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A Delphi consensus on diagnosis, management, and treatment with allergen immunotherapy of polysensitized children in Spain: CAPP study, Part 2

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Abstract
Background: The study aimed to evaluate the level of agreement between specialists in pediatric allergology regarding the diagnosis and indications for allergen immunotherapy (AIT) for dust mites, molds, animal dander, and Hymenoptera venom allergen, as well as mixtures of several allergen sources in polysensitized children in Spain.
Materials and methods: A Delphi study was performed using an online survey designed by a committee of pediatric AIT experts: 46 and 44 panelists participated in Rounds 1 and 2, respectively. In Round 1, 204 statements on 8 dimensions were evaluated (Diagnosis, Therapeutic management, and Pollens - Part I; Mites, molds, animals, hymenoptera venom, and mixtures - Part II). A total of 148 statements were finally accepted after Round 2. Panel members rated their level of agreement with assessments on a 9-point Likert scale based on acceptance by ≥ 66.7 of them.
Results: Panel experts recommended molecular diagnosis for dust mite allergy diagnosis in polysensitized pediatrics and mixtures of nonhomologous mites (*Dermatophagoides* and *Lepidoglyphus*) for optimal AIT management. Subcutaneous AIT with mold extracts is recommended, but no agreement was reached on mixing different mold types. Panel experts

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agreed that Fel d 1 and Can f 1 sIgE are better predictors for animal dander allergy , but no agreement exists on the acceptance of AIT with dander mixtures. Panelists accepted that Api m 2 (hyaluronidase) sIgE indicates *Vespid* and *Apis mellifera* cross-reactivity in children; and Api m 4 (melittin) sIgE is a marker of risk for systemic reaction with AIT in *Apis mellifera* allergy. According to the consensus, SCIT is more suitable for allergen mixtures than SLIT. and agreement was reached for pollen allergens and *Alternaria alternata* mixtures if stability, safety, and efficacy have been demonstrated.
Conclusions: This Delphi study provides, where evidence is lacking, current expert-based opinions on clinical decision-making for managing polysensitized children.

Introduction

Polysensitization refers to a state where an individual is sensitized to multiple allergens from unrelated sources.[1] This condition is more common than monosensitization in the general populations of Europe and the USA.[2,3] Spain's diverse climate and geography contribute to varying allergen profiles across different regions, complicating the diagnosis and treatment of these patients.[4] In Spain, according to epidemiological data, 23.3% of patients are sensitized to at least two types of allergens and 10.1% to three or more.[5] Polysensitization escalates the likelihood of developing allergic diseases, including allergic asthma, with the severity of the allergic disease being directly linked to the number of sensitizations.[6,7] The identification of allergen IgE binding molecules responsible for allergic manifestations, known ascomponent-resolved diagnosis (CRD) has expanded in clinical practice, enhancing the precision of the diagnostic process and the specific prescription of allergen immunotherapy (AIT).[8,9] AIT, the only treatment currently available that targets the root cause and potentially modifies the disease, is recommended for patients with allergic rhinitis (AR) who exhibit moderate-to-severe symptoms despite regular and/or avoidance strategies and show evidence of IgE sensitization to one or more clinically relevant allergens.[10] In Europe, the typical treatment approach for polysensitized patients involves one or more allergens deemed most clinically relevant.[7,11,12] The CONDOR consensus project in Spain advised that a maximum of three allergen sources could be combined in the same AIT vaccine for polysensitized patients and that AIT treatments should be supported by their own safety and efficacy studies.[4]

Nonetheless, the ongoing need to conduct new consensus efforts specifically for pediatric polysensitized patients and their management with AIT is recognized. This article presents the findings of the second part of the Delphi consensus on the management of polysensitized children (CAPP study), the first part of which is also available in this issue.

Materials and Methods

Study design

The CAPP project was a nationwide Spanish multicenter, two-round Delphi study to seek expert opinion on the clinical management of polysensitized children in Spain to guide the indication for and prescription of AIT. The study was started as an initiative of the Spanish Society of Pediatric Allergy, Asthma, and Clinical Immunology (SEICAP).

The approval of the Institutional Review Board (IRB) or by the equivalent ethics committee(s) was not required as this Delphi study does not involve research with human subjects. No patient data were collected, and this study was based entirely on experts' feedback and opinions.

For a detailed description of the Delphi process, see the "Methods" section in Part I of this issue.

Delphi process

Selection of Delphi participants

The scientific expert committee comprised 10 specialists experienced in managing polysensitized patients and AIT and recognized experts in the field, who are also members of the SEICAP AIT group. For a detailed description of the functions of the scientific expert committee, see the "Methods" section in Part I of this issue.

A total of 46 specialists from 40 hospitals distributed across Spain were invited to participate in the project as Delphi panel experts (panelists) in Rounds 1 and 2 of the Delphi process. The expert panel consisted of allergists and pediatric allergists with at least 10 years of full-time dedication to allergology and extensive experience in prescribing AIT. Participants were selected, with representation from all Spanish regions, from members of the SEICAP and Spanish Society of Allergology and Clinical Immunology (SEAIC), the two most influential allergology societies in Spain. Most panelists worked in the Public Health Service and had participated in clinical trials and studies, with publications and/or communications to conferences related to AIT. This selection process aimed to ensure a diverse group of experts with varied backgrounds and perspectives while maintaining a high level of expertise in managing polysensitized pediatric patients and AIT.

The purpose of the expert panel was to reach a consensus based on the current clinical evidence and their daily practice and knowledge on AIT management for polysensitized children. For a detailed description of the Delphi process, see the "Methods" section in Part I of this issue.

Selection of Delphi questionnaire dimensions and items

The scientific expert committee carried out a systematic literature review regarding the main topics, focusing on current controversial and unresolved topics.

Delphi rounds

The members of the Delphi expert panel were asked during March 2022 (Round 1) and between July and September 2022 (Round 2) to rate their level of agreement with each questionnaire item on a 9-point Likert scale from 1 (completely disagree) to 9 (completely agree). Each item was categorized according to the scores as rejected (scores 1–3), undetermined (scores 4–6), or accepted (scores 7–9). Panelists were also encouraged to provide comments after scoring each item using open-text comment fields included in the online survey.

Item selection was based on the acceptance of questionnaire items by ≥66.7% of the expert panel and the agreement of the scientific committee. Statements not achieving 66.7% agreement were removed or modified according to the feedback provided by the expert panel. After completion of Round 1 and summarization of expert comments, amendments were made to some questionnaire items. The updated questionnaire was redistributed to the panelists for Round 2. After analysis of the responses described for Round 1, the statements that did not meet expert agreement were retained for discussion.

Concluding round

The concluding round comprised a teleconference meeting among the scientific committee experts to assess the nonconsensus items in Round 2 until an agreement was reached to retain or eliminate them from the final consensus guidelines.

Statistical analysis

A descriptive statistical analysis of the characteristics of the Delphi expert and the data obtained from the expert panel assessment of the Delphi questionnaire items in Rounds 1 and 2 was conducted. For a detailed description of the statistical analysis conducted, refer to the "Methods" section in Part I of this issue.

Results

Panel experts

The characteristics of the 46 and 44 Delphi panel experts who participated in Rounds 1 and 2, respectively, are summarized in Table 1 of the article detailing Part 1 of this study (see in the current issue).

Overview of the Delphi study

Global results of the Delphi study are illustrated in Figure 1 of the article detailing Part 1 (see in the current issue). As commented there, due to the scope of the project and the volume of results, the scientific expert committee decided to split the work into two publications. The first part included the results related to diagnosis, therapeutic management, and pollen allergy (dimensions 1–3); while this second part (present article) includes the results related to AIT in pediatric patients polysensitized to mites, molds, animal dander, Hymenoptera venom, and the use of allergen mixtures (dimensions 4–8).

Results from dimensions 4–8

Tables S1–S5 summarize the results from the Delphi process and the level of agreement after the two rounds for the statements related to the management of the polysensitized child with dust mites (Table S1), mold (Table S2), animal dander (Table S3), *Hymenoptera* venom (Table S4) allergies, and the AIT mixing allergens from multiple sources (Table S5).

Dimension 4: Dust mites

Consensus was reached for 14 items (56%; Figure 1). A total of 13 and 1 statements reached agreement in Rounds 1 and 2, respectively. Eleven statements did not achieve consensus in Round 2.

With an agreement of 100%, it was established that house dust mites (HDM) of the genus *Dermatophagoides* (including *D. pteronyssinus* or *D. farinae*) are the most important source of indoor allergens. The need for SPT and determination of total and specific IgE to the whole complete extract and its components in patients with suspected HDM sensitization by clinical history reached 100 and 84.8% agreement, respectively. In addition, 71.7% of panel experts agreed that it is necessary to know the component profile before prescribing AIT in the case of *Dermatophagoides* species sensitization. On the other hand, there was no sufficient agreement to recommend the identification of Der p 1, Der p 2, Der p 23, and/or Der p 10 by molecular diagnosis for the correct diagnosis of mite allergy in a polysensitized pediatric population (statements 8–10). Besides, panelists did not accept that sensitization to a single group (1 or 2) predicts lower severity of disease and worse response to AIT (statement 2, 47.7%; statement 12, 15.9%).

No consensus was reached among the panelists on whether the sublingual or subcutaneous AIT route of administration is superior in the treatment of mite allergy-related rhinitis (statement 13, 43.2%). A total of 73.9% of panel experts considered it advisable to indicate AIT early in case of progressive sensitization to avoid asthma and/or rhinitis or increased severity of symptoms. The mixing of *Lepidoglyphus* and *Dermatophagoides* AIT is recommended if sensitization to both species is shown to be clinically relevant by 91.3% of panelists, as well as the use of mixtures of mites from nonhomologous families, which was acceptable to 89.1% of panel experts.

If after 1 year of AIT treatment with mite extracts, there is no evidence of the efficacy of the therapy, panelists agreed (97.8%) in assessing compliance with treatment. In contrast, no agreement was reached regarding whether to discontinue treatment (54.5%), consider a change of product (61.4%), or increase the dose (45.5%).

Dimension 5: Molds

Consensus was reached for 10 items (83.3%; Figure 2). A total of eight and two statements reached an agreement in Rounds 1 and 2, respectively. Two statements did not achieve consensus in Round 2.

Table 1 Expert-based Delphi consensus recommendations for the management of polysensitized children.

Dimension	Recommendation
Dust mites	1. House dust mites are the most important source of indoor allergens
	2. Identification of Der p 1 and Der p 2 by molecular diagnosis is recommended for the correct diagnosis of mite allergy in a polysensitized pediatric population, but identification of Der p10 and Der p23 is not necessary.
	3. The use of mixtures of *Lepidoglyphus* and *Dermatophagoides* is acceptable.
Mold	4. Pediatric patients sensitized to *Alternaria* have a higher risk of developing severe asthma and asthma exacerbations.
	5. Identification of Alt a 1 by molecular diagnosis is recommended for the correct diagnosis of mold allergy.
	6. In pediatric patients with mold allergy in whom it is decided to prescribe AIT, the administration of the subcutaneous form is advisable.
	7. AIT mixing mold and pollen extracts is acceptable if the stability is demonstrated and with certain specific products.
Animals	8. Children with polysensitization to cats and dogs have a higher risk of developing asthma during adolescence.
	9. Identification of Fel d 1, Can f 1 and Can f 5 by molecular diagnosis is recommended for the correct diagnosis of cat and dog allergy.
	10. The mixing of pollen allergens and animal dander is possible if mixture stability, safety, and efficacy have been demonstrated.
Hymenoptera venom	11. The factors that should be considered for the therapeutic decision on the initiation of AIT in the pediatric population with *Hymenoptera* allergy include systemic reaction, generalized local overreaction reaction but being at high risk of exposure, and distance to a health center/hospital.
	12. Identification of Api m 1, Api m 2, Ves v 1/Pol d 1, and Ves v 5/Pol d 5 by molecular diagnosis is recommended for the correct diagnosis of *Hymenoptera* venom allergy, with Api m 2 determination being a marker of cross-reactivity between *Vespid* and *Apis melifera*, and Api m 4 determination a marker of systemic reactions with *Apis* AIT.
	13. The efficacy of AIT to *Hymenoptera* is highly dependent on the maintenance dose (100 µg).
	14. In polysensitized patients, AIT should not include mixtures of *Hymenoptera* venoms with other allergens.
Mixtures	15. When prescribing mixtures of allergen extracts for AIT, the factors to be considered include: high-quality standardized extracts with proven efficacy and safety; awareness on the possible dilution effect of the concentration of the individual allergen components; ensure that each allergen reaches its therapeutic dose/effective concentration in the final mixture.
	16. SCIT is more suitable than SLIT in the case of mixtures.

An agreement of 97.8% was reached for the statement indicating that *Alternaria* is responsible for the clinical manifestations in the majority of the pediatric patients (statement 1). In addition, 93.5% of panelists agreed that pediatric patients sensitized to *Alternaria* have a higher risk of developing severe asthma (compared to other aeroallergens) and asthma exacerbations (statements 2 and 3). The optimal diagnostic strategy in polysensitized patients with suspected mold allergy is the prick test, total and specific IgE, and molecular diagnosis with Alt a 1 with an agreement of 95.7% (statement 8). However, prick tests and specific IgE as optimal diagnostic strategies did not achieve consensus (statement 5, 52.3%). Finally, the administration of subcutaneous AIT form was advisable in this patient profile, according to the consensus reached (statement 11, 76.1%). In contrast, no agreement was made on the acceptance of mixing different types of molds in the same AIT preparation (statement 12, 18.2%).

Dimension 6: Animal dander

Consensus was reached for nine items (60%) (Figure 3). A total of nine statements reached an agreement in Round 1, while no statements reached consensus in Round 2. Six statements did not achieve consensus in Round 2.

Regarding sensitization to major cat (Fel d 1) and dog (Can f 1) allergens during childhood, panelists agreed with 84.8 and 73.9%, respectively, that increased the risk of development of respiratory allergy symptoms in adolescence. On molecular diagnostics, panel experts agreed that Fel d 1, Can f 1, and Can f 5 sIgE are better predictors than specific IgE determination to cat or dog entire extracts (82.6%) and should be performed in case of suspected cat and dog allergy in polysensitized patients (89.1%). In contrast, no agreement was reached regarding the acceptance of AIT with mixtures of different animal extracts (15.9%).

Dimension 7: Hymenoptera venom

Consensus was reached for 28 items (82.3%; Figure 4). A total of 27 and 1 statements reached agreement in Rounds 1 and 2, respectively. Six statements did not achieve consensus in Round 2.

The main accepted factors that can be highlighted for the therapeutic decision on AIT initiation in the pediatric polysensitized population with *Hymenoptera* allergy, were

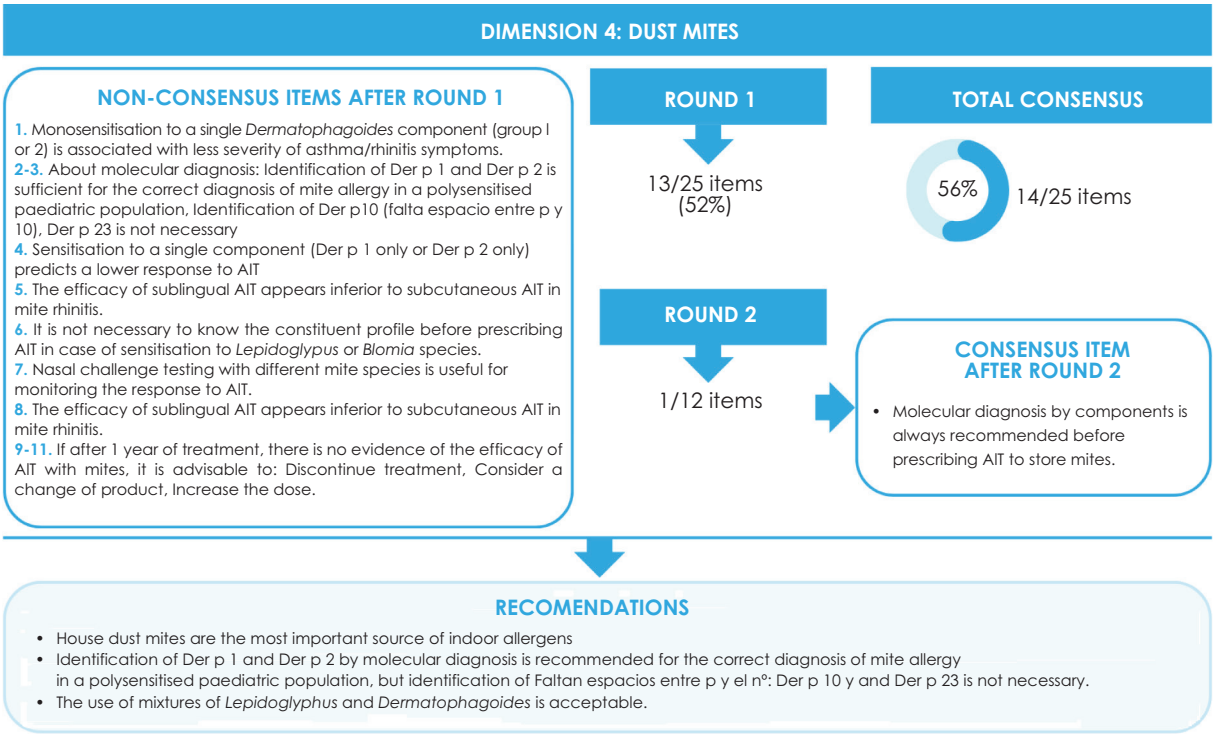

Figure 1 Consensus achievement and key recommendations emerging from the consensus in Dimension 4 (Dust mites). AIT, allergen immunotherapy.

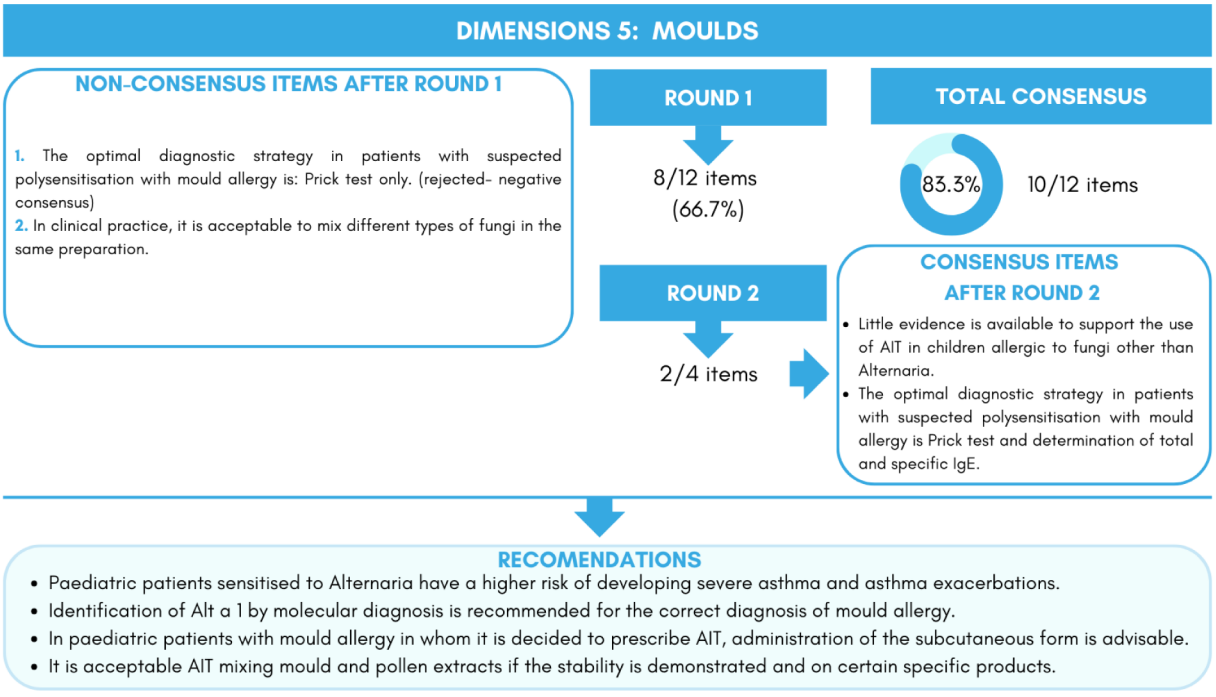

Figure 2 Consensus achievement and key recommendations emerging from the consensus in Dimension 5 (Molds). AIT, allergen immunotherapy; IgE, immunoglobulin E.

have suffered a generalized reaction limited to the skin but at high risk of exposure to *Hymenoptera* (100% of consensus), and other risk factors such as geographical location (95.7% of consensus).

The expert panelists agreed that IgE determination against entire extract complemented by molecular diagnostics improve the correct decision on the AIT to be administered (statement 16, 100% of agreement). In this

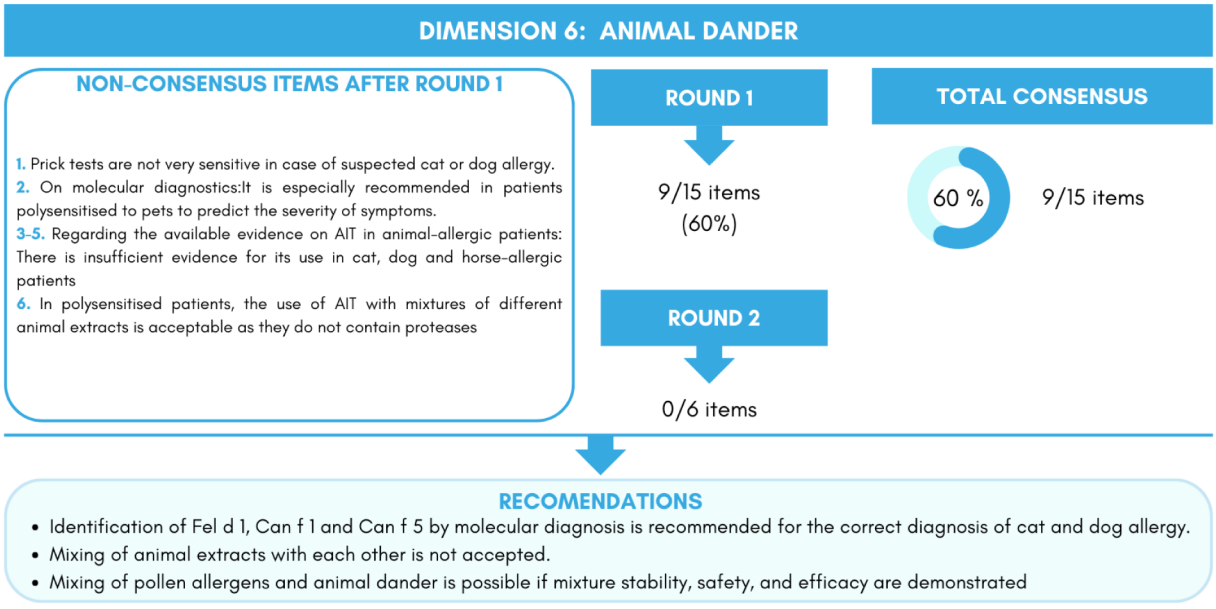

Figure 3 Consensus achievement and key recommendations emerging from the consensus in Dimension 6 (Animals). AIT, allergen immunotherapy.

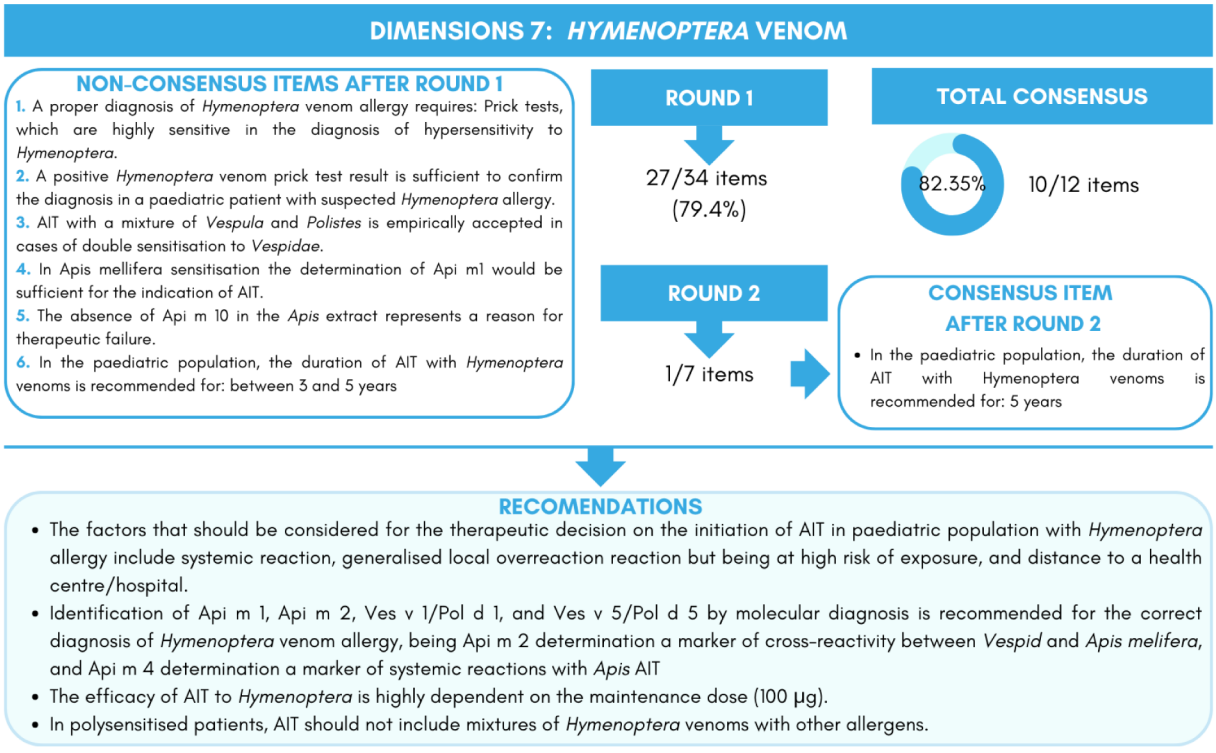

Figure 4 Consensus achievement and key recommendations emerging from the consensus in Dimension 7 (*Hymenoptera* venom). AIT, allergen immunotherapy; µg, micrograms.

way, panelists agreed that Api m 2 sIgE is a marker of cross-reactivity in children with *Vespid* and *Apis mellifera* IgE (88.9% of agreement), and Api m 4 sIgE has been identified as a marker for systemic reaction with AIT in *Apis mellifera* venom allergies (91.1%).

Finally, agreement was reached on the high dependency of the efficacy of *Hymenoptera* AIT on the venom used as a maintenance dose (100 µg) (91.3% of consensus). Panelists also agreed that mixtures of *Apis* and *Vespid* venom extracts are not recommended (86.7% of agreement).

Dimension 8: AIT with mixtures of multiple allergen sources

Consensus was reached for 15 items (65.2%; Figure 5). A total of 15 statements reached an agreement in Round 1, while no statement reached a consensus in Round 2. Eight statements did not achieve consensus in Round 2.

When preparing mixtures of allergen extracts for AIT, agreement was reached regarding several factors (statements 2-7). Panelists also agreed with 80.4% of the consensus that SCIT is more suitable than SLIT in the case of mixtures. In addition, agreement was achieved on the possible dilution effect of the concentration of the individual allergen components, since maybe the final mixture is less concentrated than the individual allergens (statement 5, 84.8%).

In general, no agreement was achieved regarding the recommendation to mix the following allergens (statements 11-15): pollen and mites (25%); pollen and molds (40.9%) (although the mixture of *Alternaria* and pollen in the same SCIT preparation was accepted, statement 19: 67.4%); pollen and animal dander (61.4%); mites and molds (36.4%); and mites and animal danders (54.5%). The use of AIT mixtures of animal dander and other allergen sources (mites, molds or pollens) was not accepted by 80.4% of panelists (statement 23). In contrast, agreement was achieved on the statement indicating that mixing pollen allergens and animal dander is possible if mixture stability, safety and efficacy are demonstrated (statement 16, 71.7% of consensus).

Discussion

Polysensitization is common in Spain and other Mediterranean regions, and it has impacts on allergic disease management.[1,7] The decision-making process is complicated by the lack of scientific evidence.[11] With that in mind, the Delphi approach assists in gathering expert perspectives, reaching consensus, encouraging reflection, and ensuring the dependability of conclusions.[13-15]

Overall, consensus was reached respectively in 14 (56%), 10 (83.3%), 9 (60%), 28 (82.3%), and 15 (65.2%) of the statements for AIT management in pediatric patients allergic to HDM, molds, animal dander, *Hymenoptera* venom allergy management, as well as AIT with mixtures of multiple allergen sources. To simplify the interpretation of the results, a set of recommendations was developed with the most relevant items that reached expert consensus in the Delphi process (Table 1).

Dust mites

Regarding HDM allergy management, no sufficient agreement was reached to recommend the identification of Der p 1, Der p 2, Der p 23, and/or Der p 10 by molecular diagnosis for the correct diagnosis in a polysensitized pediatric population (statements 8-10). tt This conclusion may be attributed, in part, to the continuous discovery of novel molecular markers whose clinical relevance remains uncertain. Furthermore, the limited availability of these newly identified molecules for diagnostic purposes in many healthcare facilities complicates their selection and implementation in routine clinical practice. The data on sensitization to Der p 1, Der p 2, and Der p 23 allergens are clinically significant as early sensitization to these allergens is related to bronchial asthma development.[16,17] There is also evidence that patients with allergic rhinitis respond to a larger number of HDM allergens and are more often sensitized to Der p 23 and Der p 7.[18-20]

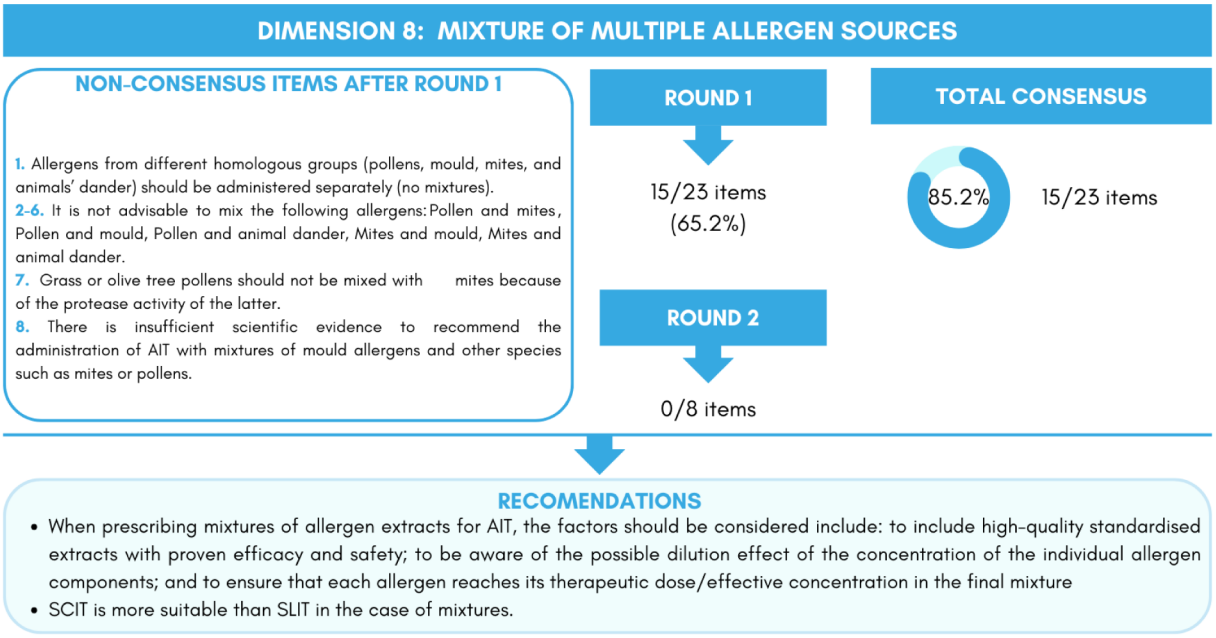

Figure 5 Consensus achievement and key recommendations emerging from the consensus in Dimension 8 (Mixtures). AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

The panel experts agreed that it is necessary to know the component profile before prescribing AIT in the case of *Dermatophagoides* species sensitization. Studies have shown that molecular profiling of sensitization to HDM is an important aspect for predicting AIT efficiency.[21] Current EAACI pediatric guidelines indicate the importance of knowledge on the specific epidemiology of each geographic region and assessment of the patient's sensitization status (monoallergic or polyallergic).[20] Recent research on AIT efficacy in individuals with diverse sensitization profiles suggested that the treatment elicited protective IgG, primarily to Der p 1 and Der p 2, but not to other allergens such as Der p 5, Der p 7, and Der p 21.[22] This suggesting that AIT has a higher therapeutic efficacy in patients who are sensitized to Der p 1 and/or Der p 2 when compared to patients who are sensitized to additional allergens.

Overall, 91.3 and 89.1% of panelists recommended the mixing of *Lepidoglyphus* and *Dermatophagoides* AIT (if sensitization to both species is shown to be clinically relevant) and the use of mixtures of mites from nonhomologous families, respectively. The Delphi consensus study previously conducted in Spain indicated that in circumstances where the sensitization to *Dermatophagoides* and minor mites coexists and clinical relevance for both types of mites is suspected, AIT containing both species could be suitable.[4] When preparing allergen extract mixtures, the prescribing physician must consider the possibility of allergen degradation caused by proteolytic enzymes.[23] In previous studies, mite allergens were found to be resistant to insect and fungal proteases when stored in ≥ 10% glycerin. After mixing grass pollen with mite extracts from various manufacturers at concentrations equivalent to current immunotherapy practices, no detectable loss of allergen reactivity was observed.[24] However, the majority of the studies demonstrating AIT efficacy have used a single allergen, with little data to support multiallergen AIT.[25] An important recommendation, included in the current guidelines, would be to conduct specific studies in pediatrics to confirm the safety and efficacy of AIT products already used in adults.[20]

Molds

A broad agreement (97.8%) was reached indicating that *Alternaria* is responsible for the clinical manifestations in the majority of the cases. *Alternaria* is a common outdoor fungus with a high prevalence in the environment because its spores are present in the air throughout the year.[26] With a consensus of 76.1%, the subcutaneous route is recommended for *Alternaria* AIT. Although *Alternaria* SLIT has shown efficacy in clinical trials, the product is not marketed in Spain.[27,28] A few studies have been conducted on the efficacy and safety of specific immunotherapy with allergen extracts of fungi compared with other allergen extracts.[29] Current pediatric guidelines agree that, based on existing evidence, there is low-quality evidence to support the effectiveness and safety of SCIT for *Alternaria* in the treatment of allergic respiratory symptoms.[20] In the case of *Alternaria* extracts SLIT and *Cladosporium* extracts SCIT, the claim is of very low quality.[20] Subcutaneous administration with Alt a 1 had demonstrated efficacy and safety, with reductions of rhinoconjunctivitis-associated symptoms and medication consumption, after 1 year of treatment.[30] In addition, the post-hoc analysis of the treated patients showed that AIT with Alt a 1 eliminated their Alt a 1 sensitization.[31]

No agreement was reached regarding the acceptance of mixing different types of molds in the same AIT preparation (18.2%). Fungal allergen extracts contain proteases that can degrade other allergens (e.g., mites and pollens) if they are combined in a single vaccine.[32]

Animal dander

In the case of animal dander allergy management and, more specifically, molecular diagnostics, panel experts agreed that Fel d 1 and Can f 1 sIgE are better predictors than specific IgE for cat and dog complete allergens and that Fel d 1 and Can f 1 and Can f 5 sIgE should be performed in case of suspected cat and dog allergy in polysensitized patients. These allergens are highly prevalent in the environment and are responsible for the majority of cases of animal dander allergy. Several studies found that the levels of Fel d 1 and Can f 1 allergens in homes, cars, and schools were associated with the presence of symptoms of animal dander allergy, even in individuals who did not have detectable levels of specific IgE antibodies to these allergens.[33,34] In addition, another major allergen Can f 5 is a prostatic kallikrein found in male dog urine and is highly prevalent in the environment.[35] In a large study of Swedish adults, Can f 5 was the most common dog component to cause sensitization.[36] Another large population-based study found that Can f 5 was the most commonly recognized dog allergen across all age groups of children with cat and dog allergies, even though only about 1 in 10 of these individuals reported symptoms to dogs.[37] However, current literature suggests limited high-quality evidence supporting AIT for cat allergy, no clear clinical evidence of effectiveness for dog allergy, and insufficient evidence regarding the efficacy and safety of AIT for other animal allergens, such as horses.[20,38,39]

Hymenoptera venom

Regarding *Hymenoptera* venom allergy management, panelists agreed that Api m 2 and Api m 4 sIgE are markers of *Vespid* and *Apis mellifera* cross-reactivity in children (88.9%) and systemic reaction with AIT in *Apis mellifera* venom allergies (91.1%), respectively. Several studies have shown that Api m 2 is implicated in cross-reactivity phenomena with *Vespid* venom hyaluronidases, such as Ves v 2a and its isoform Ves v 2b.[40] Other allergens, such as the dipeptidyl peptidases Api m 5 and Ves v 3, are also likely to be cross-reactive based on sequence homology.[41,42] In the case of Api m 4 sIgE, although its value as a marker allergen is limited, recent studies demonstrated a high prevalence of Api m 4 sensitization among *Hymenoptera* venom-allergic patients who experienced systemic reactions during the induction phase of AIT.[43] It is crucial to recognize that many recommendations for managing pediatric patients are extrapolated from adult studies due to the limited number of large-scale studies specifically

involving children. Moreover, effectiveness data are primarily collected during AIT treatment rather than after its completion. Consequently, current guidelines emphasize the need for pediatric-specific clinical evidence on long-term effectiveness and optimal treatment duration.[20]

Panelists also agreed that mixtures of *Apis* and *Vespid* venom extracts are not recommended (86.7%), which is in line with previously published recommendations.[23,24]

Mixtures

To simplify the interpretation of the results related to mixtures, a graphical summary of the results of the Delphi process is shown in Figure 6.

When the use of mixtures of multiple allergen sources in AIT was addressed in detail in the present project, panelists agreed that SCIT is more suitable than SLIT in the case of mixtures (80.4%). In this sense, SLIT with multiple allergen mixtures has demonstrated efficacy, but further studies are needed to confirm its effectiveness.[44]

A high consensus was reached on the concept of the dilution effect of the concentration of the individual allergen components in the final mixture (84.8%). In this sense, multiallergen immunotherapy could face formulation issues, especially in the case of more than two allergen components, with significant quality, efficacy and safety limitations.[12,45] Regarding allergen mixtures, the European Medicines Agency (EMA) recommends mixing only homologous allergens, which are typically taxonomically related.[46] Additionally, EMA advises against including allergens with enzymatic activities, such as house dust mites, in these mixtures. Conversely, the Delphi CONDOR study concluded that results from single allergen treatment studies cannot be directly extrapolated to allergen mixtures.[4] Specifically, the study recommended ensuring the effective concentration of each allergenic source in the final mixture composition.

In general, no agreement was achieved regarding the recommendation of the following allergen mixtures: pollen and mites (25%); pollen and molds (40.9%); pollen and animal danders (61.4%); mites and molds (36.4%); and mites and animal dander (54.5%). This is justified by the fact that it has been demonstrated that the allergenic products with the highest protease activity are insect and fungal extracts.[24] However, the statement regarding the mixture of *Alternaria* and pollen in the same SCIT preparation was accepted (67.4%; Table S5, Statement 19). There is no published evidence on this, so it is an agreement derived from real-life clinical practice. Despite the lack of agreement

SOURCE		POLLENS			DUST MITES		MOULDS		ANIMALS			*HYMENOPTERA* VENOM		
		Grasses	Olive	*Cupressaceae*	*Dermatophagoides*	*Lepidoglyphus*	*Alternaria*	Other	Cat	Dog	Horse	*Apis*	*Vespula*	*Polistes*
POLLENS	Grasses		95.7%	93.5%	37–54.5%		67.4%		61.4%	61.4%	61.4%	0%	0%	0%
	Olive	95.7%		93.5%	37–54.5%		67.4%		61.4%	61.4%	61.4%	0%	0%	0%
	Cupressaceae	93.5%	95.7%		37–54.5%		67.4%		61.4%	61.4%	61.4%	0%	0%	0%
DUST MITES	*Dermatophagoides*	37–54.5%	37–54.5%	37–54.5%		91.3%	36.4%		54%	54%	54%	0%	0%	0%
	Lepidoglyphus				91.3%				13.6%	13.6%	13.6%	0%	0%	0%
MOULDS	*Alternaria*	67.4%	67.4%	67.4%	36.4%			18.2%	13.6%	13.6%	13.6%	0%	0%	0%
	Other						18.2%							
ANIMALS	Cat	61.4%	61.4%	61.4%	54%		13.6%			15.9%	15.9%	0%	0%	0%
	Dog	61.4%	61.4%	61.4%	54%		13.6%		15.9%		15.9%	0%	0%	0%
	Horse	61.4%	61.4%	61.4%	54%		13.6%		15.9%	15.9%		0%	0%	0%
HYMENOPTERA VENOM	*Apis*	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%		0%	0%
	Vespula	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%		50%
	Polistes	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	50%	

Single component
Accepted (Consensus ⩾66%)
Consensus ⩾60% – <66%
Not accepted (Consensus <60%)
Not asked

Figure 6 Graphical summary of the results of the Delphi process related to mixtures. Consensus agreements are displayed in colors as shown in the key.

on the mixture of pollen and animal dander, consensus was achieved on the mixing of pollen allergens and animal dander if mixture stability, safety and efficacy are demonstrated.

Limitations and strengths

The Delphi methodology is a valuable tool for gathering insights and making informed decisions in healthcare practice. One of its limitations is that, although its anonymity can mitigate biases, participants may still exhibit response predisposition. The methodology also implies that high agreement among experts does not necessarily imply that a recommendation is effective. The results of this study serve as the starting point for developing recommendation documents and management guidelines.

Due to the Delphi methodology employed in this study, a variable percentage of statements across dimensions did not reach consensus. This outcome can be attributed to several factors, particularly those related to the unique aspects of clinical experience and practice in Spain. These factors collectively contribute to this variability, highlighting the complex interplay between clinical practice, healthcare system structure, and evolving regulatory landscapes in shaping expert opinions on the management of polysensitized pediatric patients.

Firstly, most participating panelists work within the Spanish Public Health System, a context where both diagnosis and treatment are publicly funded, unlike the European average. This setting influences appointment scheduling for initial consultations and follow-ups (determined by factors such as severity, age, and waiting lists), as well as the diagnostic sequence for polysensitized patients. Secondly, while molecular diagnostics are widely used in Spain, the experience and availability vary considerably depending on the specific allergens involved.[10,47,48] Additionally, Spanish clinical practice predominantly uses SCIT over SLIT, with some exceptions as noted in the study.[49] Apart from that, chemically modified allergen extracts are frequently used in AIT in Spain and Europe.[49] The modification decreases allergenicity, maintaining the extract's immunogenicity. However, the standardization and quality control processes for modified extracts are more complex compared to those for native allergen extracts, due to the chemical modifications involved.[50] Finally, the regulatory process for AIT in Spain is ongoing. This study reflects the current circumstances, and future consensus analyses may be necessary once the regulatory framework is fully established.

In summary, the findings of this Delphi study indicated that, while the general lines of recommendations and suggestions are consistent with established management recommendations, an adaptation to the specific characteristics of Spain polysensitized children is required.

Conclusion

When prescribing mixtures, the following are necessary: 1) to include high quality standardized extracts with proven efficacy and safety; 2) in the case of allergens without proteolytic activity between them, to include only one allergen of a homologous group; and 3) to take into account the dilution effect and the maximum dose of each allergen in the final preparation.

Given the emerging local regulations for AIT treatments and the ongoing improvement in molecular diagnosis of less common allergen sources, it is probable that the landscape will change significantly in the medium term. Consequently, future consensus-building efforts will likely be necessary to address these evolving circumstances.

In the current context, the expert consensus recommendations derived from this Delphi panel study may provide support and guidance on clinical decision-making regarding the management of polysensitized children in real-world clinical practice. Additionally, this consensus analysis may encourage discussion on controversial issues addressed in the consensus statements.

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Authors Contribution

All authors contributed equally to this work.

Conflicts of Interest

A.I.T. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ALK, Diater, Inmunotek, InnoUp, ITAI, Leti Pharma, Probelte and Roxall. C.R.-J. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ALK, Diater, Leti Pharma, Merck and Novartis; and has received payment for expert testimony from ALK. F.J.C.C. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ALK, Allergopharma, Diater, Leti Pharma, and Stallergenes. A.M.-C. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ALK, Diater, Inmunotek, Leti Pharma, and Roxall. M.M. del C. has received payment or honoraria as speaker in educational events from Diater and Leti Pharma. H.L.C., M.M.F., M.T.-G., A.M.-T., and J.M.L.M. declare no conflict of interest.

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Ethics Approval

Not applicable.

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Supplementary

Table S1 Results of the two-step Delphi process for the items regarding therapeutic management of the polysensitised child with dust mite allergy.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
1. **House dust mites of the genus *Dermatophagoides*, such as *D. pteronyssinus* or *D. farinae*, are the most important source of indoor allergens associated with allergic pathology.**	**9 (9-9)**	**100**	**Agreed in round 1**
2. Monosensitisation to a single *Dermatophagoides* component (group 1 or 2) is associated with less severity of asthma/rhinitis symptoms.	6 (2.5-7.5)	47.7	Not agreed in round 2
3. **In areas with high exposure to storage mites, *Lepidoglyphus destructor* may be the initiating mite for sensitisation.**	**8 (7-9)**	**93.5**	**Agreed in round 1**
In patients in whom mite sensitisation is suspected by clinical history, the appropriate diagnostic strategy would be:			
4. **Skin testing with skin prick test as a first step**	**9 (9-9)**	**100**	**Agreed in round 1**
5. **Skin prick test and determination of total and specific IgE to the whole source and its components.**	**9 (7-9)**	**84.8**	**Agreed in round 1**
6. **For the correct interpretation of the skin prick test and specific IgE to complete mite extract, it is important to take into account cross-reactivity with tropomyosins.**	**8 (7-9)**	**84.8**	**Agreed in round 1**
7. **Increased sensitisation to storage mites is relevant in the initial diagnosis of mite allergy and has implications for prescribing AIT.**	**8 (7-9)**	**93.5**	**Agreed in round 1**
8. Identification of Der p 1 and Der p 2 by molecular diagnosis is sufficient for the correct diagnosis of mite allergy in a polysensitised paediatric population.	5.5 (2-7)	36.4	Not agreed in round 2
9. Identification of Der p 23 by molecular diagnosis is not necessary for the diagnosis of mite allergy in the paediatric population.	5 (3-7)	36.4	Not agreed in round 2
10. The identification of Der p 10 by molecular diagnosis is not necessary for the diagnosis of mite allergy in the paediatric population.	7 (3.5-8.5)	56.8	Not agreed in round 2
11. **Molecular diagnosis by components is always recommended before prescribing AIT to store mites.**	**7 (3.5-8.5)**	**68.2**	**Agreed in round 2 after being reformulated**
12. Sensitisation to a single component (Der p 1 only or Der p 2 only) predicts a lower response to AIT.	4 (2-5)	15.9	Not agreed in round 2
13. The efficacy of sublingual AIT appears inferior to subcutaneous AIT in mite rhinitis.	6 (3.5-7)	43.2	Not agreed in round 2
14. **It is advisable to indicate AIT early in case of increased sensitisation to the number of allergen components or different mite species, to avoid asthma and/or rhinitis or increased severity of symptoms.**	**8 (6-9)**	**73.9**	**Agreed in round 1**
15. **It is necessary to know the component profile before prescribing AIT in case of sensitisation to *Dermatophagoides* species.**	**7 (6-9)**	**71.7**	**Agreed in round 1**
16. It is not necessary to know the constituent profile before prescribing AIT in case of sensitisation to *Lepidoglyphus* or *Blomia* species.	6.5 (4-7)	50	Not agreed in round 2
17. **In AIT, the mixing of *Lepidoglyphus* and *Dermatophagoides* is recommended if sensitisation to both species is shown to be clinically relevant.**	**8 (8-9)**	**91.3**	**Agreed in round 1**
18. **The use of mixtures of mites from non-homologous families is acceptable.**	**8 (7-9)**	**89.1**	**Agreed in round 1**
19. **AIT to mites is recommended as an additional treatment to symptomatic asthma control medication.**	**9 (8-9)**	**87**	**Agreed in round 1**

(*continues*)

Table S1 Continued.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
20. Nasal challenge testing with different mite species is useful for monitoring the response to AIT.	7 (5-7)	61.4	Not agreed in round 2
If after 1 year of treatment, there is no evidence of the efficacy of AIT with mites, it is advisable to			
21. Discontinue treatment	7 (4-7.5)	54.5	Not agreed in round 2
22. Consider a change of product	7 (5-8)	61.4	Not agreed in round 2
23. Increase the dose	6 (2.5-7)	45.5	Not agreed in round 2
24. **Assess further sensitisation**	**9 (7-9)**	**89.1**	**Agreed in round 1**
25. **Assess compliance with treatment**	**9 (9-9)**	**97.8**	**Agreed in round 1**

Table S2 Results of the two-step Delphi process for the items regarding therapeutic management of the polysensitised child with mould allergy.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
1. **In paediatric patients sensitised to mould, *Alternaria* is responsible for the clinical manifestations in the majority of cases.**	**9 (8-9)**	**97.8**	**Agreed in round 1**
Paediatric patients sensitised to *Alternaria* have a higher risk of:			
2. **Developing severe asthma than those with sensitisations to other aeroallergens.**	**8.5 (7-9)**	**93.5**	**Agreed in round 1**
3. **Develop asthma exacerbations.**	**8.5 (7-9)**	**93.5**	**Agreed in round 1**
The optimal diagnostic strategy in patients with suspected polysensitisation with mould allergy is:			
4. **Skin prick test only.**	**2 (1-4)**	**67.4 [Rejected (scores 1-3)]**	**Rejected in round 1**
5. Skin prick test and determination of specific IgE.	7 (4.5-7.5)	52.3	Not agreed in round 2
6. **Skin prick test and determination of total and specific IgE.**	**8 (7-9)**	**84.1**	**Agreed in round 2**
7. **Skin prick test and molecular diagnosis including Alt a 1.**	**7 (5-8)**	**69.6**	**Agreed in round 1**
8. **Skin prick test, determination of total and specific IgE and molecular diagnosis with Alt a 1.**	**9 (8-9)**	**95.7**	**Agreed in round 1**
9. **Little evidence is available to support the use of AIT in children allergic to fungi other than *Alternaria*.**	**8 (7-9)**	**84.1**	**Agreed in round 2 after being reformulated**
10. **The production of standardised mould allergens is limited by the variability and stability of the strains used.**	**8 (7-8)**	**89.1**	**Agreed in round 1**
11. **In paediatric patients with mould allergy in whom it is decided to prescribe AIT, administration of the subcutaneous form is advisable, as the marketed sublingual form has not demonstrated efficacy to date.**	**7 (7-9)**	**76.1**	**Agreed in round 1**
12. In clinical practice, it is acceptable to mix different types of fungi in the same preparation.	2 (1-5)	18.2	Not agreed in round 2

Table S3 Results of the two-step Delphi process for the items regarding therapeutic management of the polysensitised child with animal dander allergy.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
1. Skin prick tests are not very sensitive in case of suspected cat or dog allergy.	4 (2-6.5)	25	Not agreed in round 2
2. **Children with polysensitisation to cats and dogs are at increased risk of developing allergic rhinitis during adolescence.**	**7 (5-7)**	**73.9**	**Agreed in round 1**
3. **Polysensitisation to two or more relevant marker allergens of cat, dog, and horse is associated with more severe respiratory symptoms.**	**7 (7-9)**	**84.8**	**Agreed in round 1**
4. **Sensitisation to major cat allergens (Fel d 1) during childhood increases the risk of developing respiratory allergy symptoms in adolescence.**	**7 (7-9)**	**84.8**	**Agreed in round 1**
5. **Sensitisation to major dog allergens (Can f 1) during childhood increases the risk of developing respiratory allergy symptoms in adolescence.**	**7 (6-8)**	**73.9**	**Agreed in round 1**
On molecular diagnostics:			
6. It is especially recommended in patients polysensitised to pets to predict the severity of symptoms.	7 (3.5-8)	59.1	Not agreed in round 2
7. **Sensitisation to Fel d 1 (cat) and Can f 1 (dog) is a better predictor of cat or dog allergy than the determination of specific IgE to whole extracts.**	**8 (7-9)**	**82.6**	**Agreed in round 1**
8. **In polysensitised patients with suspected cat allergy, molecular diagnosis with the determination of Fel d 1 should be performed.**	**8.5 (7-9)**	**87**	**Agreed in round 1**
9. **In case of suspected dog allergy, the molecular diagnosis should include Can f 1 and Can f 5.**	**8 (7-9)**	**89.1**	**Agreed in round 1**
10. **Avoidance of pet exposure in the paediatric population is particularly challenging due to the emotional impact.**	**8 (7-9)**	**91.3**	**Agreed in round 1**
11. **AIT with animal epithelium should be indicated when contact avoidance is not possible or if symptoms persist after avoidance of exposure.**	**8 (7-9)**	**82.6**	**Agreed in round 1**
Regarding the available evidence on AIT in animal-allergic patients:			
12. There is insufficient evidence for its use in cat-allergic patients.	4 (2.5-5.5)	20.5	Not agreed in round 2
13. There is insufficient evidence for its use in patients allergic to dogs.	7 (4.5-7)	52.3	Not agreed in round 2
14. There is insufficient evidence for use in horse-allergic patients.	7 (4-8)	52.3	Not agreed in round 2
15. In polysensitised patients, the use of AIT with mixtures of different animal extracts is acceptable as they do not contain proteases.	3 (2-5)	15.9	Not agreed in round 2

Table S4 Results of the two-step Delphi process for the items regarding therapeutic management of the polysensitised child with *Hymenoptera venom* allergy.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
1. **The main *Hymenoptera* causing allergic reactions in Europe are wasps (*Vespideae*) and bees (*Apoideae*).**	**9 (9-9)**	**100**	**Agreed in round 1**
2. **Vespid species (*Vespula* and *Polistes*) have high cross-reactivity.**	**8 (7-9)**	**89.1**	**Agreed in round 1**
Factors that should be taken into account for the therapeutic decision on the initiation of AIT in paediatric population with *Hymenoptera* allergy include:			
3. **Age**	**7.5 (7-9)**	**82.6**	**Agreed in round 1**
4. **Systemic reaction after *Hymenoptera* sting**	**9 (9-9)**	**100**	**Agreed in round 1**
5. **Having suffered a generalised reaction limited to the skin but being at high risk of exposure to *Hymenoptera* (e.g. children of beekeepers)**	**9 (8-9)**	**100**	**Agreed in round 1**
6. **The severity of the reaction**	**9 (9-9)**	**100**	**Agreed in round 1**
7. **The risk of exposure (e.g. children of beekeepers)**	**9 (8-9)**	**100**	**Agreed in round 1**
8. **Other risk factors such as geographical location (e.g. areas with higher exposure to *Hymenoptera*, distance to a health centre/hospital, etc.)**	**9 (8-9)**	**95.7**	**Agreed in round 1**
9. **Concomitant diseases**	**8.5 (7-9)**	**93.5**	**Agreed in round 1**
A proper diagnosis of *Hymenoptera* venom allergy requires:			
10. **Clinical history as a first step**	**9 (9-9)**	**100**	**Agreed in round 1**
11. **Intradermal testing with suspected venoms.**	**8 (7-9)**	**89.1**	**Agreed in round 1**
12. Skin prick tests, which are highly sensitive in the diagnosis of hypersensitivity to *Hymenoptera*.	7 (3-7)	59.1	Not agreed in round 2
13. **Skin prick tests and assessment of total, specific and component IgE have high sensitivity and specificity for identifying the responsible venom in most patients.**	**9 (8-9)**	**84.8**	**Agreed in round 1**
14. A positive *Hymenoptera* venom skin prick test result is sufficient to confirm the diagnosis in a paediatric patient with suspected *Hymenoptera* allergy.	4 (2-7)	36.4	Not agreed in round 2
15. **In patients sensitised to more than one venom, a distinction should be made between double sensitisation or cross-reactivity between the components of the different venoms.**	**9 (9-9)**	**100**	**Agreed in round 1**
16. **Determination of IgE against complete extract, complemented by molecular diagnostics, may improve patient selection for the indication of AIT in patients with *Hymenoptera* venom allergy.**	**9 (9-9)**	**100**	**Agreed in round 1**
17. **Dual sensitisation to *Vespula* and *Polistes* venom often reflects the inability of available tests to make a diagnosis with certainty.**	**8 (7-9)**	**91.3**	**Agreed in round 1**
18. **The determination of Ves v 1/Pol d1 and Ves v 5/Pol d 5 allows up to 75% identification of the responsible *Vespid* species.**	**8 (7-9)**	**93.5**	**Agreed in round 1**
19. **Today, some AIT products of *Polistes* venom come from American species (*Polistes spp*) with a higher Pol d5 content than the Spanish *Polistes dominula*.**	**7 (7-8)**	**78.3**	**Agreed in round 1**
20. **In children allergic to *Vespa cabro*, AIT with *Vespula* has a protective effect.**	**7 (7-8)**	**78.3**	**Agreed in round 1**
21. AIT with a mixture of *Vespula* and *Polistes* is empirically accepted in cases of double sensitisation to *Vespidae*.	6.5 (2-7)	50	Not agreed in round 2
22. In *Apis mellifera* sensitisation, the determination of Api m1 would be sufficient for the indication of AIT.	5 (3-7)	40.9	Not agreed in round 2
23. **The efficacy of AIT to *Hymenoptera* is highly dependent on the dose of venom used as a maintenance dose (100 µg).**	**8.5 (7-9)**	**91.3**	**Agreed in round 1**

(*continues*)

Table S4 Continued.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
24. **In children with *Vespid* and *Apis mellifera* IgE, the determination of Api m2 as a marker of cross-reactivity between the two is useful.**	**8 (7-9)**	**88.9**	**Agreed in round 1**
25. **In patients allergic to *Apis mellifera* venom, Api m4 has been identified as a marker for systemic reactions with AIT.**	**8 (7-9)**	**91.1**	**Agreed in round 1**
26. The absence of Api m 10 in the *Apis* extract represents a reason for therapeutic failure.	7 (5-8)	61.4	Not agreed in round 2 after being reformulated
27. **Mixtures of *Apis* and *Vespid* venom extracts are not recommended.**	**8 (7-9)**	**86.7**	**Agreed in round 1**
28. **AIT with *Hymenoptera* venom is an effective treatment that provides a good level of protection against re-bites in the paediatric population.**	**9 (8-9)**	**100**	**Agreed in round 1**
29. **Protocols and doses of AIT with *Hymenoptera* venom administered in adults can be extrapolated to the paediatric population, in the absence of own data.**	**7.5 (7-9)**	**89.1**	**Agreed in round 1**
30. **In polysensitised patients, AIT should not include mixtures of *Hymenoptera* venom with other allergens.**	**9 (9-9)**	**100**	**Agreed in round 1**
In the paediatric population, the duration of AIT with *Hymenoptera* venom is recommended for:			
31. between 3 and 5 years	7 (4-8)	52.3	Not agreed in round 2
32. **5 years**	**8 (7-9)**	**86.4**	**Agreed in round 2 after being reformulated**
33. **at least 5 years**	**8 (7-9)**	**76.1**	**Agreed in round 1**
34. **The duration of IT with *Hymenoptera* venom in children depends on the severity of the systemic reaction and the risk of future stings.**	**7 (5-9)**	**67.4**	**Agreed in round 1**

Table S5 Results of the two-step Delphi process for the items regarding therapeutic management of the polysensitised child with AIT for a mixture of multiple allergen sources.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
1. **It would be appropriate to administer two types of AIT in case of polysensitisation to allergic sources which are not recommended to be mixed.**	**8 (7-9)**	**89.1**	**Agreed in round 1**
When preparing mixtures of allergen extracts for AIT, the following factors should be considered:			
2. **Preparations with allergen mixtures for AIT should include high-quality standardised extracts with proven efficacy and safety.**	**9 (9-9)**	**100**	**Agreed in round 1**
3. **Mixing of non-homologous allergen extracts should only be considered in case of allergens without proteolytic activity between them.**	**9 (8-9)**	**87**	**Agreed in round 1**
4. **It is correct to include only one allergen from a homologous group and not a mixture of all (e.g. grasses, mites).**	**8 (7-9)**	**87**	**Agreed in round 1**
5. **The possible dilution effect of the concentration of the individual allergen components, which makes the final mixture less concentrated than the individual allergens.**	**7 (7-9)**	**84.8**	**Agreed in round 1**
6. **It must be ensured that each allergen reaches its therapeutic dose/effective concentration in the mixture to achieve the desired immunological effect.**	**9 (8-9)**	**100**	**Agreed in round 1**
7. **Adjuvants improve the efficacy and tolerance of the product.**	**9 (8-9)**	**97.8**	**Agreed in round 1**
8. **Subcutaneous IT (SCIT) is more suitable than sublingual IT (SLIT) in the case of mixtures.**	**7 (7-9)**	**80.4**	**Agreed in round 1**
9. **Mixing allergens in SLIT is not recommended.**	**7 (6-8)**	**71.7**	**Agreed in round 1**
10. Allergens from different homologous groups (pollen, mould, mites, and animal dander) should be administered separately (no mixtures).	5 (2.5-7)	31.8	Not agreed in round 2
It is not advisable to mix the following allergens:			
11. Pollen and mites	4 (2-6.5)	25	Not agreed in round 2
12. Pollen and mould	6 (2.5-7)	40.9	Not agreed in round 2
13. Pollen and animal dander	7 (5.5-8)	61.4	Not agreed in round 2
14. Mites and mould	5 (3-7.5)	36.4	Not agreed in round 2
15. Mites and animal dander	7 (5-8)	54.5	Not agreed in round 2
16. **The mixing of pollen allergens and animal dander is possible if mixture stability, safety, and efficacy have been demonstrated.**	**7 (5-9)**	**71.7**	**Agreed in round 1**
17. **In polysensitised patients, the use of mixtures of non-homologous allergens is acceptable if clinical evidence is available.**	**8 (7-9)**	**93.5**	**Agreed in round 1**
18. **The 100% polymerised mixtures guarantee the stability of mixtures of pollens and *Alternaria* or mites during the whole shelf life of the extract (until the expiry date).**	**8 (7-9)**	**84.8**	**Agreed in round 1**
19. **In children allergic to *Alternaria* and pollens, a mixture of these allergens in the same SCIT preparation is acceptable.**	**7 (6-8)**	**67.4**	**Agreed in round 1**
20. Grass or olive tree pollens should not be mixed with mites because of the protease activity of the latter.	4 (2-6.5)	25	Not agreed in round 2
21. **Administration of AIT with mixtures of mite allergens (*D. pteronyssinus* and *D. farinae*) and fungi (*Alternaria*) could be an effective alternative in patients with asthma and/or rhinitis who are polysensitised to mites and mould.**	**7 (7-9)**	**76.1**	**Agreed in round 1**
22. There is insufficient scientific evidence to recommend the administration of AIT with mixtures of mould allergens and other species such as mites or pollens.	7 (5-8)	54.5	Not agreed in round 2
23. **The use of immunotherapy with mixtures of animal dander extracts and extracts from other allergen sources (mites, mould or pollen) is not recommended.**	**7.5 (7-9)**	**80.4**	**Agreed in round 1**

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