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REVIEW

Decision-making for pediatric allergy immunotherapy for aeroallergens: a narrative review

Miguel Tortajada-Girbés[1,2,3] · María Mesa del Castillo[4] · Helena Larramona[5] · José Manuel Lucas[6] · Montserrat Álvaro Lozano[7] · Ana Isabel Tabar[8] · Begoña Soler López[9] · Ana Martínez-Cañavate[10] · on behalf of the Immunotherapy Working Group of the Spanish Society of Pediatric Clinical Immunology and Allergology (SEICAP)

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Abstract

There has been exciting progress in diagnosis and in the treatment of allergic patients. The objective of this review is to summarize the most relevant contributions in the past 10 years with a special focus on the pediatric population allergic to aeroallergens and provide the most relevant references and practical issues for the decision-making. Current guidelines on allergy diagnosis recommend a thorough clinical history as the first step, followed by allergen extract testing using an in vivo prick test and/or an in vitro specific IgE test. Molecular diagnosis is recommended when previous tests are inconclusive. In practice, the most important factors to decide the AIT treatment are the actual intensity and duration of the patient's symptoms and the availability of appropriate AIT products for the patient's sensitization profile at high allergen concentrations and with confirmed efficacy and safety from clinical trials. This document summarizes outstanding references for allergic immunotherapy decision-making and provides summary tables and figures analyzing the most important factors related to the decision for allergen immunotherapy and the safety risks related. The experts concluded that AIT is efficacious and safe for the treatment of allergic patients that is available for the most frequent aeroallergens.

What is Known:
- *The prevalence of allergic asthma and rhinitis in children has increased in recent decades.*
- *The efficacy and safety of allergen immunotherapy has been shown in multiple studies and systematic reviews.*

What is New:
- *This document summarizes outstanding references for allergic immunotherapy decision-making and provides summary tables and figures analyzing the most important factors related to the decision for allergen immunotherapy and the safety risks related. Recommendations of expert authors for the decision of the patients more suitable for allergen immunotherapy are included.*

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✉ Begoña Soler López
bsoler@ecbio.net

Miguel Tortajada-Girbés
tortajadamig@gmail.com

María Mesa del Castillo
mesadelcastillomaria@hotmail.com

Helena Larramona
hlarramona@gmail.com

José Manuel Lucas
cuenta-jm@hotmail.com

Montserrat Álvaro Lozano
malvaro@hsjdbcn.org

Ana Isabel Tabar
ana.tabar.purroy@cfnavarra.es

Ana Martínez-Cañavate
anamartinezcanavate@gmail.com

Extended author information available on the last page of the article

Keywords Allergen immunotherapy · Aeroallergens · Allergic rhinitis · Asthma · Subcutaneous immunotherapy · Sublingual immunotherapy

Abbreviations

ACAAI	American College of Allergy, Asthma and Immunology
AIT	Allergen immunotherapy
ARIA	Allergic Rhinitis and its Impact on Asthma
EAACI	European Academy of Allergy and Clinical Immunology
EMA	European Medicines Agency
GINA	Global Initiative for Asthma
HEP	Histamine equivalent prick
Ig	Immunoglobulin
IL	Interleukin
ISAC	Immuno-solid phase allergen chip
ISU	ISAC standardized units
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
TGF-b	Transforming growth factor beta
WAO	World Allergy Organization

Introduction

There has been remarkable progress in diagnosis and new evidence in the treatment of allergic patients in the last years. Allergen immunotherapy (AIT) has its own unique characteristics, as it is a treatment developed to decrease and modulate the immune response to allergens that do not usually elicit an immune response in the general population. The purpose of immunotherapy in other diseases is the opposite, namely, to increase the immune response against selected allergens.

The objective of this review is to summarize the most relevant contributions in the past 10 years related to diagnosis of allergic diseases and the management of AIT with a special focus on the pediatric population sensitized to aeroallergens and provide the most relevant references and practical issues for the decision-making.

Differential diagnosis

Respiratory tract symptoms are the most commonly seen in pediatric practice. They may be related to bacterial or viral infections, or to allergic, hyperreactive, or inflammatory conditions. As the seasonality of these etiologies can be concomitant, a complete differential diagnosis is required to select the most effective treatment [1]. According to large population-based studies, the prevalence of asthma and allergic rhinitis (AR) in children has increased in the last decades to a prevalence of 15% [1–4]. Recent updated guidelines for the diagnosis and treatment of rhinitis and asthma are useful tools for evidence-based management of patients and include special features for the pediatric population (Supplementary digital material-1) [2–4].

Rhinitis, conjunctivitis, asthma, dermatitis, urticaria, gastrointestinal symptoms, and anaphylaxis are the most common syndromes related to an allergic etiology.

Etiological diagnosis

Accuracy in the identification of relevant sensitizing allergen(s) responsible for clinical symptoms will allow for exposure control and for allergen avoidance whenever possible, and for selection of specific AIT.

All allergy diagnostic tests should be evaluated considering the patient's clinical history. The results of diagnostic tests must explain the symptoms, as patients can show positive results to specific allergens in the diagnostic tests (sensitized patients) but this may not be associated with clinical symptoms in some cases [5].

In vivo and in vitro etiological diagnostic tests are available, but none of them is considered the gold standard. A comprehensive update of allergy diagnostic testing is provided by Bernstein et al. [6]. Table 1 shows a comparison of the main diagnostic tests available for etiological diagnosis of allergy. A brief description is given below:

Prick test

The prick test is most widely used and is the reference test for measuring the sensitivity and specificity of other tests. It allows for immediate reading of the results of many different allergens at the same time, is minimally invasive and inexpensive but requires trained staff. The composition and concentration of the allergens contained in the commercial diagnostic tests vary widely [7]. A European project encourages the standardization of allergen extracts based on their content of major allergen(s). Major and minor allergens are those against which at least 50% (major allergens) or less than 50% (minor allergens) of patients tested have allergen-specific immunoglobulin E (IgE) antibodies [8–10]. All positive result in the prick test can or cannot be related to current symptoms but interestingly, it could be predictive of future clinical allergies [11].

Specific IgE

An allergy blood test measures circulating IgE directed against a specific allergen molecule or extract. The specific

Table 1 Comparison of the main allergy diagnostic tests

	Prick test	Specific IgE	Molecular diagnosis
Sensitivity	85–87%	70–75%	
Reproducibility	Manual procedure requiring trained staff	Automated	
Number of tests by allergen	One test by allergen	Singleplex: one test by allergen Multiplex: multiple allergens in one test	
Blood sample needed	None needed	Singleplex: 40 μl of serum per allergen tested ADVIA-Centaur 25 μl serum per allergen	
Allergens than can be tested	Natural, recombinant proteins, or crude extracts	Natural, recombinant proteins, or crude extracts. Not all allergic sources are included	
Results	Qualitative, positive, or negative results	Quantitative, kUa/L, kilo international units of allergen-specific antibody per unit volume of sample ISAC: semiquantitative (ISU)	
Results related to clinical symptoms	No	No	
Safety	Skin reactions uncomfortable for patients; risk of anaphylaxis	Safe, in vitro	
Polysensitized patients	Common standardized battery with 18 allergens	One test for each allergen Detects low-affinity IgE that may have no clinical relevance Multiplex: one test for more than 100 allergens	
Identify cross-reactivity	Yes	No	
Useful to assess efficacy	No	No	
Cost	Low	High In young children requires total IgE measurement.	
Recommended in	• Suspicion of mono or oligosensitized patients • If other tests are not available • Young children	• For patients not cooperating in prick test • Severe skin disease (extensive eczema, dermographism, urticaria) • Patients receiving drugs that interfere with in vivo tests • Polysensitized patients • Cross-reactivity suspected • When the physician has not suspected allergens	

IgE threshold that indicates the presence or absence of clinical symptoms is unknown. Low specific IgE levels do not rule out allergic symptoms, especially in very young children [12]. In subjects with very high total IgE levels (> 300 kU/L), as commonly seen in young children, low specific IgE levels may be found. Total IgE levels should therefore be measured at the same time as specific IgE testing [13]. It has been noted that for some allergens, positive results in the prick test are not associated with positive results in specific IgE levels, and vice versa [14]. The number of sensitized patients who could be misdiagnosed if only one diagnostic test is used may be up to 58% if only the prick test is used, or 34% if only specific IgE levels are measured [15]. It is therefore recommended that both methods are used for diagnosis.

Molecular diagnosis

This in vitro test measures specific IgE that binds to single allergenic protein components. This allergenic protein may be an allergen source but also a cross-reactivity marker that shows positive results for different sources. In polysensitized patients, molecular diagnosis can improve the resolution of conventional diagnostic tests, either by detecting new relevant sensitizations or by ruling out clinically irrelevant sensitizations caused by non-symptomatic cross-reactive allergens. A comprehensive Molecular Allergology User's Guide reviewing the general concepts of molecular allergology, use of the test in clinical practice to diagnose allergies related to the most common allergens, and the clinical relevance of the cross-reactive molecules has been published by the EAACI [16]. The most important aeroallergenic molecules described in this reference are included in the Supplementary digital material-2.

Which test to use and when?

Current guidelines on allergy diagnosis recommend a thorough clinical history as the first step, followed by allergen extract testing using an in vivo prick test and/or

an in vitro specific IgE test. Molecular diagnosis is recommended as a third step when previous tests are inconclusive [17]. In order to know for which allergen the patient should be candidate to available AIT, an algorithm using a panel of specific markers of allergen sources and screening for panallergens has been proposed to assess patients from southern Europe suitable for AIT-based extracts and is shown in Fig. 1 [18]. In mono-oligosensitized patients, assessment of sensitization to specific major molecules contained in AIT extracts is recommended. For polysensitized patients, testing for panallergens such as specific IgE against profilins/polcalcins is advised.

We recommend the use of Prick test when there is suspicion of mono- or oligosensitized patients, when no other tests are available and in young children. The specific IgE test is useful for patients not cooperating in Prick test, when the patient shows severe skin disease (extensive eczema, dermographism, urticaria), for patients receiving drugs interfering the in vivo tests, in polysensitized patients or when cross-reactivity is suspected.

Relevant factors for the decision of treatment with allergen immunotherapy

Multiple factors related to the diagnosis of allergy in respiratory diseases affect the decision to administer AIT. In Table 2 are listed different factors to be considered in the decision-making for the initiation or not of allergy immunotherapy and related findings of the most recent scientific references.

Geographic factors determine the presence of the allergen in the patient's environment but also local genetic factors that determine different sensitization profiles. Patients living in the coast can be sensitized to mites more frequently than in interior zones [19].

Some specific allergens have been related to most severe symptoms (cat, dog, olive tree), presence of rhinitis (*Phleum pratense*, a grass pollen), risk of asthma development (*Alternaria*, a fungus), and risk of atopic dermatitis (*Dermatophagoides farinae*, a mite) [20–24].

The moment when the symptom appears, and its duration is related to seasonal or perennial allergens.

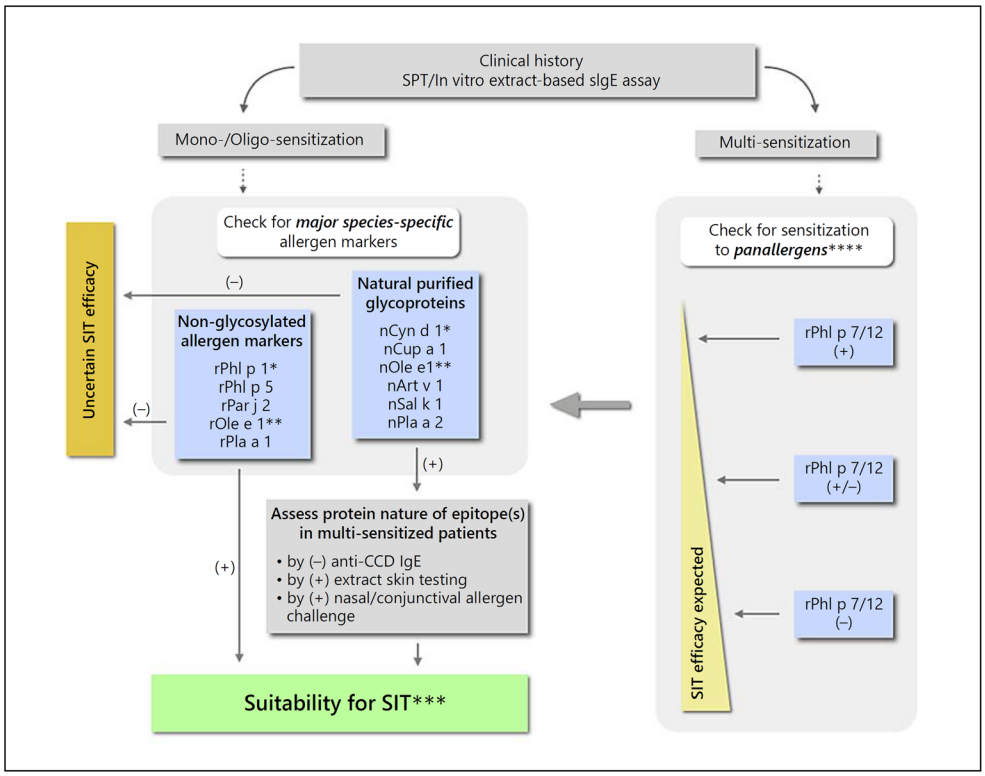

Fig. 1 Algorithm using a panel of specific markers of allergen sources and screening for panallergens. For the purposes of the current figure, component allergens' names denote the detection of corresponding specific IgE. *In cases with nCyn d 1 (+) > rPhl p 1 (+) and negative species-specific allergen markers for Timothy grass (e.g., rPhl p 2, rPhl p 5, and rPhl p 6), a Bermuda grass standardized extract may be sufficient for the treatment of clinical allergy to grass pollen. **Both natural nOle e 1 and recombinant rOle e 1 are commercially available in Europe. ***For optimal SIT efficacy, the use of standardized extracts containing the species-specific major allergen at high-dose concentration may be required. ****rPhl p 7, as a polcalcin marker and rPhl p 12, as a profilin marker are typically used. In areas with a high prevalence of birch pollen allergy (not typical of the Mediterranean region), rBet v 4 and rBet v 2 may respectively be used, along with the essential rBet v 1 birch pollen major allergen [18]

Table 2 Factors affecting decision of the need for allergen immunotherapy in each patient

Geographic	Different presence of allergens	Results of allergic tests should be related to local risk of exposure
	Different pollination periods	Results of allergic tests should be related to symptoms in the pollination periods
	Local genetic factors	Different sensitization profiles and disease expression
Type of allergen	Mites	Patients become polysensitized more often than those mono-sensitized to pollens (45.4% vs 32.1%) [19] *Dermatophagoides farinae* has been associated with atopic dermatitis [24]
	Cat and dog	Fel d 1 (cat) and Can f 5 (dog) have been related with severe asthma in children [23]
	Dermatophagoides farinae	Related with atopic dermatitis [24]
	Alternaria	Is a risk factor for asthma development, persistence, and exacerbation in children [22]
	Phleum pratense	Sensitization predicts the presence of rhinitis in the future [20]
	Profilins and polcalcins	Longer duration of allergic disease Increase the risk of sensitization to other allergen sources Profilins associated to more severe respiratory symptoms [21]
	Polysensitized to several allergens from a single-allergen source	Symptom severity may increase 5 or 6 sensitizations increase the risk of rhinitis (OR 12.73); 7 or more sensitizations increase the risk of asthma (OR 6.12) [63]
	Aeroallergens	Strongly related to rhinitis, conjunctivitis, and asthma symptoms [22]
	Ole e 9 and LPT Ole e 7	Related with more severe symptoms and increased risk of systemic reactions during AIT [21]
Age	Children versus adults	Children have higher risk of respiratory diseases with lower number of sensitizations than adults
	Children	Children are more frequently mono-sensitized at lower age, and poly-sensitized at higher age
Symptoms	Moderate to severe symptoms	AIT shows more efficacy in moderate to severe than in mild allergic rhinitis or conjunctivitis
	Allergic asthma	Lung function must exclude patients with severe uncontrolled asthma, forced expiratory volume in one second (FEV1) should be higher than 70% of predicted. Patients with mild initial asthma can benefit far more from AIT than those with moderate to severe asthma, who first require stabilization. Asthma patients have higher risk of adverse reactions to AIT [4]
	Rhinitis with asthma	Patients should benefit from AIT for the treatment of both symptoms
	Symptom duration	Perennial symptoms or seasonal symptoms appearing for years can influence the decision to use AIT
	Comorbidities	May interfere with response to symptomatic treatment May be affected by symptomatic treatment
Triggering factors	Identification	Triggering factors such as exercise, contamination, and smoking should be considered to assess symptom control
Quality of life	Patients affected	No response to symptomatic treatment Side effects of symptomatic treatment Sleep disturbances due to symptoms interfere with work or school performance
Costs	Indirect cost of illness	Work or school time lost
	Direct costs	Emergency room visits Visits to doctor's office due to symptoms Visits to doctor's office for AIT Costs of symptomatic treatment Costs of AIT
Symptomatic treatment	Patients with inadequate symptom control	Drug measures and allergen avoidance are not effective Or require high-dose therapy Or experience side effects from use of multiple drugs Or wish to avoid long-term drug treatment
AIT products	Most AITs contain standardized major allergens with minimal or variable amounts of minor allergens	Only one major allergen at high doses is usually ensured in the extract Patients sensitized to minor allergens only will not receive adequate amounts of allergen

Table 2 (continued)

	AIT products must have high allergen concentrations to be effective	Not all commercial AIT products contain high allergen concentrations
	AIT products must have been shown to be effective and safe	Each AIT product must have been shown to be effective and safe in randomized clinical trials
	Subcutaneous or sublingual AIT	Patient preferences should be considered when AIT is available in different administration routes Sublingual immunotherapy is indicated for patients who have suffered systemic reactions with subcutaneous immunotherapy and in those who have trouble adhering to SCIT
Compliance	Expected AIT compliance should be considered	As AIT should be continued for at least 3 years with monthly administration, patients should be aware and committed to the procedure
AIT contraindications	Contraindicated in conditions that increase the risk of severe systemic reactions	Severe or poorly controlled asthma Patients with angioedema Cardiovascular diseases, cancer, immunodeficiency, and autoimmune diseases First trimester of pregnancy Use of β-blockers and angiotensin-converting enzyme inhibitors, as they may amplify the severity of systemic reactions to AIT and also mask early signs of anaphylaxis

AIT allergen immunotherapy, *SCIT* subcutaneous immunotherapy

All the previous factors are useful to determine the most probable allergen and the risk of symptoms, but the most important factors to decide the AIT treatment are the actual intensity and duration of the patient's symptoms. AIT shows more efficacy in moderate to severe allergic rhinitis or conjunctivitis, and patients with mild initial asthma can benefit far more from AIT than those with moderate to severe asthma. Perennial symptoms or seasonal symptoms appearing for years can influence the decision to use AIT. If the quality of life of the patient is affected due to no response to symptomatic treatment, the appearance of side effects or due to sleep or work or school disturbance due to the symptoms, the decision of AIT treatment can be the best choice.

But also, the availability of the appropriate AIT product, containing the same allergen for which the patient shows symptoms, at high allergen concentrations, and that have available results on clinical trials are relevant factors for the decision-making. The AIT product cost and the duration of the treatment for at least 3 years are important factors to discuss with the patient as could condition the treatment success.

Allergen immunotherapy

AIT consists on administration of specific allergenic extracts to the patient by different routes at increasing concentrations until a maintenance dose is reached. There are unmodified allergen extracts such as purified allergens, adsorbed allergens, recombinant allergens, and synthetic peptides, but also allergen extracts physically, chemically, or physically-chemically modified to increase their efficacy and safety. Aqueous extracts, depot extracts, and chemically modified extracts or their combination are available.

Current allergen extracts are manufactured into two forms: standardized and non-standardized. For the standardized allergen extracts, manufacturers compare the allergen extract to a US reference standard for potency also adopted by EMA. There are currently 19 standardized allergen extracts licensed for distribution in the USA. (https://www.fda.gov/BiologicsBloodVaccines/Allergenics/ucm391514.htm). Extracts for which there are no US reference standards are called non-standardized extracts. Table 3 contains the main aeroallergens extracts available for AIT.

Mechanisms of allergen-specific immunotherapy

AIT inhibits both the allergic early-phase reaction and the late immune response, and characteristically causes decreases in end-organ sensitivity and changes in the humoral and cellular responses to the allergens administered [25–28].

When AIT is started, changes are seen in humoral immunity. Allergen-specific IgE levels usually increase, but a gradual decrease subsequently occurs during the years of treatment. There is also an increase in allergen-specific IgG antibodies that may persist for many years after AIT is discontinued [29, 30]. IgG1, IgG4, and IgA levels increase, but none of these changes in antibody levels has been shown to correlate with clinical improvement [22]. IgG4 is thought to act as a "blocking" antibody that inhibits IgE-facilitated allergen uptake by dendritic cells and prevents IgE-mediated allergen activation of basophils and mast cells with the resultant inhibition of the release of inflammatory mediators [30]. It is thought that allergen-specific IgG4 may decrease the sensitivity of antigen-

Table 3 Standardized injectable aeroallergen extracts licensed for distribution

	Source
Epidermal	Cat hair (*Felis domesticus*)
	Cat pelt (*Felis domesticus*)
Insects	Mite D.f. (*Dermatophagoides farinae*)
	Mite D.p. (*Dermatophagoides pteronyssinus*)
Pollens	Bermuda grass (*Cynodon dactylon*)
	Kentucky (June) bluegrass (*Poa pratensis*)
	Meadow fescue grass (*Festuca elatior*)
	Orchard grass (*Dactylis glomerata*)
	Redtop grass (*Agrostis alba*)
	Perennial ryegrass (*Lolium perenne*)
	Sweet vernal grass (*Anthoxanthum adoratum*)
	Timothy grass (*Phleum pratense*)
	Short ragweed (*Ambrosia artemisiifolia*)
	Olive tree (*Olea europaea):* Both natural (nOle e 1) and recombinant (rOle e 1) are commercially available in Europe

presenting B cells, and therefore T cells, to allergens by competing with IgE [29]. Therefore, the shift in balance between IgE and IgG4 may be essential to a successful AIT [31].

AIT also induces changes in cell-mediated immunity. Induction of tolerance in peripheral T cells is an essential step in AIT and is defined as a sustained decrease in allergen-specific T cell responsiveness. With continued immunotherapy, there was a predominance of the immune deviation from Th2 to Th1 cytokine response to the administered allergen [22]. Thus, decreased levels of IL-4 and IL-5 produced by Th2 are seen, as well as enhanced synthesis of interferon gamma (IFN-γ), IL-10, and transforming growth factor beta (TGF-β) produced by Th1 cells for controlling the allergic inflammatory response. A third subset of T lymphocyte, called regulatory T cell (Treg), plays a significant role for development of a balanced Th2/Th1 profile with downregulatory tone in allergic reaction [32]. Early IL-10 production after AIT and maintained TGF-β levels are related to an effective AIT [33, 34].

The last phase in a patient treated with AIT after several months is a decrease in tissue mast cells and eosinophils and the release of their mediators, accompanied by a decrease in type I skin test reactivity [35].

Selection of the best allergen immunotherapy

AIT is only indicated to treat diseases where an IgE-mediated allergy mechanism is central to their pathogenesis: rhinitis, allergic asthma, in patients aged 5–50 years, although there is increasing evidence of the efficacy in patients under 5 years old [22].

To select the best AIT for a patient, it is essential to recognize the allergen or allergens that cause symptoms in the patient, as not all allergens are represented in AIT products. The presence in the patient of specific IgE to the same major allergen used in the extract increases the potential response to AIT.

There is no agreement on the therapeutic approach to polysensitized subjects. While single-allergen AIT is preferred in European countries, use of more than 8 allergens in the same shot is common in the USA.

Allergen immunotherapy doses, administration routes, and schemes

Low-dose allergen immunotherapy is usually ineffective. Doses ranging from 5 to 20 μg of major allergen per injection are associated with a significant improvement in patient symptom scores [36].

Subcutaneous AIT (SCIT) is the traditional route of AIT, must be administered in the clinic, and requires patient monitoring for systemic adverse reactions for at least 30 min. In the past decade, several sublingual AIT (SLIT) products, including drops or lyophilized tablets, have been marketed. A comparison of both routes may be found in Table 4.

Table 4 Advantages and disadvantages of allergen immunotherapy administration routes

AIT administration route	SCIT	SLIT
Number of doses	Buildup phase: variable, weekly for 7 weeks Maintenance: monthly	Buildup phase: daily Maintenance: daily or 3 times a week
Maintenance period	At least 3 years	At least 3 years
Visits to the clinic for administration	Needed	Not needed
Patient discomfort	Injections and patient observation for 30 min	No discomfort
	Frequent local reactions	Frequent local reactions
Compliance	Visits required for AIT administration help increase compliance	Long-term daily doses increase the risk of non-compliance

AIT allergen immunotherapy, SCIT subcutaneous immunotherapy, *SLIT* sublingual immunotherapy

AIT is administered in two phases: an initial buildup phase, with increasing doses and concentrations of the extract at weekly intervals for about 4–16 weeks; and a maintenance phase with fixed, optimal, and maximum doses monthly administered for at least 3 years and no more than 5 years. The technical data sheet of each AIT product determines the dosing interval. Intervals in the SLIT maintenance treatment regimens range from one dose daily to three doses per week, and lyophilized tablets should be administered daily [37].

Allergen immunotherapy efficacy

The ARIA guidelines consider AIT effective for adult and children with moderate to severe, persistent, or intermittent allergic rhinitis [38]. According to ARIA, adults with allergic rhinitis without asthma may use SCIT or SLIT to treat pollen or house dust mite allergy. However, ARIA only places a high value on SCIT for reduction of symptoms and potential prevention of asthma development in children. SLIT may be recommended for adults with pollen or house dust mite allergy but is only recommended for pollen allergy in children because its efficacy for house dust mite allergy at this age has not been shown in clinical trials. As the Global Initiative for Asthma (GINA) states, AIT effectiveness has been shown in asthma patients [4].

Initial data on the long-term efficacy of AIT in adults have recently been reported [39]. There is however no evidence that allows for concluding whether long-term efficacy in children might be extrapolated from adult data [40]. The basic pathophysiological mechanism of type I allergies, seasonal or perennial, is not fully understood, but is assumed to be identical in the adult and pediatric populations. However, the magnitude of the effect and the safety profile may differ; therefore, studies in children are needed [41, 42]. It must be emphasized that there should be evidence of the efficacy and safety of each AIT product and marketed allergen.

It should be noted that the methods and experimental designs used in clinical trials are quite heterogeneous and there is no validated symptom score to measure efficacy [43]. To help solve this problem, allergy organizations and health authorities have published recommendations for future studies [41, 42, 44]. For rhinoconjunctivitis, symptom assessment on a 4-point rating scale is accepted in adults and for children provided the symptoms are always rated in the same way by the parent throughout follow-up. The intensity of each symptom is scored from 0 (absent) to 3 (severe). Symptoms that should mandatorily be assessed include obstruction, sneezing, rhinorrhea, nasal itching, and ocular itching. Chest tightness, shortness of breath, cough, and wheezing should also be considered in patients with concomitant lower airway symptoms [44, 45]. This is the best way for the measurement of the efficacy of AIT that should be used in clinical practice as no laboratory parameter modified by AIT has shown a definitive association with the course of clinical symptoms.

Allergen immunotherapy safety

The general conclusion of the experts is that AIT is a safe treatment for allergic patients when properly administered [46]. Adverse reactions to AIT may be local or systemic. A classification of adverse reactions was updated by the World Allergy Organization (WAO) in 2010 to standardize reporting and to improve recognition of potentially severe reactions such as anaphylaxis [47]. The local reaction grading system for SLIT was described in 2013 [48]. Complete information about the classifications can be found at Supplementary digital material 3.

The American College of Allergy, Asthma and Immunology (ACAAI) noted 0.1% of systemic reactions per dose in a study including more than 23 million doses administered with only one fatal reaction [49]. Anaphylactic reactions were estimated at three per million doses in patients with risk factors (bronchial asthma) and at one per million doses in patients without risk factors [50].

Weber et al., in a study including 12,895 patients, 2441 children, reported systemic reaction rates of 0.5% per dose in adults and 1.2% in children [51]. Most systemic reactions occurred within 30 min of administration and in the buildup phase. Similar results were found in a group of 581 children, although local and systemic reactions occurring later than 30 min after injection were seen more often than expected, which should be considered by pediatricians and parents [52].

SLIT is safer than SCIT and can be administered at home, while SCIT has to be administered by a specialist and requires an observation period of at least 30 min. Systematic reviews of SLIT administered to more than 5131 patients (1814 children) reported local reactions in up to 79% of patients, while systemic reactions only occurred after 0.056% of the administered doses [53].

Table 5 lists several factors that have been reported as possible risk factors for systemic reactions to AIT, but only uncontrolled asthma at the time of AIT administration has been shown to be a risk factor for systemic reactions [54]. In supplementary material 1 main reference for safety information are provided [55–61].

As conclusion, current guidelines on allergy diagnosis recommend a thorough clinical history as the first step, followed by allergen extract testing using an in vivo prick test and/or an in vitro specific IgE test. Molecular diagnosis is recommended as a third step when previous tests are inconclusive.

The most important factors to decide the AIT treatment are the actual intensity and duration of the patient's symptoms and the availability of appropriate AIT products for the patient's

Table 5 Risk factors for systemic reactions to allergen immunotherapy

Patient-related risk factors		
Age	Differences between adults and children not shown	
Bronchial asthma	Uncontrolled disease is a risk factor in SCIT	Odds ratio 12.1 (95% CI 2.6–61; $p < 0.001$) in partially controlled asthma patients and 37.4 (95% CI 5.7–251.1; $p < 0.001$) in uncontrolled asthma patients [54]
	More common in patients with asthma than in rhinitis alone	4.1% in patients with asthma and 1.1% if rhinoconjunctivitis alone [62]
Previous local reactions	Local reactions with diameter greater than 25 mm	No conclusive results seen
Systemic reactions to previous doses	Risk of systemic recurrence requires dose adjustment	AIT dose must be adjusted in the startup phase [51] There is inadequate evidence for dose adjustment in the maintenance phase after a systemic reaction [63]
Premedication	Antihistamines before AIT doses	Decrease the frequency of local reactions Decrease the frequency of systemic reactions in cluster and rush regimens only [64]
Polysensitization	No conclusive results [65]	More studies on the safety of double or multiple AIT are needed
Risk factors dependent on the AIT extract		
Type of extract	Modified extracts have lower systemic reaction rates than those with native allergen extracts	[10, 41, 42, 44]
Type of allergen	No allergen appears to be less safe	[10, 41, 42, 44]

AIT allergen immunotherapy, *SCIT* subcutaneous immunotherapy

sensitization profile at high allergen concentrations and with confirmed efficacy and safety from clinical trials. If the allergen for which the patient is sensitized and symptomatic is not available in an AIT product, AIT is not indicated. The general conclusion is that AIT is an efficacious and safe treatment for allergic patients sensitized to aeroallergens.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Eigenmann PA, Atanaskovic-Markovic M, O'B Hourihane J, Lack G, Lau S, Matricardi PM, Muraro A, Namazova Baranova L, Nieto A, Papadopoulos NG et al (2013) Testing children for allergies: why, how, who and when: an updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. Pediatr Allergy Immunol 24:195–209
2. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van Weel C, Agache I, Aït-Khaled N, Bachert C, Blaiss MS, Bonini S, Boulet LP, Bousquet PJ, Camargos P, Carlsen KH, Chen Y, Custovic A, Dahl R, Demoly P, Douagui H, Durham SR, van Wijk R, Kalayci O, Kaliner MA, Kim YY, Kowalski ML, Kuna P, le LT, Lemiere C, Li J, Lockey RF, Mavale-Manuel S, Meltzer EO, Mohammad Y, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Ouedraogo S, Palkonen S, Papadopoulos N, Passalacqua G, Pawankar R, Popov TA, Rabe KF, Rosado-Pinto J, Scadding GK, Simons FE, Toskala E, Valovirta E, van Cauwenberge P, Wang DY, Wickman M, Yawn BP, Yorgancioglu A, Yusuf OM, Zar H, Annesi-Maesano I, Bateman ED, Ben Kheder A, Boakye DA, Bouchard J, Burney P, Busse WW, Chan-Yeung M, Chavannes NH, Chuchalin A, Dolen WK, Emuzyte R, Grouse L, Humbert M, Jackson C, Johnston SL, Keith PK, Kemp JP, Klossek JM, Larenas-Linnemann D, Lipworth B, Malo JL, Marshall GD, Naspitz C, Nekam K, Niggemann B, Nizankowska-Mogilnicka E, Okamoto Y, Orru MP, Potter P, Price D, Stoloff SW, Vandenplas O, Viegi G, Williams D, World Health Organization, GA(2)LEN, AllerGen (2008) Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 63(Suppl 86):8–160
3. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, Brignardello-Petersen R, Canonica GW, Casale T, Chavannes NH et al (2017) Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 140:950–958
4. Global initiative for asthma. Global strategy for asthma management and prevention. 2018 GINA report. Avaliable in: http:// http://www.ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accesed 26 june 2018

5. Migueres M, Davila I, Frati F, Azpeitia A, Jeanpetit Y, Lhéritier-Barrand M, Incorvaia C, Ciprandi G (2014) Types of sensitization to aeroallergens: definitions, prevalences and impact on the diagnosis and treatment of allergic respiratory disease. Clin Transl Allergy 4:16
6. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, Sicherer S, Golden DB, Khan DA, Nicklas RA et al (2008) Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol 100:S1–S148
7. Focke M, Marth K, Valenta R (2009) Molecular composition and biological activity of commercial birch pollen allergen extracts. Eur J Clin Investig 39:429–436
8. Schmid-Grendelmeier P, Crameri R (2001) Recombinant allergens for skin testing. Int Arch Allergy Immunol 125:96–111
9. Van Ree R, Chapman MD, Ferreira F, Vieths S, Bryan D, Cromwell O, Villalba M, Durham SR, Becker WM, Aalbers M et al (2008) The CREATE project: development of certified reference materials for allergenic products and validation of methods for their quantification. Allergy 63:310–326
10. European Medicines Agency. Guideline on allergen products: production and quality issues; 2008. EMEA/CHMP/BWP/304831/2007. http://www.ema.europa. eu/docs/en GB/document library/Scientific guideline/2009/09/WC500003333.pdf. Accessed 26 June 2018
11. Bodtger U, Poulsen LK, Malling HJ (2003)Asymptomatic skin sensitization to birch predicts later development of birch pollen allergy in adults: a 3-year follow-up study. J Allergy Clin Immunol 111(1): 149–154
12. Schoos AM, Chawes BL, Følsgaard NV, Samandari N, Bønnelykke K, Bisgaard H (2015) Disagreement between skin prick test and specific IgE in young children. Allergy 70:41–48
13. de Vos G, Nazari R, Ferastraoaru D, Parikh P, Geliebter R, Pichardo Y, Wiznia A, Rosenstreich D (2013) Discordance between aeroallergen specific serum IgE and skin testing in children younger than 4 years. Ann Allergy Asthma Immunol 110:438–443
14. Calabria CW, Dietrich J, Hagan L (2009) Comparison of serum-specific IgE (ImmunoCAP) and skin-prick test results for 53 inhalant allergens in patients with chronic rhinitis. Allergy Asthma Proc 30:386–396
15. de Vos G (2014) Skin testing versus serum-specific IgE testing: which is better for diagnosing aeroallergen sensitization and predicting clinical allergy? Curr Allergy Asthma Rep 14:430
16. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, Aalberse RC, Agache I, Asero R, Ballmer-Weber B, Barber D, Beyer K, Biedermann T, Bilò MB, Blank S, Bohle B, Bosshard PP, Breiteneder H, Brough HA, Caraballo L, Caubet JC, Crameri R, Davies JM, Douladiris N, Ebisawa M, EIgenmann PA, Fernandez-Rivas M, Ferreira F, Gadermaier G, Glatz M, Hamilton RG, Hawranek T, Hellings P, Hoffmann-Sommergruber K, Jakob T, Jappe U, Jutel M, Kamath SD, Knol EF, Korosec P, Kuehn A, Lack G, Lopata AL, Mäkelä M, Morisset M, Niederberger V, Nowak-Węgrzyn AH, Papadopoulos NG, Pastorello EA, Pauli G, Platts-Mills T, Posa D, Poulsen LK, Raulf M, Sastre J, Scala E, Schmid JM, Schmid-Grendelmeier P, van Hage M, van Ree R, Vieths S, Weber R, Wickman M, Muraro A, Ollert M (2016) EAACI molecular allergology user's guide. Pediatr Allergy Immunol 27(Suppl 23):1–250
17. Canonica GW, Ansotegui IJ, Pawankar R, Schmid-Grendelmeier P, van Hage M, Baena-Cagnani CE, Melioli G, Nunes C, Passalacqua G, Rosenwasser L, Sampson H, Sastre J, Bousquet J, Zuberbier T, WAO-ARIA-GA2LEN Task Force, Allen K, Asero R, Bohle B, Cox L, de Blay F, Ebisawa M, Maximiliano-Gomez R, Gonzalez-Diaz S, Haahtela T, Holgate S, Jakob T, Larche M, Matricardi PM, Oppenheimer J, Poulsen LK, Renz HE, Rosario N, Rothenberg M, Sanchez-Borges M, Scala E, Valenta R (2013) A WAO-ARIA-GA^{2}LEN consensus document on molecular-based allergy diagnostics. World Allergy Organ J 6:17
18. Douladiris N, Savvatianos S, Roumpedaki I, Skevaki C, Mitsias D, Papadopoulos NG (2013) A molecular diagnostic algorithm to guide pollen immunotherapy in southern Europe: towards component-resolved management of allergic diseases. Int Arch Allergy Immunol 162:163–172
19. Silvestri M, Rossi GA, Cozzani S, Pulvirenti G, Fasce L (1999) Age-dependent tendency to become sensitized to other classes of aeroallergens in atopic asthmatic children. Ann Allergy Asthma Immunol 83:335–340
20. Hatzler L, Panetta V, Lau S, Wagner P, Bergmann RL, Illi S, Bergmann KE, Keil T, Hofmaier S, Rohrbach A et al (2012) Molecular spreading and predictive value of preclinical IgE response to Phleum pratense in children with hay fever. J Allergy Clin Immunol 130(894–901):e5
21. Barber D, de la Torre F, Feo F, Florido F, Guardia P, Moreno C, Quiralte J, Lombardero M, Villalba M, Salcedo G, Rodríguez R (2008) Understanding patient sensitization profiles in complex pollen areas: a molecular epidemiological study. Allergy 63:1550–1558
22. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, Nelson M, Weber R, Bernstein DI, Blessing-Moore J et al (2011) Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 127:S1–S55
23. Grönlund H1, Adédoyin J, Reininger R, Varga EM, Zach M, Fredriksson M, Kronqvist M, Szepfalusi Z, Spitzauer S, Grönneberg R et al (2008) Higher immunoglobulin E antibody levels to recombinant Fel d 1 in cat-allergic children with asthma compared with rhinoconjunctivitis. Clin Exp Allergy 38:1275–1281
24. Fuiano N, Fusilli S, Incorvaia C (2010) House dust mite-related allergic diseases: role of skin prick test, atopy patch test, and RAST in the diagnosis of different manifestations of allergy. Eur J Pediatr 169:819–824
25. Till SJ, Francis JN, Nouri-Aria K, Durham SR (2004) Mechanisms of immunotherapy. J Allergy Clin Immunol 113:1025–1034 quiz 35
26. James LK, Durham SR (2008) Update on mechanisms of allergen injection immunotherapy. Clin Exp Allergy 38:1074–1088
27. Akdis CA, Akdis M (2011) Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol 127:18–27 quiz 8-9
28. Shamji MH, Durham SR (2011) Mechanisms of immunotherapy to aeroallergens. Clin Exp Allergy 41:1235–1246
29. Wachholz PA, Durham SR (2003) Induction of 'blocking' IgG antibodies during immunotherapy. Clin Exp Allergy 33:1171–1174
30. Wilcock LK, Wachholz PA, Na DH (2005) Time-course of serum IgG4 levels and IgG inhibitory activity following withdrawal of grass pollen immunotherapy (IT). J Allergy Clin Immunol 115: S265
31. James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, Jacobson MR, Kimber I, Till SJ, Durham SR (2011) Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. J Allergy Clin Immunol 127(509–516):e1–e5
32. Braga M, Quecchia C, Cavallucci E, Di Giampaolo L, Schiavone C, Petrarca C, Di Gioacchino M (2011) T regulatory cells in allergy. Int J Immunopathol Pharmacol 24:55S–64S
33. Francis JN, Till SJ, Durham SR (2003) Induction of IL-10+CD4+ CD25+ T cells by grass pollen immunotherapy. J Allergy Clin Immunol 111:1255–1261
34. Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszcz M, Blaser K, Akdis CA (2003) IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol 33:1205–1214

35. Akdis M, Akdis CA (2014) Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol 133:621–631
36. Bousquet J, Lockey RF, Malling HJ (1998) WHO position paper. Allergen immunotheraphy: therapeutic vaccines for allergic diseases. Geneva: January 27-29 1997. Allergy. 53(44 Suppl):1–42
37. Lombardi C, Incorvaia C, Braga M, Senna G, Canonica GW, Passalacqua G (2009) Administration regimens for sublingual immunotherapy to pollen allergens: what do we know? Allergy 64: 849–854
38. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, Ohta K, Zuberbier T, Schünemann HJ (2010) Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 126:466–476
39. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, Scadding GK, Andersen JS, Riis B, Dahl R (2010) Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol 125:131–138
40. Calderon MA, Gerth van Wijk R, Eichler I, Matricardi PM, Varga EM, Kopp MV, Eng P, Niggemann B, Nieto A, Valovirta E, Eigenmann PA, Pajno G, Bufe A, Halken S, Beyer K, Wahn U (2012) Perspectives on allergen-specific immunotherapy in childhood: an EAACI position statement. Pediatr Allergy Immunol 23: 300–306
41. Guideline on the clinical development of medicinal products for the treatment of allergic rhino-conjunctivitis. CHMP/EWP/2455/02. Committee for medicinal products for human use (CHMP). European Medicines Agency, 21 October 2004. (http://emea.europa.eu)
42. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. CHMP/EWP/18504/2006. European Medicines Agency, 20 November 2008 (http://emea.europa.eu)
43. Calderon A, Casale TB, Nelson HS, Demoly P (2013) An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. J Allergy Clin Immunol 132(6): 1322–1336
44. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, Passalacqua G, Potter P, Valovirta E (2007) Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy 62:317–324
45. Malling HJ (2003) Criteria for clinical efficacy – readout and monitoring of clinical studies. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 94:119–123
46. Schaffer FM, Naples AR, Ebeling M, Hulsey TC, Garner LM (2015) The safety of self-administered allergen immunotherapy during the buildup and maintenance phases. Int Forum Allergy Rhinol 5:149–156
47. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G (2010) Speaking the same language: the world allergy organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol 125:569–574 574 e1-574 e7
48. Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox L, Durham SR, Larenas-Linnemann D, Ledford D, Pawankar R, Potter P, Rosario N, Wallace D, Lockey RF (2013) Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. J Allergy Clin Immunol 132:93–98
49. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI (2014) AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. J Allergy Clin Immunol Pract 2:161–167
50. Caminati M, Dama AR, Djuric I, Montagni M, Schiappoli M, Ridolo E, Senna G, Canonica GW (2015) Incidence and risk factors for subcutaneous immunotherapy anaphylaxis: the optimization of safety. Expert Rev Clin Immunol 11:233–245
51. Webber CM, Calabria CW (2010) Assessing the safety of subcutaneous immunotherapy dose adjustments. Ann Allergy Asthma Immunol 105:369–375
52. Tophof MA, Hermanns A, Adelt T, Eberle P, Gronke C, Friedichs F, Knecht R, Ernst M, Schöpfer H, Schwerk N et al (2018) Side effects during subcutaneous immunotherapy in children with allergic diseases. Pediatr Allergy Immunol 29:267–274
53. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, Ward D, Segal JB (2013) Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA 309:1278–1288
54. Bernstein DI, Epstein T (2011). Systemic reactions to subcutaneous allergen immunotherapy. Immunol Allergy Clin North Am 31:241-249, viii-ix
55. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S (2007) Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database of Systematic Reviews Issue 1. Art. N°.: CD001936. https://doi.org/10.1002/14651858.CD001936.pub2
56. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S (2011) Sublingual immunotherapy for treating allergic conjunctivitis. Cochrane Database Syst Rev 6(7):CD007685. https://doi.org/10.1002/14651858.CD007685.pub2
57. Abramson M, Puy R, Weiner J (2010) Injection allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews Issue 8. Art. No.: CD001186. https://doi.org/10.1002/14651858.CD001186.pub2
58. Normansell R, Kew KM, Bridgman AL (2015) Sublingual immunotherapy for asthma. Cochrane Database of Systematic Reviews Issue 8. Art. N°: CD011293. https://doi.org/10.1002/14651858.CD011293.pub2
59. Lin SY, Azar A, Suárez-Cuervo C, Diette GB, Brigham E, Rice J, Ramanathan M, Gayleard J, Robinson KA (2015) The role of immunotherapy in the treatment of asthma. Comparative effectiveness review n°. 196 (Prepared by the Johns Hopkins University Evidence-based Practice Center under contract n°. 290-2015-00006-I). AHRQ publication n°. 17(18)-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2018. https://doi.org/10.23970/AHRQEPCCER196
60. Rice JL, Diette GB, Suárez-Cuervo C, Brigham EP, Lin SY, Ramanathan M, Robinson KA, Azar A (2018) Allergen-specific immunotherapy in the treatment of pediatric asthma: a systematic review. Pediatrics 141(5):e20173833
61. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, Barton P, Dretzke J (2013) A systematic review and economic evaluation of subcutaneous and sublingual immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess 17(27). https://doi.org/10.3310/hta17270
62. Burbach GJ, Heinzerling LM, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, Bousquet-Rouanet L, Bousquet PJ, Bresciani M, Bruno A, Canonica GW, Darsow U, Demoly P, Durham S, Fokkens WJ, Giavi S, Gjomarkaj M, Gramiccioni C, Haahtela T, Kowalski ML, Magyar P, Muraközi G, Orosz M, Papadopoulos NG, Röhnelt C, Stingl G, Todo-Bom A, von Mutius E, Wiesner A, Wöhrl S, Zuberbier T (2009) GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. Allergy 64:1507–1515
63. Schiappoli M, Ridolo E, Senna G, Alesina R, Antonicelli L, Asero R, Costantino MT, Longo R, Musarra A, Nettis E, Crivellaro M, Savi E, Massolo A, Passalacqua G (2009) A prospective Italian

survey on the safety of subcutaneous immunotherapy for respiratory allergy. Clin Exp Allergy 39:1569–1574
64. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ (1996) Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 97:1207–1213
65. Barth C, Anero F, Pfaar O, Klimek L, Hormann K, Stuck BA (2010) Safety aspects of subcutaneous immunotherapy with multiple allergens - a retrospective analysis on polysensitized patients. Eur Arch Otorhinolaryngol 267:1873–1879

Affiliations

Miguel Tortajada-Girbés[1,2,3] · María Mesa del Castillo[4] · Helena Larramona[5] · José Manuel Lucas[6] · Montserrat Álvaro Lozano[7] · Ana Isabel Tabar[8] · Begoña Soler López[9] · Ana Martínez-Cañavate[10] · on behalf of the Immunotherapy Working Group of the Spanish Society of Pediatric Clinical Immunology and Allergology (SEICAP)

1 Paediatric Allergology and Pulmonology Unit, Dr. Peset University Hospital, Valencia, Spain

2 Fundación IVI, Valencia, Spain

3 Department of Pediatrics, Obstetrics and Gynecology, University of Valencia, Valencia, Spain

4 Paediatric Allergology and Neumology Unit, Hospital El Escorial, Madrid, Spain

5 Paediatric Allergology and Pulmonology Unit, Department of Paediatrics, University Autonoma of Barcelona, and Corporacio Sanitaria Parc Tauli, Hospital of Sabadell, Barcelona, Spain

6 Pediatric Allergy and Immunology Unit, Virgen Arrixaca Clinic Universitary Hospital, Murcia, Spain

7 Allergy and Clinical Immunology Section, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

8 Complejo Hospitalario de Navarra; IdiSNA, Navarra Institute for Health Research, Pamplona, Spain

9 Medical Department, E-C-BIO, S.L., c/ Rosa de Lima, 1, Edificio ALBA, Office 016, Las Rozas, 28230 Madrid, Spain

10 Paediatric Allergology and Neumology Unit, Complejo Hospitalario Universitario de Granada, Coordinator of the SEICAP Immunotherapy Working Group, Granada, Spain