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A Delphi consensus on diagnosis, management, and treatment with allergen immunotherapy of polysensitized children in Spain: CAPP study, Part 1

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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 pollen allergen immunotherapy (AIT) of 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; Pollens – Part I; Mites; Moulds; 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: According to the results, the polysensitization determination in allergic patients is confirmed by clinical history, skin prick test, total and specific IgE, and molecular diagnostics. Clinical assessments are recommended for the AIT effectiveness evaluation. Follow-ups

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should be performed 6 months after AIT initiation. According to experts, pollens are the most representative allergens in allergic rhinitis but AIT is more effective in bronchial asthma treatment. The IgE levels are positively related to the intensity of the symptomatology and the efficacy of *Grass* AIT. In pollen mixtures, a maximum mixture of three AIT allergens is established between *Grass, Olive*, and *Cupressaceae*. Mixing pollen from *Platanus acerifolia* and *Parietaria* is not recommended.
Conclusions: This study provides, where evidence is lacking, current expert-based opinions on clinical decision-making for managing pollen AIT in polysensitized children.

Introduction

Polysensitization can be defined, in line with different published descriptions, as sensitization, according to standardized skin prick tests (SPTs) or specific immunoglobulin E (sIgE) assays, to two or more allergens from nonrelated sources.[1] Polysensitization is more prevalent than monosensitization as defined in several surveys using standard panels of allergens in the general population of Europe (12.8–25.3%) and the USA.[2,3] These data are transferred from the general population to the specialized practice, where a majority of patients (up to 80%) are polysensitized.[4,5] In Spain, polysensitization is also frequent. According to epidemiological data, 23.3% of patients are sensitized to two types of allergens and 10.1% to three or more.[6] The mean ± standard deviation (SD) number of positive SPT per patient was 6.5 ± 2.[7]

Not all sensitizations induce allergic symptoms, while all polyallergic patients are polysensitized.[1,4,8] Pollen is the most common allergen related to respiratory diseases, followed by house dust mites, animal dander, and moulds.[6] In patients polysensitized to pollens, it is difficult to distinguish whether the symptoms are due to pollen or other allergen sources. Moreover, it is difficult to establish which pollen source is responsible for the respiratory symptoms. The situation is more complicated when the patient is sensitized to pollens with similar pollination periods.[8,9]

The severity of the allergic disease is directly proportional to the number of sensitizations.[10,11] In addition to classical diagnostic methods, molecular diagnosis and component-resolved diagnosis (CRD) have become widespread in clinical practices.[12] This has led to improved accuracy of the diagnostic process and the specific AIT prescription.[12,13] The therapeutic approach to respiratory allergy is based on allergen avoidance when possible, treatment with symptomatic drugs (including antihistamines, inhaled, intranasal and systemic corticosteroids, bronchodilators, and leukotriene receptor antagonists), and allergen immunotherapy (AIT).[11,14,15] AIT represents the only currently available treatment targeting the underlying pathophysiology of respiratory allergy and has shown a disease-modifying effect.[16] AIT is recommended for patients with allergic rhinitis (AR) who have moderate-to-severe symptoms and controlled bronchial asthma despite regular and/or avoidance strategies, and evidence of IgE sensitization to one or more clinically relevant allergens.[16] AIT may also be considered in less severe AR where a patient wishes to take advantage of its long-term effect on rhinitis and the potential to prevent asthma with Grass pollen AIT.[16] However, ways to modulate AIT as a function of the number or nature of the patients' sensitizations are not clearly stated. In Europe, polysensitized patients are typically treated for one or several allergens that are considered clinically relevant.[11,17,18] In the CONDOR Delphi consensus carried out in Spain in recent years, it was concluded that the choice of allergens for AIT in polysensitized patients is an enormously difficult task.[9] The conclusions of this work recommended that no more than three allergenic sources should be mixed in the same AIT vaccine.[9] Furthermore, the results recommended that the AIT prescription should be based on solid scientific evidence and that AIT treatments should have their own safety and efficacy studies.[9]

The debate on whether to prescribe single or multiallergen formulations of AITs and the timing of AIT initiation are currently ongoing. Hence, there is a need to carry out and analyze new consensus works in polysensitized patients and, more specifically, in the case of pediatric patients.

The CAPP project was a nationwide, multicenter, two-round Delphi study to determine the expert opinion on the clinical management of polysensitized children in Spain in order to provide guidance on the AIT indication and prescription.

Materials and Methods

Study design

The study 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 for this study, based on feedback and opinions from experts.

The present study followed a modified two-round Delphi methodology, which is an established approach in consensus-building studies.[19,20] The Delphi process is a widely accepted scientific method of systematic collection of information from a group of experts (termed as Delphi expert panel) on controversial or complex topics.[21] Each panel expert provides opinions individually and anonymously without the biasing effect of dominant individuals or group pressure.[22-24] The Delphi process ends when an agreement has been reached on the discussed topics.

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 board. The scientific expert committee was responsible for reviewing the existing literature on the subject, drawing up the list of dimensions and items to be evaluated, and establishing the criteria to be met by the panelists who participated in rounds 1 and 2 in the development of this Delphi project.

A total of 46 specialists from 40 hospitals across Spain were invited to participate in the project as Delphi panel experts (panelists) in both rounds 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 SEICAP and the Spanish Society of Allergology and Clinical Immunology (SEAIC), the two most influential allergology societies in Spain. Most panelists worked in the Public Health Service. They 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 expert panel members were provided with an informative leaflet outlining the aims and the study procedure, including an electronic link to the online survey. The purpose of the expert panel was to reach a consensus based on the current clinical evidence and their daily practice in and knowledge of the AIT management of polysensitized children.

Selection of Delphi questionnaire dimensions and items

The scientific expert committee carried out a systematic literature review on the main topics, focusing on current controversial and unresolved topics. After a careful and critical review of the selected literature and based on their knowledge of the clinical management of the pathology, the scientific expert committee developed the first set of domains and items for the Delphi questionnaire in a meeting.

Round 1

The members of the Delphi expert panel were asked during March 2022 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.

After analyzing the data from the first Delphi round, the scientific committee experts participated in a meeting where the Delphi survey results were presented and discussed. 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. The updated questionnaire was redistributed to the panelists for round 2.

Round 2

In round 2, the same panel members were asked between July and September 2022 to evaluate the list of items that did not meet the consensus from round 1. For this evaluation, the panel members were provided with a summary of the opinions issued anonymously by the participants in the first round, in addition to any other information that the scientific committee deemed appropriate to make available to the panelists to achieve consensus, without conditioning their decision.

After analysis of the responses described in round 1, the statements that did not meet the 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 data obtained from the assessment of the Delphi questionnaire items in rounds 1 and 2 was conducted. The distribution of frequencies of panel responses on the 9-point scale was calculated to establish the level of consensus for each questionnaire item.

A descriptive statistical analysis of the characteristics of the Delphi expert panel was also performed, including calculation of central tendency and dispersion (mean ± standard deviation, median and interquartile range) for quantitative variables and frequencies and valid percentages for qualitative variables.

The online survey was designed to prevent missing data and inconsistencies. Only complete responses were included in the analysis; partial responses were automatically excluded from the final dataset. This approach ensured data integrity and consistency across all participants' responses.

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Panel experts

All 46 panel experts participated in round 1, whereas 44 completed the round 2 survey. The characteristics of the Delphi experts are summarized in Table 1. Briefly, the median (range) professional experience in pediatric

Table 1 Characteristics of the Delphi expert panel.

Characteristics	(N = 46)
Age, median (range), years	52.5 (44.8–61.5)
Professional experience, median (range), years	
Pediatric allergology	20.5 (14.0–28.5)
General pediatrics	20.0 (13.5–28.5)
Hospital position, n (%)	
Associate physician	23 (50.0)
Head of department	22 (47.8)
Other	1 (2.2)
Speciality, n (%)	
Paediatrics and related areas	23 (49.95)
Allergology	11 (23.9)
Pediatrics and allergology	11 (23.9)
Immunology	1 (2.2)
Educational activity, n (%)	44 (95.7)
Research activity, n (%)	39 (84.8)
Type of institution, n (%)	
Public hospital	39 (84.8)
Private practice	7 (15.2)

allergology was 20.5 (14.0–28.5) years. Most participants were specialists in pediatrics (n = 21; 45.65%), followed by allergology, and double speciality in pediatrics and allergology (n = 11; 23.9%).

Overview of the Delphi study

Figure 1 illustrates the results of the Delphi study. 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 (present article) includes the results related to diagnosis, therapeutic management, and allergy to pollens (dimensions 1 to 3); while the second part includes the results related to allergy to mites, moulds, animals, Hymenoptera venom, and allergen mixtures (dimensions 4–8).

Results from dimensions 1-3

Tables S1-S3 summarize the results from the Delphi process and the level of agreement after the 2 rounds for the statements related to the diagnosis (Table S1), therapeutic management with AIT (Table S2), and pollens (Table S3).

Dimension 1: Diagnosis

Consensus was reached for 24 items (88.9%) (Figure 2). A total of 23 and 1 statements reached an agreement in rounds 1 and 2, respectively. Three statements did not achieve consensus in round 2.

With an agreement of 79.5%, polysensitization is defined as "Sensitisation to two or more allergens of different homologous groups." As for the diagnosis of sensitized children, the agreements vary between 73.9 and 100% in which SPT and total IgE, specific to the whole source and its components, are fundamental. No agreement was achieved (27.3%) on the size of the prick papule and its relationship with the symptomatology. With 91.3-100% agreement, the importance of molecular diagnosis and the distinction between co-sensitisation and cross-reactivity is emphasized.

Dimension 2: Therapeutic management

Consensus was reached for 21 items (63.6%) (Figure 2). A total of 19 and 1 statements reached an agreement in rounds 1 and 2, respectively. Fourteen statements did not achieve consensus in round 2, of which the scientific experts committee decided to accept two statements.

The refusal to set a minimum age for AIT prescription (items 1 and 2) stands out among different agreed items. Regarding the preference for prescribing SCIT mixtures of two or more allergens, rather than SLIT, the agreement achieved 78.3%.

Regarding the evaluation of the effectiveness of the treatment, the agreement was broad among the participants on the use of clinical practice tools (including symptom scales, medication savings, and quality of life), but not on the use of *in vitro* methods (total IgE, sIgE, and sIgG4 for whole allergen sources, and components and/or ratios among them), or the use of nasal provocation test.

Importantly, no agreement was achieved on whether to discontinue, continue for another year, or change the route of administration in the case of no clinical improvement in the first year of treatment with AIT.

Dimension 3: Pollens

The consensus was reached for 27 items (77.1%) (Figure 3). A total of 24 and 1 statements reached agreements in rounds 1 and 2, respectively. Ten statements did not achieve consensus in round 2, of which the scientific experts committee decided to accept two statements.

With 79.5% agreement, the participants considered that pollens are the most representative allergens in AR. In addition, the consideration that allergens such as *Php p 1* are initiator molecules (molecular spreading) achieved an agreement of 84.8%. Likewise, it is accepted that pollen AIT is more effective in the treatment of bronchial asthma than AR. In the case of routes of administration, the experts believed that SCIT does not show more effectiveness than SLIT for the AR treatment.

Among other issues, the question of whether the levels of IgE to the whole allergen source and its components are positively related to the intensity of the symptomatology stands out with an agreement of 65.9%. Similarly, the statement related to the level of Phl p 1/Phl p5 pretreatment and the efficacy of *Gramineae* AIT achieved an agreement of 73.9%.

Regarding pollen mixtures, it was accepted that AIT with mixtures of more than three pollen sources is not as effective as a monocomponent AIT with a single pollen (63.6% agreement, agreed after scientific committee

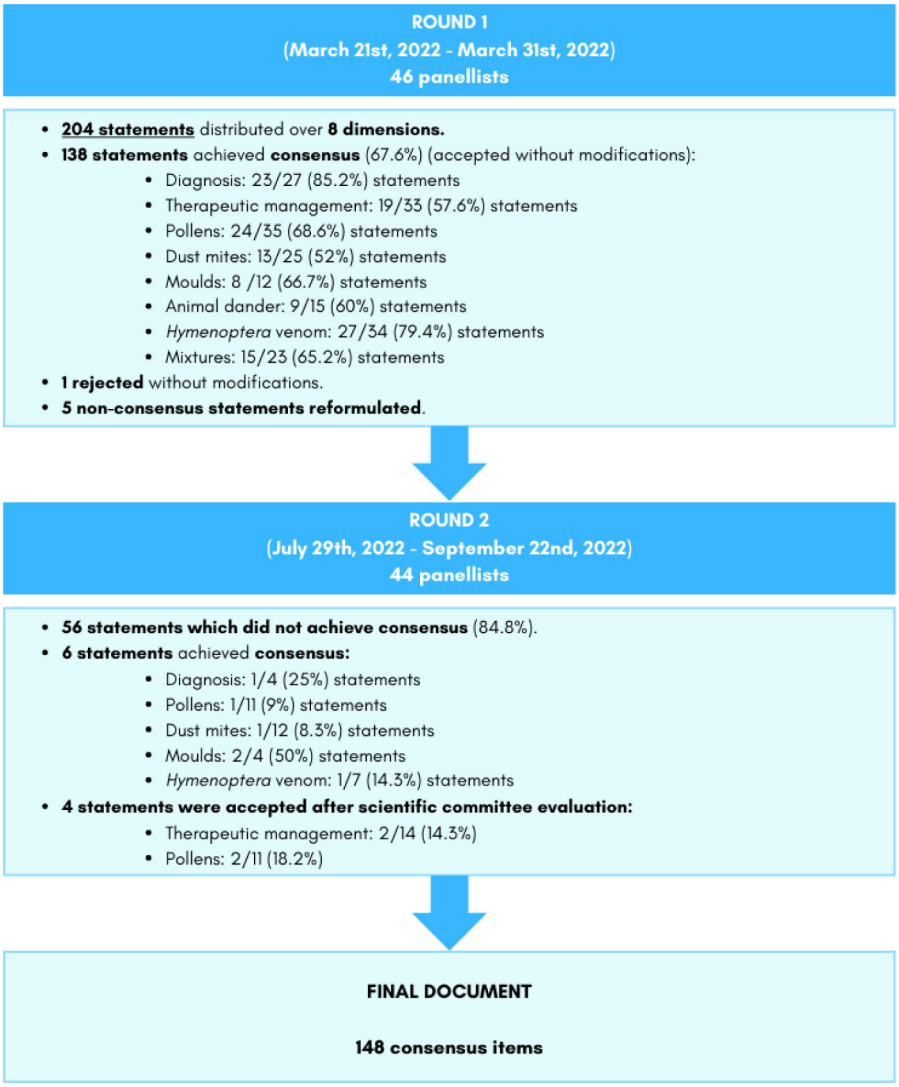

Figure 1 Summary of results of the Delphi study.

evaluation). However, it was agreed that mixtures, including *Gramineae* and *Olea, Gramineae* and *Cupressaceae, Cupressaceae* and *Olive,* are suitable, establishing a maximum mixture of three allergens. On the other hand, an agreement was not achieved about mixing pollen from *Parietaria* with any other allergen.

Discussion

Polysensitization is common in Spain, as in other surrounding countries.[1,4,6,11] This fact is even present in the management of children with allergic conditions. However, there is a lack of scientific evidence concerning the diagnosis and therapeutic management of polysensitized children.[17] All these make decision-making difficult for the specialist. In this context, the Delphi method is important in medical science as it makes it possible to collect experts' opinions, promote reflection and opinion sharing, reach a consensus, and ensure the reliability of the results.[20,25,26]

Overall, in the present study, a total of 148 of 204 statements (72.5%) were agreed upon. However, the consensus reached was different depending on the area of interest evaluated. Regarding the data analyzed in the present article, consensus was reached in 24 (88.9%), 21 (63.6%), and 27 (77.1%) of the statements for the areas of diagnosis, AIT management, and pollen allergy, respectively. 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 2).

Diagnosis

One of the first important aspects when analyzing the results of the group of statements related to diagnosis in polysensitized children is linked to the definition of polysensitization. The two definitions that reach consensus (although <80%) are those that introduce the concept of sensitization to ≥2 allergens without cross-reactivity and

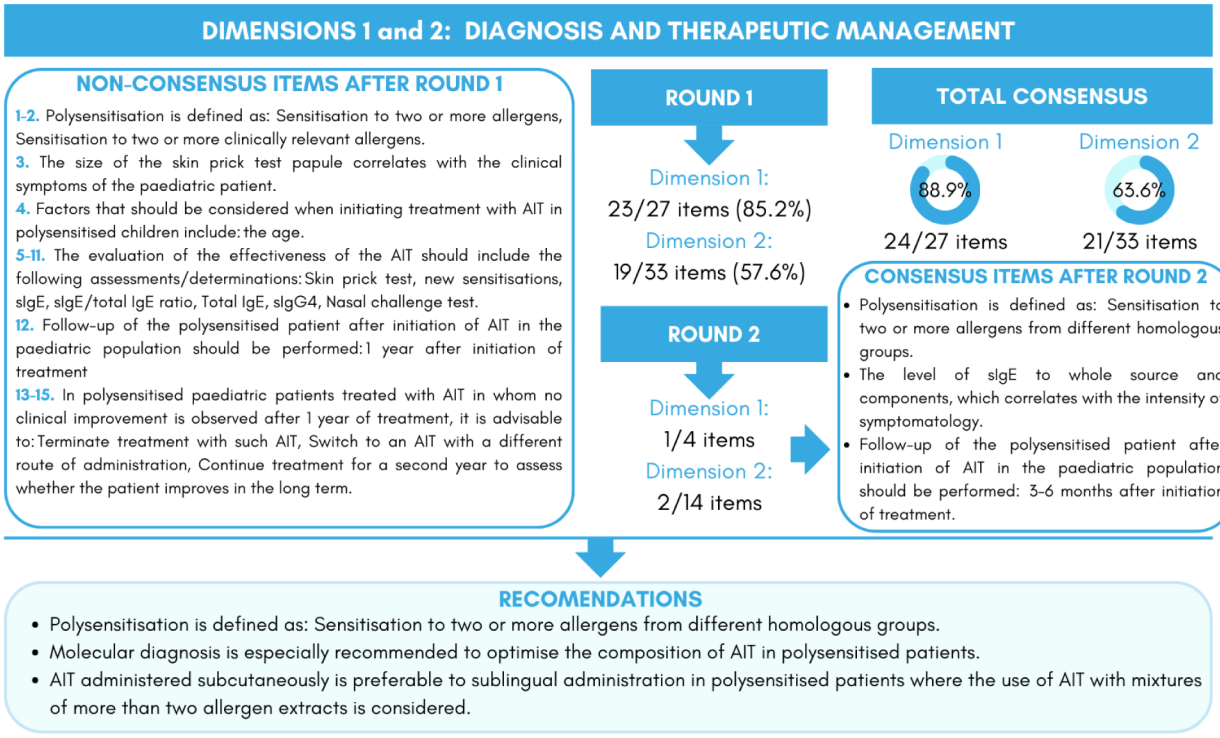

Figure 2 Consensus achievement and key recommendations emerging from the consensus in Dimensions 1 (Diagnosis) and 2 (Therapeutic management).
AIT, allergen immunotherapy; IgE, immunoglobulin E; sIgG4, specific immunoglobulin G4; sIgE, specific immunoglobulin E.

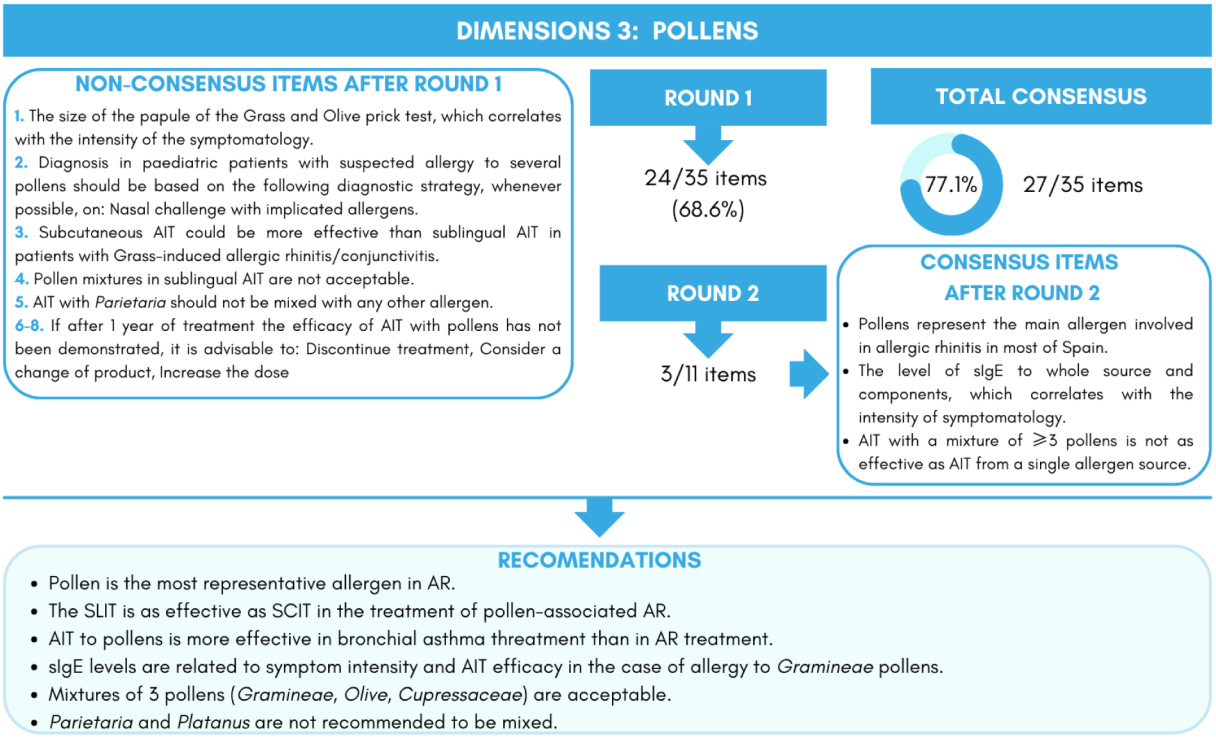

Figure 3 Consensus achievement and key recommendations emerging from the consensus in Dimension 3 (Pollens).
AIT, allergen immunotherapy; IgE, immunoglobulin E; SCIT, subcutaneous immunotherapy; sIgE, specific immunoglobulin E; SLIT, sublingual immunotherapy.

Table 2 Expert-based Delphi consensus recommendations for the management of polysensitised children.

Dimension	Recommendation
Diagnosis	Polysensitization is defined as the sensitization to ≥2 different homologous groups of allergens
	Molecular diagnostics differentiates between cross-reactivity and cosensitization
Therapeutic management	SCIT is preferred in mixtures of ≥2 allergens over SLIT
Pollens	Pollens are the most representative allergens in AR
	SLIT is as effective as SCIT in the treatment of pollen-associated AR
	AIT for pollens is more effective in bronchial asthma treatment than in AR treatment
	sIgE levels are related to symptom intensity and AIT efficacy in the case of allergy to *Gramineae* pollens
	Mixtures of three pollen extracts (*Gramineae*, *Olea* and Cupressaceae) are acceptable
	Mixtures of *Parietaria* and *Platanus* extracts are not recommended

of different homologous groups. In this sense, European Medicines Agency (EMA) guidelines on allergen products indicate that allergen extracts may be grouped into homologous groups according to several criteria, including comparable physicochemical and biological properties of the source material; cross-reactivity or structural homology; and identical formulation and production process of the finished product.[27]

Since diagnosis is the first step in determining appropriate and personalized management for each patient, it is important to establish a definition of polysensitization, especially from a clinical point of view. Recommendations from the European Academy of Allergy and Clinical Immunology (EAACI) and Allergic Rhinitis and its Impact on Asthma (ARIA) clearly state that the number of sensitisations is less important than the clinical relevance of each allergen.[28-30] For that reason, the identification of the clinically relevant allergen should be the basis of the diagnosis, in terms of type and severity of symptoms, duration of these symptoms over the year, the impact on quality of life (QoL) and the possibility of avoiding the allergen.[28-30]

Furthermore, emphasis is placed on the fact that sensitization must be confirmed by SPT and/or IgE determination. In addition, the results reflect a broad consensus on the limitations of SPT itself, especially in terms of the AIT treatment decision. A high percentage of experts (97.8%) recognize the impossibility of distinguishing between cosensitization and cross-reactivity, except for single component prick tests (Profilin, Alt a 1 and Cup a 1). In addition, experts also agreed that, once the usefulness of SPT and total and sIgE testing has been established, it would be advisable to perform CRD (defined as the detection in the blood serum of sIgE against single allergen components or molecules from a specific allergen source) to accurately determine the relevant allergens. The experts also agreed on the potential of molecular diagnostics, even considering the current limitations in relation to the number of allergens available, mainly to establish the most accurate indication for AIT. In particular, molecular diagnosis-related items reached agreement levels from 95.7 to 100%, indicating the essential use of these tools to distinguish between cosensitization and cross-reactivity, the specific allergens of each source, and to clarify the composition of the AIT. Several studies in real clinical practice have shown that the use of CRD molecular diagnostics was an essential tool for the management of AIT and the follow-up of the disease.[8,31] In addition, current EAACI guidelines establish to use the adequate diagnosis algorithms, including molecular diagnosis.[32]

Regarding the nasal challenge test, experts show a large degree of agreement regarding its use and possible limitations, especially concerning the methodology. These unmet needs are mainly allergen dose and quality, allergen application technique, the need for titration process, or the methodology to assess objective outcomes.[33,34] However, a position paper of the EAACI established nasal allergen challenge as an important tool.[35] In addition, a recent work indicated that the nasal allergen challenge tests are safe and highly reproducible diagnostic tests in clinical practice, both in children and adults.[36]

Therapeutic management

In the present study, a broad consensus was reached that AIT prescription should only be made once the relevant allergens have been identified and the factors to be considered for initiating treatment (including clinical factors, the widely described recommendations previous to AIT treatment, the use of extracts with proven efficacy, and the assessment of possible patient adherence, among others). EAACI guidelines established that if single AIT extracts cannot cover clinically relevant allergens, consider a maximum of three allergens.[32] The experts also agreed that the evaluation of the AIT effectiveness should include mainly clinical assessments, quality of life evaluations, and treatment adherence. Long-term effects of AIT include reductions in symptoms and rescue medication use, as well as improvement in QoL.[37] AIT benefits for asthma control are reflected in an improvement in airway hyperreactivity, the reduction of regular pharmacologic treatment, and a steroid-sparing effect.[38,39] The time after inhaled corticosteroid withdrawal to first exacerbation was recently considered for the EAACI as the primary outcome measure of asthma endpoints in AIT trials.[40] However, no consensus was achieved on the use of *in vitro* methods (total IgE, sIgE, sIgG4, and ratios among them) for the evaluation of the efficacy of AIT treatments. This is probably due to the fact that biomarkers of efficacy are not yet developed for clinical practice. Follow-up should be performed 6 months after treatment initiation, and a switch to another type of AIT should be advisable in patients without clinical improvement after

1 year of treatment. Switching between different types of AIT may be necessary if the initial treatment is not effective or well-tolerated. The decision to switch AIT should be made individually considering the patient's clinical history and symptoms.[41]

Several studies showed that for a specific allergen extract, the benefit received for polysensitized patients should be similar to monosensitized patients treated with a single-allergen extract.[42–45] In this respect, in the present consensus, the statement "AIT administered subcutaneously is preferable to sublingual administration in polysensitized patients where the use of AIT with mixtures of more than two allergen extracts is considered" reached an agreement of 78.3%. In this sense, this perception, evidenced by the degree of agreement reached, would have no scientific evidence to support it and seems to be rather based on clinical experience and routine clinical practice.[18,46,47]

AIT efficacy and safety are dose- and time-dependent.[48,49] According to several studies, the treatment effect plateaus after 16–26 weeks of treatment.[50] Switching between different types of AIT may be necessary if the initial treatment is not effective or well-tolerated. The decision to switch AIT should be made on a case-by-case basis considering the patient's clinical history and symptoms.[41]

Pollens

The results in the block of statements related to pollen polysensitization and therapeutic approach with pollen extract AIT indicated a high degree of agreement on the use of the diagnostic tools discussed above (medical history, SPT). In general, there is a high degree of agreement in considering molecular diagnostics analysis to make an appropriate prescription of AIT and to identify possible good effectiveness or even the possible risk of adverse reactions. In this sense, panelists agreed that, in the case of *Gramineae* pollens, sIgE to rPhl p 1, rPhl p 5b, rPhl p 7, and rPhl p 12 should be identified to assess the AIT indication, and sensitization to Phl p 12 indicates a worse AIT response. According to the experts' opinion, when assessing Olive pollen allergy, Ole e 7, and Ole e 9 determinations are related to a higher risk of more severe bronchial asthma symptoms and worst AIT safety.

Previous consensus studies have already indicated a high degree of agreement in considering Phl p 1, Phl p 5, and Ole e 1 sIgE measurements as phenotypic markers of Grass and Olive pollen sensitization and their usefulness for the composition of AIT prescription.[9] Likewise, other allergens such as Ole e 7 and Ole e 9 would also be of importance in regions with high levels of Olive pollen exposure.[9]

The role of Phl p 12 (profilin), as one of the main components related to cross-reactivity, makes the determination of sIgE levels to this allergen a particularly important tool.[51,52] However, sensitization to this allergen may be influenced by specific patient characteristics (men and children seem to have higher values) and by geographical location.[53–55] In line with what the experts of the present study agree, different works showed that the detection of IgE to Phl p 12 could predict oral allergy syndrome and an increased risk of adverse reactions during AIT with Grass extract.[56,57]

Regarding the statement related to the level of sIgE to Phl p 1 and/or 5 and the correlation with the effectiveness of AIT to Grass pollen, this item reached an agreement of 73.9%. The literature does not appear to be conclusive in this regard, with some published work claiming that the sIgE/total IgE ratio could be used for predicting the clinical response for specific allergens.[58,59] On the contrary, some recent work suggests that the relationship between pretreatment allergen-sIgE concentration, or demographic characteristics, and the effect of AIT is unclear.[60]

Experts agreed that AIT with pollen extracts is more effective for the treatment of bronchial asthma than rhinoconjunctivitis. No agreement was reached, however, on possible differences in the use of SCIT or SLIT in patients polysensitized to pollens of different origins. The efficacy of SCIT in allergic rhinoconjunctivitis induced by pollen allergy presents strong evidence for adult patients.[61] However, only a few studies showed it for children and adolescents.[41] Treatment with SCIT indicated the control of bronchial asthma, as reported by the Global Initiative for Asthma (GINA) if a clear causal link between respiratory symptoms and the relevant allergen is demonstrated.[39,41,62] However, more evidence would be needed for SCIT. In the case of SLIT, efficacy in Grass pollen-induced allergic rhinoconjunctivitis was demonstrated to a greater extent than in tree pollen allergy.[63] In contrast, only a few studies examined the efficacy of SLIT with pollen extracts in allergic asthma.[41]

Regarding the use of pollen mixtures in AIT, it is important to note the degree of agreement reached on the types of mixtures recommended. The utilization of Grass, Olive and Cupressus (three pollens) in the same preparation was accepted by 95.7% of panelists. Experts agreed that AIT with a single Grass species (e.g., *Phleum pratense*) is effective for the treatment of sensitisation to the whole group (87%). Several works reported the use of primarily single-allergen AIT in polysensitized patients and showed that symptoms and medication scores decreased and the quality of life improved.[43,64,65] The statements indicating that a mixture of Grasses and *Cupressaceae* is acceptable in polysensitized patients and can prevent AR progression to asthma achieved an agreement of 93.5% and 80.4%, respectively. Finally, after identification of the relevant allergens, experts agreed that AIT could be indicated by including a maximum of three allergens in the AIT composition (87%). The EAACI guidelines recommend limiting allergen formulations to a maximum of two allergens for pollens when possible.[32] However, some working groups propose using up to three allergens, despite the lack of clinical evidence supporting this practice.[32] The Delphi study conducted in Spain exploring consensus on treatment strategies for polysensitized patients reached a high agreement for the two primary pollen sources in the country (Grasses and Olive).[9] However, no consensus was achieved for patients sensitized to more than two allergens, highlighting the ongoing debate and need for further research in managing polysensitized patients.

Limitations and strengths

The Delphi method is a valuable tool for gathering insights and making informed decisions in healthcare practice. However, one of its limitations is that the anonymity of the Delphi method can help mitigate biases, but it is still possible for participants to exhibit response bias. In addition,

it should be considered that the Delphi methodology itself means that the fact that experts express a high degree of agreement does not directly imply that a recommendation is necessarily effective. The results of the study represent the starting point to design appropriate studies related to the field, and for the development of recommendation documents and management guidelines.

The variability in consensus observed in this Delphi study can be attributed to several factors specific to clinical practice and healthcare in Spain. Most panellists work within the Spanish Public Health System, where diagnosis and treatment are publicly funded, influencing appointment scheduling and diagnostic approaches for polysensitized patients. Molecular diagnostics are widely used, but their availability and experience vary depending on the allergens involved.[8,13,66] Spanish clinical practice predominantly favours SCIT over SLIT, and chemically modified allergen extracts (allergoids) are frequently used in AIT, though their standardization and quality control are more complex than native extracts.[67,68] Additionally, the regulatory process for AIT in Spain is still evolving, suggesting that future consensus analyses may be needed as the regulatory framework becomes more established.

In summary, the results of this Delphi study suggested that, although the general lines of recommendations and suggestions are in line with the management recommendations established by, among others, the EAACI, an adaptation to the specific characteristics of the polysensitized children and the Spanish population is necessary.

Conclusion

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

M.M. del C. has received payment or honoraria as speaker in educational events from Diater and Leti Pharma. 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. 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. 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. H.L.C., M.T.-G., J.M.L.M., M.M.F., and A.M.-T. 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 the diagnosis in polysensitised children.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
Polysensitisation is defined as:			
1. Sensitisation to two or more allergens.	7 (3-9)	56.8	Not agreed in round 2
2. **Sensitisation to two or more allergens without cross-reactivity as assessed by skin testing and/or IgE determination.**	**8 (7-9)**	**76.1**	**Agreed in round 1**
3. **Sensitisation to two or more allergens from different homologous groups.**	**8 (7-9)**	**79.5**	**Agreed in round 2**
4. Sensitisation to two or more clinically relevant allergens.	3 (2-7)	34.1	Not agreed in round 2
5. **To diagnose the polysensitised patient, the first step is to differentiate between co-sensitisation and cross-reactivity.**	**9 (8-9)**	**97.8**	**Agreed in round 1**
In most paediatric patients in whom allergic pathology is suspected based on clinical history:			
6. **Skin testing should be performed as a first step in the detection of allergic sensitisation.**	**9 (8-9)**	**100**	**Agreed in round 1**
7. **Skin prick test and determination of total IgE, specific to the whole source and its components should be performed.**	**8 (6-9)**	**73.9**	**Agreed in round 1**
8. **The results should be correlated with the clinical history to detect the relevant allergen(s).**	**9 (9-9)**	**100**	**Agreed in round 1**
9. **The skin prick test is a rapid method with high sensitivity and specificity for the diagnosis of sensitisation to pneumoallergens.**	**8 (7-9)**	**89.1**	**Agreed in round 1**
10. **The skin prick test can be used in paediatric patients of any age.**	**9 (9-9)**	**97.8**	**Agreed in round 1**
11. **For the skin prick test, in addition to the allergens recommended by European guidelines, the allergen battery should include local allergens.**	**9 (9-9)**	**97.8**	**Agreed in round 1**
12. The size of the skin prick test papule correlates with the clinical symptoms of the paediatric patient.	5 (2-7)	27.3	Not agreed in round 2
Some limitations of the prick test are:			
13. **Variability of extracts due to different standardisation methods.**	**9 (8-9)**	**97.8**	**Agreed in round 1**
14. **The impossibility to distinguish between co-sensitisation and cross-reactivity except for single component prick tests (Profilin, Alt a 1, Cup a 1).**	**9 (8-9)**	**97.8**	**Agreed in round 1**
15. **The presence of cross-reactive allergens in the extracts used in the skin test makes it difficult to distinguish the sensitising allergen source(s).**	**9 (7-9)**	**95.7**	**Agreed in round 1**
16. **Evaluation by skin prick test alone is not sufficient to decide on AIT in polysensitised patients.**	**9 (9-9)**	**95.7**	**Agreed in round 1**
17. **The determination of total IgE does not show sufficient sensitivity and specificity for the detection of sensitisation.**	**9 (8-9)**	**93.5**	**Agreed in round 1**
18. **In polysensitised patients, it is advisable to perform total IgE and sIgE testing.**	**9 (8-9)**	**91.3**	**Agreed in round 1**
19. **If patients show polysensitisation by prick test and/or determination of sIgE to complete allergic source, the molecular diagnosis should be performed to determine the relevant allergens to assess the composition of the AIT.**	**9 (9-9)**	**91.3**	**Agreed in round 1**
Molecular diagnostics:			
20. **Makes it possible to distinguish between cross-reactivity and co-sensitisation.**	**9 (8-9)**	**95.7**	**Agreed in round 1**
21. **Allows for the identification (better than methods based on extracts from whole allergenic sources) of genuinely sensitising allergens.**	**9 (8-9)**	**100**	**Agreed in round 1**
22. **Allows precise indication of AIT.**	**8 (7-9)**	**89.1**	**Agreed in round 1**
23. **Is especially recommended to optimise the composition of AIT in polysensitised patients.**	**9 (8-9)**	**95.7**	**Agreed in round 1**
24. **Can change the selection of AIT.**	**9 (8-9)**	**95.7**	**Agreed in round 1**

(*continues*)

Table S1 Continued.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
25. **The nasal challenge test represents a useful complementary test in polysensitised patients in whom the clinical history does not allow discriminating with sufficient precision the most relevant sensitisation.**	**7 (7-9)**	**76.1**	**Agreed in round 1**
The limitations of the nasal challenge test on the target organ (conjunctival, nasal) for the correct diagnosis of the polysensitised child lie in:			
26. **the lack of homogeneity in extracts from different manufacturers.**	**8 (7-9)**	**91.3**	**Agreed in round 1**
27. **27. that they are long-lasting tests that require trained personnel and the treatment of possible allergic reactions.**	**8.5 (8-9)**	**89.1**	**Agreed in round 1**

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

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
1. **AIT should only be prescribed if the relevant allergens responsible are identified.**	**9 (8-9)**	**97.8**	**Agreed in round 1**
Factors that should be considered when initiating treatment with AIT in polysensitised children include:			
2. Age.	7 (4-8.5)	56.8	Not agreed in round 2
3. **Intensity and duration of symptoms**	**9 (9-9)**	**100**	**Agreed in round 1**
4. **Persistence of symptoms despite avoidance of the allergen.**	**9(8-9)**	**95.7**	**Agreed in round 1**
5. **Persistence of symptoms despite symptomatic medication.**	**9 (7-9)**	**91.3**	**Agreed in round 1**
6. **Possible avoidance of exposure to the allergen.**	**8 (7-9)**	**93.5**	**Agreed in round 1**
7. **Identification of clinically relevant allergens.**	**9 (9-9)**	**100**	**Agreed in round 1**
8. **Quality standardised extracts with studies supporting their efficacy.**	**9 (9-9)**	**100**	**Agreed in round 1**
9. **Patient and parent/guardian preference on dosage, treatment regimen, route of administration, duration, type of allergens (native/modified), and potential adverse effects. Children and their families should be appropriately informed of AIT protocols in case of unregistered products.**	**9 (8-9)**	**87**	**Agreed in round 1**
10. **Risk of non-adherence to treatment.**	**9 (8-9)**	**100**	**Agreed in round 1**
11. **Risk-benefit balance.**	**9 (8-9)**	**97.8**	**Agreed in round 1**
12. **Patient comorbidities.**	**9 (9-9)**	**97.8**	**Agreed in round 1**
13. **AIT administered subcutaneously is preferable to sublingual administration in polysensitised patients where the use of AIT with mixtures of more than two allergen extracts is considered.**	**7 (7-9)**	**78.3**	**Agreed in round 1**
The evaluation of the effectiveness of the AIT should include the following assessments/determinations:			
14. **Rhinoconjunctivitis/asthma symptom score**	**9 (8-9)**	**100**	**Agreed in round 1**
15. Skin prick test	5 (2-8)	40.9	Not agreed in round 2
16. **Use of rescue medication**	**9 (9-9)**	**97.8**	**Agreed in round 1**
17. **Control of asthma symptoms**	**9 (9-9)**	**100**	**Agreed in round 1**
18. New sensitisations	6.5 (3-8.5)	50	Not agreed in round 2
19. sIgE	5 (3-7)	34.1	Not agreed in round 2
20. sIgE/total IgE ratio	6 (3-7)	43.2	Not agreed in round 2
21. Total IgE	3 (1-6)	25	Not agreed in round 2
22. sIgG4	7 (4-8)	54.5	Not agreed in round 2
23. **Quality of life**	**9 (8-9)**	**100**	**Agreed in round 1**

(*continues*)

Table S2 Continued.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
24. **Adherence to treatment**	**9 (8-9)**	**97.8**	**Agreed in round 1**
25. Nasal challenge test	7 (5-8)	52.3	Not agreed in round 2
Follow-up of the polysensitised patient after initiation of AIT in the paediatric population should be performed:			
26. **6 months after initiation of treatment**	**7 (7-9)**	**78.3**	**Agreed in round 1**
27. **3-6 months after initiation of treatment**	**7.5 (5.5-9)**	**63.6**	**Not agreed in round 2 Agreed after scientific committee final evaluation**
28. 1 year after initiation of treatment	8 (5-9)	61.4	Not agreed in round 2
29. **The limited evidence with mixed AIT compared to monocomponent preparations requires closer monitoring in polysensitised children than in monosensitised children.**	**7 (6-9)**	**67.4**	**Agreed in round 1**
In polysensitised paediatric patients treated with AIT in whom no clinical improvement is observed after 1 year of treatment, it is advisable to:			
30. Terminate treatment with such AIT	5 (4-7.5)	43.2	Not agreed in round 2
31. **Switch to another type of AIT**	**6 (3-7)**	**40.9**	**Not agreed in round 2 Agreed after scientific committee final evaluation**
32. 32. Switch to an AIT with a different route of administration (e.g. lack of response to treatment associated with lack of adherence to treatment or lack of acceptance).	7 (6-8)	65.9	Not agreed in round 2
33. 33. Continue treatment for a second year to assess whether the patient improves in the long term.	6 (3-7)	31.7	Not agreed in round 2

Table S3 Results of the two-step Delphi process for the items regarding diagnosis and therapeutic approach of the polysensitised child with pollen allergy.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
1. **Pollens represent the main allergen involved in allergic rhinitis in most of Spain.**	**8 (7-9)**	**79.5**	**Agreed in round 2 after being reformulated**
2. **Patients who live in areas with high exposure to pollens have more severe symptoms.**	**8 (7-9)**	**93.5**	**Agreed in round 1**
3. **The identification of "initiator" molecules of the immune response expansion phenomenon (molecular spreading)*, such as Phl p 1, is a recommended strategy to predict the development of allergic rhinitis and asthma in children.** ***Evolution of the immune response to different molecules without cross-reactivity from the same allergen source, starting with an "initiator" molecule.***	**7 (7-9)**	**84.8**	**Agreed in round 1**
4. **The variety of sensitisation profiles and overlapping pollination periods makes it difficult to distinguish between sensitisation to different pollens and sensitisation to fungi (*Alternaria*).**	**8 (7-9)**	**95.7**	**Agreed in round 1**
5. **Cross-reactivity between Grass and Olive pollens makes it difficult to select the composition of the AIT in polysensitised patients.**	**7 (6-9)**	**73.9**	**Agreed in round 1**

(*continues*)

Table S3 Continued.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
Diagnosis in paediatric patients with suspected allergy to several pollens should be based on the following diagnostic strategy, whenever possible, on:			
6. **A correct clinical history correlated with pollen calendar.**	**9 (9-9)**	**100**	**Agreed in round 1**
7. **Skin prick test as the first diagnostic test including local pollens and panallergens (profilin, LTP...).**	**9 (9-9)**	**97.8**	**Agreed in round 1**
8. **sIgE against whole source and components.**	**9 (8-9)**	**84.8**	**Agreed in round 1**
9. The size of the papule of the Grass and Olive prick test, which correlates with the intensity of the symptomatology.	5 (3-7)	34.1	Not agreed in round 2
10. **The level of sIgE to whole source and components, which correlates with the intensity of symptomatology.**	**7 (6-8.5)**	**65.9**	**Not agreed in round 2 Agreed after scientific committee final evaluation**
11. **Molecular diagnosis, which represents the most suitable method for the detection of relevant sensitisations.**	**8 (7-9)**	**80.4**	**Agreed in round 1**
12. Nasal challenge with implicated allergens.	7 (6-8)	63.6	Not agreed in round 2
13. **In patients with symptoms of seasonal allergic rhinitis and a positive Grass-specific skin prick test/IgE, the presence of sIgE to rPhl p 1, rPhl p 5b, rPhl p 7 and rPhl p 12 should be identified by molecular diagnosis to assess the indication for AIT.**	**7 (6-9)**	**71.7**	**Agreed in round 1**
14. **Detection of molecular allergens, such as Phl p 1 and/or Phl p 5, allows confirmation of genuine Grass sensitisation.**	**9 (8-9)**	**100**	**Agreed in round 1**
15. **Sensitisation to Phl p 12 indicates a worse response to AIT.**	**7 (6-9)**	**67.4**	**Agreed in round 1**
16. **A positive prick test to profilin, Grass and Olive tree pollens requires molecular diagnosis before considering the indication for AIT.**	**9 (8-9)**	**97.8**	**Agreed in round 1**
17. **The level of sIgE to Phl p 1 and/or 5 correlates with the effectiveness of AIT to Grass pollen.**	**8 (5-9)**	**73.9**	**Agreed in round 1**
18. **Determination of the marker allergens Ole e 7 and Ole e 9 allows identification of patients at higher risk of developing more severe bronchial asthma symptoms and more adverse reactions with AIT.**	**8.5 (7-9)**	**91.3**	**Agreed in round 1**
19. **Determination of Cup a 1-sIgE is essential when prescribing *Cupressaceae* AIT.**	**8 (7-9)**	**84.8**	**Agreed in round 1**
20. **AIT with pollens is more effective for the treatment of bronchial asthma than rhinoconjunctivitis.**	**7 (6-8)**	**73.9**	**Agreed in round 1**
21. **AIT with a mixture of ≥3 pollens is not as effective as AIT from a single allergen source.**	**7 (5-8)**	**63.6**	**Not agreed in round 2 Agreed after scientific committee final evaluation**
22. **Grass and Olive tree pollens may be mixed in the same preparation if indicated.**	**9 (8-9)**	**95.7**	**Agreed in round 1**
23. **AIT with a single Grass species (e.g. *Phleum pratense*) is effective for the treatment of sensitisation to the whole group.**	**8 (7-9)**	**87**	**Agreed in round 1**
24. **A mixture of Grasses and *Cupressaceae* is acceptable in polysensitised patients.**	**9 (8-9)**	**93.5**	**Agreed in round 1**
25. **AIT with Grass and *Cupressaceae*/Olive pollen allergens can prevent the progression of allergic rhinitis to asthma in pollen polysensitised patients.**	**8 (7-9)**	**80.4**	**Agreed in round 1**
26. **In areas without a predominance of one pollen type, after identification of the relevant allergens, AIT could be indicated by including a maximum of 3 allergens in the composition of the AIT.**	**8 (7-9)**	**87**	**Agreed in round 1**
27. Subcutaneous AIT could be more effective than sublingual AIT in patients with Grass-induced allergic rhinitis/conjunctivitis.	5 (3-8)	38.6	Not agreed in round 2
28. Pollen mixtures in sublingual AIT are not acceptable.	5 (3-7)	34.1	Not agreed in round 2

(*continues*)

Table S3 Continued.

Statements	Median (range)	Accepted (scores 7-9) (%)	Result of the Delphi process
29. **AIT with pollens such as *Platanus acerifolia* and *Arecaceae* (palm) has no studies to support its use.**	**7 (6-8)**	**73.9**	**Agreed in round 1**
30. AIT with *Parietaria* should not be mixed with any other allergen.	3.5 (2-5)	47.7	Not agreed in round 2
If after 1 year of treatment the efficacy of AIT with pollens has not been demonstrated, it is advisable to			
31. Discontinue treatment	6 (3.5-7)	47.7	Not agreed in round 2
32. Consider a change of product	7 (4.5-7.5)	54.5	Not agreed in round 2
33. Increase the dose	6 (2-7)	38.6	Not agreed in round 2
34. **Assess further sensitisation**	**9 (7-9)**	**91.3**	**Agreed in round 1**
35. **Assess compliance with treatment**	**9 (9-9)**	**100**	**Agreed in round 1**