP extract for SPT.	202 (90.17%)
	Monocomponent specific IgE	211 (94.19%)
	Allergenic protein platform for molecular diagnosis	140 (62.5%)
	Oral food challenge	206 (91.96%)
Experience		
	Oral food challenge performed in patients with suspected LTP allergy	205 (91.51%)
	Pru p 3 sublingual immunotherapy use	165 (73.66%)

Table 2. Widespread clinical practice in patients sensitized to LTP.

<b>Clinical Practice</b>	<b>Homogeneity degree</b>
Patients with LTP allergy are systematically questioned about the involvement of cofactors in the reaction.	98.70%
Patients with sensitization/allergy to LTP are directly asked about their tolerance to foods frequently involved in LTP syndrome.	99.60%
In patients with LTP sensitization/allergy, the use of a questionnaire to assess tolerance to different foods is considered useful, but it is not commonly used.	86.20%
Skin prick test (SPT) with purified LTP or LTP quantified extract is routinely performed in the screening of patients with suspected food allergy.	94.60%
Specific IgE to individual LTP allergens is frequently or commonly determined in the diagnosis of patients with suspected LTP sensitization/allergy.	94.79%
An adrenaline autoinjector is prescribed to patients with LTP allergy and anaphylaxis	100%
Patients allergic to a plant-food due to LTP are not advised to avoid those foods showing sensitization and current tolerance.	99.11%

Patients allergic to any food due to LTP allergy are not instructed to avoid a fixed list of foods.	97.32%
Specific immunotherapy prescription in patients with LTP allergy is based on criteria of severity and frequency of reactions, allergy to multiple families, and nutritional and/or quality of life impairment.	91.52%-9.39%
The intention of prescribers of specific immunotherapy to patients with LTP allergy is to expand the diet and reduce the number of reactions	88.49% and 99.39%, respectively
Omalizumab use in patients with LTP allergy is exceptional	81.72%

**Box1. Clues in LTP sensitized patient management.**

<b>Practices to be improved</b>
In areas with high prevalence of LTP sensitization and susceptibility to cofactors, it seems advisable to screen for LTP allergy in reactions to NSAIDs.
There is no evidence in patients with LTP sensitization to distrust the tolerance to foods with negative SPT (prick or prick-prick) and specific IgE.
Oral food challenge in LTP sensitized patients should be preferably performed, when there is not a clear involvement in a previous reaction, for foods that show sensitization compared to those that show negative tests.
<b>Evidence needs</b>
Identification of risks factors for developing new food allergies in patients with LTP sensitization.
Identification of cofactor susceptibility prediction biomarkers

Convenience of indicating frequent consumption in consumption of foods with sensitization
Development and validation of questionnaires on tolerance/reactivity or precautionary avoidance of foods in patients sensitized to LTP
Increasing evidence of the efficacy of peach sublingual immunotherapy in patients with allergy to LTP
Evaluation of the efficacy of sublingual immunotherapy with peach in cofactor-dependent reactions
Role of peach sublingual immunotherapy in the appearance of new clinical reactivity with new foods

## LEGEND FIGURES

Figure 1. LTP sensitization can manifest with lack of reactivity with plant foods or different severity manifestations with different plant foods in the same individual. The fact that in some cases a high threshold or cofactors are required for the reaction could favor this duality of clinical response conditioned to the amount of food and/or presence/absence of cofactors. LTP allergen is present in many plant foods and cross-reactivity has been observed between many of them. The absence of clinically allergic cross-reactivity established patterns with plant foods difficult to predict reactions. Finally, it has been observed that food allergy and sensitization to LTP can evolve in some patients, presenting reaction with new plant foods.

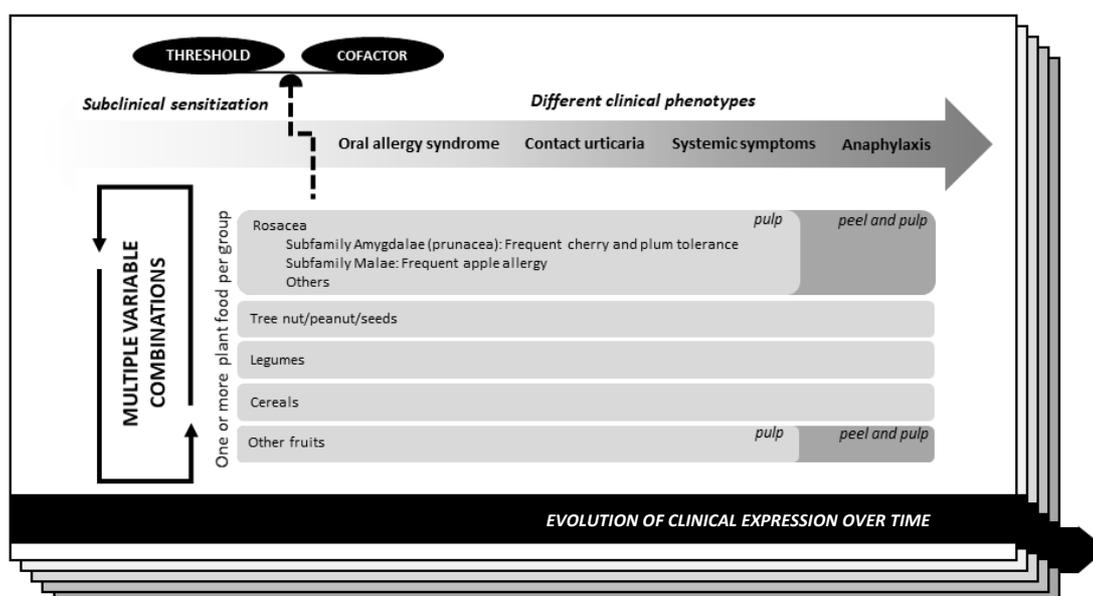


Figure 2. Distribution by topic of proposed and selected questions of the survey.

54 questions regarding LTP sensitization management:			51 questions regarding LTP sensitization management:		
Diagnostic (N=18)			Diagnostic (N=18)		
Clinic history	3		Clinic history	3	
Skin prick test	4		Skin prick test	4	
Serum IgE	2		Serum IgE	2	
Oral food challenge	8		Oral food challenge	8	
Co-sensitizations	1		Co-sensitizations	1	
Treatment (N=36)			Treatment (N=33)		
Reactions treatment	4		Reactions treatment	3	
Diet recommendations	9		Diet recommendations	9	
Cofactors management	1		Cofactors management	1	
Immunotherapy	18		Immunotherapy	16	
Omalizumab	3		Omalizumab	3	
Nutritionist support	1		Nutritionist support	1	

Two Delphi rounds

+

Demographic characteristics and job specifications  
N=9

Resource availability  
N=6