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Compromising between European and US allergen immunotherapy schools: Discussions from GUIMIT, the Mexican immunotherapy guidelines

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ABSTRACT

Background: Allergen immunotherapy (AIT) has a longstanding history and still remains the only disease-changing treatment for allergic rhinitis and asthma. Over the years 2 different schools have developed their strategies: the United States (US) and the European. Allergen extracts available in these regions are adapted to local practice. In other parts of the world, extracts from both regions and local ones are commercialized, as in Mexico. Here, local experts developed a national AIT guideline (GUIMIT 2019) searching for compromises between both schools.

Methods: Using ADAPTE methodology for transculturizing guidelines and AGREE-II for evaluating guideline quality, GUIMIT selected 3 high-quality Main Reference Guidelines (MRGs): the European Academy of Allergy, Asthma and Immunology (EAACI) guideines, the S2k guideline of various German-speaking medical societies (2014), and the US Practice Parameters on Allergen Immunotherapy 2011. We formulated clinical questions and based responses on the fused evidence available in the MRGs, combined with local possibilities, patient's preference, and costs. We came across several issues on which the MRGs disagreed. These are presented here along with arguments of GUIMIT members to resolve them. GUIMIT (for a complete English version, see Supplementary data) concluded the following:

Results: Related to the diagnosis of IgE-mediated respiratory allergy, apart from skin prick testing complementary tests (challenges, *in vitro* testing and molecular such as species-specific allergens) might be useful in selected cases to inform AIT composition. AIT is indicated in allergic rhinitis and suggested in allergic asthma (once controlled) and IgE-mediated atopic dermatitis. Concerning the correct subcutaneous AIT dose for compounding vials according to the US school: dosing tables and formula are given; up to 4 non-related allergens can be mixed, refraining from mixing high with low protease extracts. When using European extracts: the manufacturer's indications should be followed; in multi-allergic patients 2 simultaneous injections can be given (100% consensus); mixing is discouraged. In Mexico only allergoid tablets are available; based on doses used in all sublingual immunotherapy (SLIT) publications referenced in MRGs, GUIMIT suggests a probable effective dose related to subcutaneous immunotherapy (SCIT) might be: 50–200% of the monthly SCIT dose given daily, maximum mixing 4 allergens. Also, a table with practical suggestions on non-evidence-existing issues, developed with a simplified Delphi method, is added. Finally, dissemination and implementation of guidelines is briefly discussed, explaining how we used online tools for this in Mexico.

Conclusions: Countries where European and American AIT extracts are available should adjust AIT according to which school is followed.

Keywords: Allergen immunotherapy, Guideline, Subcutaneous immunotherapy, Sublingual immunotherapy, Allergen extract

BACKGROUND

Allergen immunotherapy (AIT) in Mexico has been practiced since the pioneers of allergy started allergy departments The first department was founded in the Hospital General in Mexico City in 1938 by Mario Salazar Mallén. The Hospital General had its own laboratory where allergen extracts for skin testing and AIT were prepared. These first Mexican allergists, from the 1930s to the 1970s, received their allergy training in Europe (mainly France), followed by a second wave (1960–1980) of Mexican allergists trained in the United States (US). Concurrently, from the middle of the twentieth century onward, the allergy departments in the main cities of Mexico have had training programs in allergy (and clinical immunology), and nowadays several fellows opt for completing their education with post-graduate courses and exchange programs in the United States or Europe (ie, Spain, Germany). As such, historically and until today allergology in Mexico has been influenced by both the European and US schools.

Simultaneously, allergen extracts, available on the Mexican market originate from manufacturers from the United States, Europe, and local companies. Consequently, AIT is practiced partly according to the US method and partly according to the European method; it is not rare to find the 2 techniques being practiced in 1 and the same allergy office, selecting the most appropriate method according to the sensitization and allergy profile of the patient and his/her particular needs.

Mexican guidelines on AIT and their renovation

Since the end of the past century, the first Mexican consensus on AIT was published locally,[1] and in 2011 the first official Mexican Guidelines on allergy diagnosis and allergen immunotherapy were developed by a considerable group of national experts in the field.[2] As an attempt was made to follow the GRADE approach, classifying

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the quality of evidence article-per-article together with several other factors, the methodological rigor of these 2011 guidelines was considerable. In a 2017 review, applying the AGREE-II instrument[3] they still scored among the 3 highest ranking AIT guidelines.[4] However, by 2019 renovating the Mexican AIT guideline seemed mandatory, as new, high quality evidence was published in original articles and comprehensive systematic reviews, especially those of the European Academy of Allergy, Asthma and Immunology (EAACI), new AIT formulations were developed with some of them launched on the Mexican market, and some important chapters needed to be added.

Development and structure of GUIMIT 2019

The *Guía Mexicana de Inmunoterapia* (GUIMIT) 2019 was developed following the formal process of the ADAPTE approach[5] proposed by the Guideines International Network (GIN), in which few of the best-quality guidelines globally available on the subject[6] are fused and transculturized by local experts. For GUIMIT 2019 the 3 main reference guidelines (MRG) were the AIT guideline from the societies in the German-speaking countries,[7] the EAACI AIT guideline's, sections on allergic rhinoconjunctivitis,[8] venom immunotherapy,[9] and prevention[10] and the third update of the practice parameter on allergen immunotherapy from the USA,[11] see GUIMIT 2019 English version online (see Appendix A of this article). The EAACI guideline on AIT for asthma[12] had not yet been published at that moment. The authors of each chapter developed clinical questions following the Patient-Intervention-Comparator-Outcome (PICO) format and sought the replies in the MRG. In the source Table 1 the exact pages of the MRG with evidence for the replies were tabulated. Then, in source Table 2 the evidence was fused, and a proposed recommendation for GUIMIT 2019 was formulated (for links to all source documents available in ResearchGate, see addendum 1 GUIMIT 2019-online). For some chapters, guidance from the main reference guidelines was missing and some chapter-specific reference guidelines had to be added,[13-19] following the same selection strategy using AGREE-II to sort out the best ones available.

However, the main reference guidelines, some reflecting the European school[7,8,16] and some the US school,[11,15] did not agree on several issues as the practice of AIT in both schools differs. When this happened, a detailed analysis was made of the exact wording in each reference guideline and the source documents on which the guidelines' recommendations were based. These elements were then discussed by the guideline development group in the context of the Mexican reality and local possibilities to finally emit a strong or weak recommendation for GUIMIT 2019. We selected some of these clinical questions and the discussion points around them; they constitute the basis of the here presented document. Our intention is not to polarize between different views on AIT; on the contrary, one of the main objectives of the this manuscript is to explain the differences in recommendations between both schools, as AIT is practiced differently on both sides of the ocean, and to make clear that both are valid forms of AIT with the support of many decades of experience behind them. Thus, as a starter, we briefly present some historical perspectives of both schools, before we proceed with the clinical questions under discussion.

European and US schools of AIT: historical perspectives and first land-mark trials

The European school. After the first publication by Noon in St. Mary's Hospital, London, 1911 on the efficacy of AIT with a grass pollen (GP) extract in enhancing the threshold of a conjunctival challenge in GP allergic patients out-of-season, his colleague, Freeman, confirmed in a subsequent publication the actual reduction of patients' symptoms during the hay fever season.[20] Four decades later the first double-blind, placebo controlled (DBPC) AIT trial by Frankland and Augustin was conducted in 200 patients of the same hospital. Frankland clearly describes the placebo effect leading to a very good result in almost a third of his placebo-group patients. Even so, he was able to show a highly significant symptom reduction in both active groups as compared to placebo.[21] The correct sample calculation and the detailed description of randomization, blinding, and drop-outs make this study even today rated as moderately high

Clinical question (simplified wording)	Delphi rounds results of GUIMIT experts' recommendations
Allergenic extracts based on mixtures with homologous groups (i.e. tree mix, grass mix) can be used in order to make the skin test less invasive. • If they are positive, should AIT be prescribed with such mixtures?	No (33% suggest no and 31% recommend no)
• If they are positive, should the clinician repeat the skin test in order to break down allergens from positive mixtures, to define which allergens use in the AIT?	There is no consensus (28% recommend yes, 24% suggest yes, 31% suggest no)
In a patient with skin tests positive to 5 non-homologous pollens (= of different groups): Is it cost-effective to ask for molecular diagnosis to define the exact content of the proposed AIT?	Yes (37% recommended, 45% suggest)
In a patient with a high suspicion of house dust mite allergy by clinical history, but a negative SPT: is *in vitro* diagnosis with ImmunoCAP indicated?	Yes (30% recommended, 52% suggest)
Taking the precaution of keeping the effective maintenance dose and not mixing high with low proteases allergens: is SCIT with up to 4 allergens mixed in a vial effective and safe?	Yes (37% recommended, 45% suggest) (Dilution limits the number of allergens that can be added to the maintenance concentrate if a therapeutic dose is to be administered).
US AIT school: In a patient who does not experience clinical improvement by one year of SCIT: should the SCIT application be continued to see if it improves during its 2 nd year of treatment?	No (29% recommends no, 51% suggests no)
US AIT school: SCIT should be administered in a single vial with each of the allergens at a fractional dose (e.g. three allergens: each allergen one third of the usual dose).	No (100% suggests) 100% recommends including 100% of the therapeutic doses of each of the allergens included
European AIT school: Managing a patient allergic to 2 non-homologous allergens with AIT, • Should SCIT be administered as two injections (one for each of the allergens) simultaneously, with a 30 min post injection waiting period?	Yes (20% recommends yes, 30% suggests yes, 15% neutral)

• Should SCIT be administered in a single vial with each of the allergens at a fractional dose (e.g. three allergens: each allergen one third of the usual dose).	No (100% suggests no) 100% recommends including 100% of the therapeutic dose of each of the included allergens)
Taking the precaution of maintaining the maintenance dose and not mixing allergens with high and low proteases: is SLIT with up to 4 allergens mixed in one vial effective and safe?	Yes (37% recommended, 45% suggest)
In a patient who does not experience improvement after one year of SLIT: • Should SLIT be continued to see if the patient improves during the first part of his 2nd SLIT year? • Is it probable he/she shows improvement when switching to SCIT?	• No (29% recommends no, 51% suggests no) • Yes (11% recommends, 55% suggests)

Table 1. Good practice recommendations/suggestions from the GUIMIT task force group. *AIT = Allergen immunotherapy; SCIT = subcutaneous allergen immunotherapy; SLIT = sublingual allergen immunotherapy.*

scientific quality with low risk of bias.[22] Two decades later, extracts started to be standardized, and by the end of the 1980s many European extracts started to be alum-adsorbed, aiming to enhance immunogenicity, reduce allergenicity, and obtain a depot effect that would permit augmenting the dosing interval. A few dose-finding trails were conducted with these standardized alum-adsorbed subcutaneous AIT extracts: first very small ones for house dust mite (HDM),[23–25] then a large, high-quality trial for GP.[26] As for the duration of AIT, at the turn of the millennium Durham et al showed three years of subcutaneous AIT with GP were enough.[27] Since then, many more trials have been conducted with the sublingual route and some even in search of the preventive effect of AIT.[28]

The US school. The use of skin testing, as opposed to conjunctival testing from Noon and Freeman, and new allergen extraction techniques were first described by Cooke and Coca, respectively. Both discoveries accelerated the development of SCIT in the United States, which soon became a widespread practice. The first allergy clinic was founded by Cooke in New York. The first DBPC, dose-finding trial with an allergen mix was conducted by Johnstone and published with 4 years of treatment in 1961,[29] and with up to 14 years in 1968, showing still reduced asthma prevalence in the active group 1 year off-treatment.[30] Children with allergic asthma received AIT with a mix of all allergens they showed positivity to in skin testing, with 1 of 3 doses (1:10^{-7} v/v, 1:5000 or the highest tolerated dose) or with saline placebo from the time they came to the clinic until they turned 15 years of age. The very low dose group behaved as the placebo group, but for the other 2 active treatment groups there was a clear dose-related, statistically significant benefit in the sense of reduction, or even annulation, of asthma attacks and symptoms of exacerbation.[30] Though nowadays considered unethical, the blinding was perfect as no patients knew they were part of a trial. Thenceforth, the first dose-response efficacy for a single allergen (ragweed) delivered in an allergen mix was published by Lowell and Franklin in 1965.[31] They also showed the allergen specificity of AIT,[32] which was shortly thereafter confirmed by Norman. Then, in 1997, the multi-

allergen subcutaneous AIT in asthma trial was negative, probably due to poor allergen selection.[33] Even so, it caused a strong set-back for AIT in asthma until its final inclusion. Almost twenty years later, in the Global Initiative for Asthma (GINA)-algorithm (HDM sublingual AIT)[34] and in GINA 2020, both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are mentioned cautiously: " … potential benefits of SCIT/SLIT must be weighed against the risk … "[35]

In conclusion, from the start, the focus of European AIT has been on the treatment of hay-fever patients suffering from GP-allergy with grass pollen mono-AIT, first administered subcutaneously as depot extracts, followed by sublingual AIT with drops and more recently as sublingual tablets. In Europe, a couple of studies have focused on birch and other tree pollens. HDM AIT first received little attention in small trials (n < 30 patients). It was not until recently that HDM-sublingual AIT tablets have been studied in large trials mainly in patients with asthma.[36] All this is in contrast to the initial US trials almost all with mixes showing efficacy (with the exception of 1)[33] of the extract-mix when evaluated as a whole or when the efficacy of only 1 allergen within the mix was measured (ragweed).[32] As a result, US allergists prepare AIT in their office from concentrated stock vials that allow maintaining the correct concentration of each allergen even when mixed, while in Europe AIT is more a final product meant to be administered as such to the patient without manipulation. These 2 different schools of administering AIT persist today as reflected in the US practice parameters on immunotherapy,[11] as opposed to the EAACI AIT guidelines.[10,12,37] Mexican allergists have traditionally been influenced by both schools, and in their practice have tried to take the best ideas from both schools.

Clinical question and discussion I: Diagnosis of IgE-mediated respiratory allergy: skin prick testing and secondary allergy testing (challenges, *in vitro* and molecular).

The first step for effective AIT is the correct selection of the causal allergen(s) for each patient.

Box 1. Clinical questions (1.1.3, 1.1.8, 1.2.4, 1.2.5)*

	Response GUIMIT	Agreement**
As compared to tests to determine specific IgE *in vitro* in patients with suspected IgE-mediated allergic disease: *in vivo* SPT should be considered the first option to determine IgE sensitization and to guide AIT?	We recommend: yes. *In vitro* tests are complementary to SPT for most clinical scenarios (or first choice when SPTs are contraindicated)	77%
In selected patients with allergic rhinitis or conjunctivitis and/or asthma, in addition to SPT, do specific nasal/conjunctival/bronchial challenge tests (respectively) increase the diagnostic accuracy for allergen selection to guide AIT?	We suggest: yes, as complementary tests in tertiary health care units	100%
In patients with IgE-mediated allergy, both children and adults, could molecular diagnosis increase diagnostic accuracy and thereby improve the accuracy of its management?	We suggest: Yes, see text for indications	100%
In patients with IgE-mediated allergy, both children and adults: are there species-specific allergens for allergy diagnosis that might guide the formulation of AIT? Mites, trees, grass, weeds, molds, Hymenoptera, epithelia?	We suggest: Yes for all options	100%

** Numbers related to the questions in the original GUIMIT document, see online file.** Percentage agreement among all members of the guideline development group.SPT = skin prick testing, AIT = Allergen immunotherapy, IgE = immunoglobulin D*

Therefore, the first chapter in GUIMIT is dedicated to the diagnosis of IgE-mediated allergy by *in vivo* or *in vitro* testing. The latter has undergone important development over the past decades in Europe, while in the United States *in vitro* diagnosis is still not frequently used, and AIT is almost exclusively based on SPT results. Our main reference guidelines do not dwell on diagnosis. As such, here chapter-specific reference guidelines had to be selected, using AGREE-II to evaluate those with the highest quality.[6]

Skin prick testing (SPT) is still recommended as the prime diagnostic resource to establish the allergen selection for AIT, as until now no AIT trial has solely been based on *in vitro* diagnostic testing. However, GUIMIT experts have experienced polysensitization profiles in many of their patients, showing positivity for multiple allergens, not always of importance for the patient's symptoms. Simultaneously, we recognize the importance of restricting as much as possible the number of allergens to be mixed in AIT, and as the clinical history often does not allow to differentiate between sensitization and true allergy (see below), additional tests might be needed after SPT to define those allergens to be used for AIT. To this end GUIMIT suggests the use of provocation tests or *in vitro* testing. Although European colleagues have defined details for organ-specific provocation tests in valuable position papers, this kind of test is still seldom used in Mexico. Lately, *in vitro* testing is slowly gaining ground. Looking at and learning from our Spanish colleagues who also see many polysensitized patients,[38] Mexican allergists are progressively realizing that molecular diagnosis can help to differentiate between true allergy versus SPT-positivity due to cross-reactivity between related allergen families, or due to the presence of pan-allergens. In conclusion, GUIMIT stimulates the use of secondary allergen testing to reduce the number of allergens used in AIT as much as possible. A molecular allergen table can be found in the document with species-specific and cross-reacting allergen molecules.

Clinical question and discussion II: Can AIT be prescribed in asthma or atopic dermatitis?

Although not all MRGs completely agree on the details concerning AIT in asthmatic patients, evidence of its efficacy in allergic asthma is still growing. As such, GUIMIT recommends administering SCIT or SLIT in patients with mild or moderate controlled allergic asthma, because studies suggest it reduces the risk of exacerbations and nonspecific airway hyperresponsiveness. Moreover, GUIMIT suggests to consider AIT in severe but controlled allergic asthma, weighing risks against benefits, preferably using administration schedules with a higher safety profile and/or use of concomitant treatment such as omalizumab. Administering AIT even in patients with severe asthma, even though of high-risk, is a quite common practice, as demonstrated by a survey among members of the American Academy of Allergy Asthma and Immunology (AAAAI) where 56% commented they have experience with administering SCIT in patients with severe asthma.[39]

Clinical question and discussion III: What is the correct dosing for subcutaneous AIT?

As for atopic dermatitis, GUIMIT suggests AIT might be a treatment option in extrinsic IgE-mediated atopic dermatitis when there is a founded suspicion of clinically relevant allergen(s), especially HDM. Here, evidence from randomized clinical trials is starting to appear,[40] and clinical experience from GUIMIT members has been positive.

In Mexico allergen extract vials are prescribed and provided by the treating allergist. Various options of allergen extracts exist on the Mexican market, as registration rules are generally more flexible than in Europe.[41] Mexican allergists can buy concentrated extracts to prepare AIT: 1) directly imported by US manufacturers, 2) concentrated extracts originated from US allergen distributors, but accommodated by local Mexican manufacturers, and 3) locally produced concentrated extracts. Allergists can also buy allergens and allergoids as end-products from some European manufacturers licensed to sell in Mexico. As such, the Mexican AIT guidelines have to give guidance for both modalities of AIT. In GUIMIT the subcutaneous AIT chapter is divided into 2 parts: Chapter 4.2 related to practicing AIT according to the US school and Chapter 4.3 reflecting AIT practiced according to the European school.

Box 2. Clinical question (4.1.1, 4.3.4)*

	Response GUIMIT	Agreement**
Is the efficacy and safety of SQ AIT dependent on reaching a recommended therapeutic dose or – where appropriate – the maximum tolerated dose?	We recommend yes	100%
US school: The interval between doses of immunotherapy is 15–30 days?	We recommend: YES	85%
European school: The interval between doses of immunotherapy is 4–6 weeks?	We recommend: YES	85%

** Numbers related to the questions in the original GUIMIT document, see online file.** Percentage agreement among all members of the guideline development group.AIT = Allergen immunotherapy, SQ = standard quality*

All main reference guidelines concur on the globally agreed upon fact that the efficacy of AIT is heavily dose dependent. Based on the US practice parameters for AIT, GUIMIT experts have created user-friendly dosing tables with calculations on how to prepare AIT, taking the prescribed amount of the concentrated vials to prepare the patient's vial to obtain a correct projected maintenance dose. This can only be accomplished diluting concentrated vials and never using European extracts. In chapter 4.2 GUIMIT also gives further preparation rules, such as not mixing extracts with low and high protease content, to avoid allergen degradation. Further, GUIMIT suggests not mixing more than 4 non-homologous allergens, taken into account cross-reactivity, see below. As AIT prepared from concentrated vials has natural allergens and no depot adjuvants, the administration frequency recommended is once to twice monthly.

Both reference guidelines developed in Europe do not go into detail in relation to allergen dose, as the European allergen manufacturers produce end-products that should be administered as such to the patients without manipulation. Some European allergen extracts available in Mexico are depot preparations of allergoids (Inmunotek®), that can be used for rush or cluster schedules and that allow administration every 4–6 weeks during maintenance. The pre-seasonal or pre-co-seasonal schedules used in certain parts of Europe are hardly useful in Mexico, where generally pollination is almost year-round.

The subcutaneous AIT chapter ends with generalized recommendations on how to enhance AIT safety. This starts with the identification of the correct vial and dose: GUIMIT recommends having 2 patient-identifiers on each vial and vial identification by 2 persons, the personnel administering and the patient. Also, there is a pre-administration questionnaire integrated into the manuscript, and taking vital signs, including a peak-flow measurement, is suggested. In case of detecting any risk factor present at the moment of AIT administration the dose can be reduced (especially when using native allergens, a suggested dose-adjustment table is incorporated) or postponed.

Clinical question and discussion IV: What is the correct dosing for sublingual AIT?

Similarly, for SLIT there are several different products available in Mexico. Some European manufacturers are licensed to sell their liquid products (ALK-Abelló, IPI-ASAC, Inmunotek), and there is 1 option for allergoid SLIT tablets (Lofarma®). Then, there is the option to prepare liquid SLIT products out of concentrated allergen vials, just as in SCIT. Internationally, this has been more controversial, as some experts argue that a clearly defined maintenance dose for tablet SLIT does not exist, and each product has to show its own efficacy and safety, because in tablet SLIT these do not depend only on the amount of allergen but also the vehicle.[42]

However, in Mexico two issues arise when using European end-products for SLIT. Firstly, SLIT with well-studied tablets is not available in Mexico. Secondly, more than 80% of Mexican patients are poly-sensitized,[43] and when a careful clinical

Box 3. Clinical questions (5.1.1–5.1.4)*

	Response GUIMIT	Agreement**
For products, specifically sold for SLIT: Is there a probable effective maintenance dose?	We recommend: yes	100%
What is this probable effective SLIT maintenance dose?	We suggest 5-50mcg major allergen daily	100%
For liquid SLIT products, prepared from vials with concentrate allergenic extract: Is there a probable effective maintenance dose, relative to the SCIT dose?	We suggest: yes	100%
For natural allergen extracts: what will this daily maintenance dose be, in relation to SCIT?	We suggest 50–200% of the monthly dose of SCIT	100%

** Number related to the question in the original GUIMIT document, see online file.** Percentage agreement among all members of the guideline development group.SCIT = subcutaneous allergen immunotherapy; SLIT = sublingual allergen immunotherapy.*

history is taken, almost all of them seem to be truly dual- and most even poly-allergic. Hence, mono-allergen SLIT shall only partly cover their problem. European-product-based SLIT is costly and using 2 or more European SLIT products simultaneously might be unaffordable for many patients. In preparing liquid SLIT some allergens could be mixed together. Also, some US investigators have shown that effective liquid grass-pollen and HDM SLIT can be made from concentrated US allergen vials.[44,45] Thus, following previous SLIT-dosing discussions, GUIMIT experts studied SLIT doses used in high-quality clinical trials integrated in recently conducted EAACI systematic reviews and metanalyses.[28,46,47] These are presented in a table in the GUIMIT document. Thus, it became clear the majority of effective SLIT trials used a daily dose of 50–200% of the related monthly SCIT dose. As pauci-allergen liquid SLIT is actually practiced by many Mexican allergists, GUIMIT gives some dosing suggestions for this kind of practice, based on the above-mentioned analyses. Since the Amar trial showed 10-allergen SLIT is ineffective,[44] GUIMIT suggests not to mix more than 4 non-homologous allergens, see below.

Clinical question and discussion V: Mono- versus multi-allergen AIT in multi-allergic patients

AIT is allergen-specific,[32,48,49] and Wagenmann et al elegantly demonstrated in dual birch-grass allergic patients, giving mono-allergen AIT to half of them with birch and to half of them with grass pollen that AIT only improves symptoms when exposed to the allergen included in the AIT, but not when exposed to the non-targeted allergen.[49,50]

Pollination in large parts of our country continues all year long and pollen seasons heavily overlap, making it difficult to define the causal pollen allergen in a poly-sensitized patient, based on anamnesis. Also, humidity in the whole of Mexico is high, facilitating HDM growth and HDM sensitization in Mexican allergic rhinitis patients varies between 45% and 89%.[43] Finally, national customs favor close contact with pets. As a result the vast majority of allergic patients has perennial symptoms—be it some with seasonal exacerbations[51]—caused by poly-allergy. In such a scenario, mono-allergen AIT might be insufficient for most.

Our MRGs disagree between one another on the use of allergen mixes in SCIT, with the European guidelines only allowing mixing under specific circumstances and preferentially only between homologous allergens while in the United States mixing allergens is common practice. With the progression of knowledge on the exact composition of allergens we now know that even in mono-allergen AIT the patient is exposed to multiple major allergen molecules, especially in HDM AIT.[52,53] Mixing a few non-homologous allergens together would only partly augment the number of allergenic proteins. As for now, the maximum number of allergenic proteins a patient can react to is not known, but it is very probable pauci-allergen AIT is within the acceptable range. As

Box 4. Clinical questions (4.a.4a-d, 4.3.6, 4.3.7)*

	Response GUIMIT	Agreement**
US school (SCIT or SLIT)		
Is it advisable to mix taxonomically unrelated allergens?	We recommend: YES CAVE: protease content, see below	100%
How many allergens could be mixed in one vial?	We recommend: consider dilutional effect, see below	100%
Which allergens to mix and which not to mix	We recommend: Do not mix allergens with high protease content with low-protease content allergens	100%
Can standardized allergens be mixed with non-standardized ones?	We recommend: YES	100%
European school		
Can mixtures be made with unrelated allergens?	We suggest: No	100%
How many allergens could be mixed in one vial?	We recommend: No, eventually 2	100%

** Numbers related to the questions in the original GUIMIT document, see online file.** Percentage agreement among all members of the guideline development group.SCIT = subcutaneous allergen immunotherapy; SLIT = sublingual allergen immunotherapy.*

already discussed under historical perspectives, almost all initial SCIT trials with mixes in the United States showed efficacy.

The same holds true for allergen mixes for SLIT with Japanese[19] guidelines favoring this option, the World Allergy Organization guidelines[18] stating it is safe, and the European guidelines opposing. Evidence from clinical trials shows dual allergen liquid SLIT is effective and safe,[45,54,55] but 10-allergen liquid SLIT is not effective[44].

Thus, compromising between the different schools, GUIMIT experts suggest for AIT prepared from concentrated vials–per the US school–a maximum of 4 non-homologous allergens can be mixed in one vial, both for SCIT and for SLIT. To reduce the allergens administered as much as possible, cross-reactivity should be taken into account when selecting the AIT-allergens and secondary IgE-mediated allergy tests are suggested (see discussion point).

Based on the European reference guidelines, GUIMIT suggests for the treatment of multi-allergic patients with AIT using European extracts to select the 2 most important allergens and to administer them in 2 separate shots during each AIT session. A Delphi consensus among the GUIMIT experts defined that both shots can be given simultaneously, based on long-term experience with such practice among Mexican allergists.

Practical issues related to AIT on which no evidence exists

While developing GUIMIT, experts came across several practical points of importance in AIT daily practice, but without any clear evidence. These clinical questions were submitted to a simplified Delphi round, to obtain the anonymous, unbiased opinion of the 52 GUIMIT experts. Their responses led to a consensus as to whether the proposed actions should be recommended, suggested, or recommended or suggested against. The results are presented in GUIMIT as "suggestions for good clinical practice" at the end of each chapter's evidence table. Some are presented here in Table 1.

GUIMIT further included chapters on the mechanisms of AIT, Hymenoptera allergy, allergen extracts, safety and adverse event treatment with AIT, and the future of AIT. These are not presented here but can be reviewed in the online GUIMIT file.

Dissemination and implementation of European, US, and Mexican guidelines on AIT

Guidelines generally have good dissemination strategies, as they are developed in close cooperation with specialty-specific organizations; thus ample visibility is given during annual congresses, courses, and in specialty-specific journals. The EAACI guideline especially has been disseminated extensively, as well as strategies for its implementation,[56] also paying attention to the availability of high quality allergen extracts in Europe.[57] Even so, reluctancy for change is inherent to the human being. Thus, an important focus group for guidelines should be the young fellows. For GUIMIT we used the following dissemination strategies.

1. Pre-launch: An online survey (SurveyMonkey) was conducted among all members of both the Colegio Mexicano de Inmunología Clínica y Alergia (CMICA) and the Colegio Mexicano de Pediatras Especialistas in Inmunología Clínica y Alergia (COMPEDIA). This serves both as expectation and pre-promotion of what is going to come, and it shows the guideline development group which issues to focus on for possible improvement. One survey has already been published.[58]
2. The GUIMIT launch had a major place during both national allergy congresses in 2019. During the CMICA congress, the guideline was distributed physically among all attendees.
3. GUIMIT was published as a supplement freely downloadable in *Revista Alergia México*, a PubMed indexed journal in Spanish. Since its launch, 3654 downloads have been registered, suggesting diffusion beyond Mexican boarders. GUIMIT served as an important support to colleagues in South American countries in negotiating with regulatory authorities in their countries (personal communication).
4. In the fall, COMPEDIA, held Sunday schools: one dedicated to GUIMIT with ample discussion among live and online attendees.
5. Chapter-chairs were recorded presenting core points of their chapters. This has just been made freely accessible on CMICA TV.
6. All program directors were invited to participate in the development group of GUIMIT. The guideline is part of the curriculum they teach to their students (in several places together with the North American and European guidelines).
7. Finally, and very importantly: *Consejo Mexicano de Inmunología Clínica y Alergia*, the body that certifies allergists in Mexico, recognizes GUIMIT, and several board exam questions are related to it. GUIMIT is a reference document for the students as could be confirmed during their final exam (personal communication).

However, evidence shows the main difficulty guidelines still face is the gap between their content and their application in daily patient care. For the US guideline, a survey was conducted asking members of the AAAAI and the American College of Allergy Asthma and Immunology (ACAAI) about their dosing: only 57%–65% of the standardized extract maintenance dosing fell within the dose range, recommended in the Practice Parameters.[59] In another survey, 58% (629/1085) commented to have given AIT to severe asthmatic patients, even though this is a contraindication according to the US guideline,[39] only to give some examples.

DISCUSSION

We presented here how Mexican allergists have developed their AIT guidelines, constructing a document following the ADAPTE approach based on the evidence from high-quality AIT guidelines from several regions, mainly Europe and the United States, with sometimes conflicting strategies. We showed how European and US views were fused into a harmonized presentation, adopting some new techniques more favored in Europe (challenge testing, *in vitro* and molecular diagnosis), but also more flexible forms of preparing AIT as done in the United States. Then we demonstrated how we formulated some consensus suggestions of good clinical practice on issues with lacking evidence.

Something similar is done yearly by colleagues from Europe in workshops discussing the "Future of the Allergists and Specific Immunotherapy" (FASIT),

now published in their seventh year.[60] Enhancing comprehension between forms of allergen extracts and AIT as practiced in Europe and North America seemed also to be the objective of Mahler et al in a recent CME article,[61] though their presentation might have been better balanced.[62]

The mono-multi allergen AIT discussion shall continue to be an ever-returning issue, as European colleagues are correct that no recent well-designed trial exists showing multi-allergen mixes work. Most probably no such trial shall ever see the light again, due to financial and ethical reasons. On the other hand, US colleagues are correct claiming that mixes of allergens have shown efficacy in daily practice for decades in their country. In that sense the recommendations given by a panel of experts on AIT clinical trials, addressing crucial issues like this are of high value.[63] One of the fields they addressed was the design of a study to compare the effectiveness and safety of aeroallergen AIT by using one or a few allergens, versus all or most allergens to which a patient is sensitized. As it seems rather difficult to give such a trial a double-blind placebo controlled design, for trials in poly-allergic patients, we agree with Bousquet et al there is a need for real-world evidence of AIT efficacy that might be obtained using the MASK-air App.[64]

AIT is such a complex treatment, because allergen extracts of different composition interact with the immune system of the allergic patient that in turn is molded individually by the subject's genetic background and past immunologic history. As a result, patients respond each in their own way to the doses administered during the course of an AIT treatment, some tolerating higher doses from the start, others needing slower up-dosing especially with SCIT, but also with SLIT. For some the projected maintenance dose is just right, while for others the maximum tolerated dose can be less than a quarter of that even though their symptoms are well-controlled. As a consequence, for some clinician-researchers, the idea of making AIT a pharmaceutical treatment and the concept of "one tablet fits all" can be debatable for AIT. They consider there is still room for the art of medicine in the correct management of AIT. In the end, all agree on one point: AIT is a prime example of personalized medicine.

Abbreviations

AGREE-II: Appraisal of Guidelines for Research & Evaluation Instrument; AIT: Allergen immunotherapy; CMICA: Colegio Mexicano de Inmunología Clínica y Alergia; COMPEDIA: Colegio Mexicano de Pediatras Especialistas in Inmunología Clínica y Alergia; EAACI: European Academy of Allergy; Asthma and Immunology: DBPC; double-blind: placebo controlled; FASIT: Future of the Allergists and Specific Immunotherapy; GIN: Guidelines International Network; GINA: Global Initiative for Asthma; GP: grass pollen; GRADE: grading of recommendations assessment development and evaluation; GUIMIT: by its Spanish initials of *Guía Mexicana de Inmunoterapia*; Ig: immunoglobulin; HDM: house dust mite; MRG: main reference guidelines; PICO: Patient-Intervention-Comparator-Outcome; SCIT: subcutaneous allergen immunotherapy; SLIT: sublingual allergen immunotherapy; US: United States of North America

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As there are no patients involved: does not apply.

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Availability of data and materials
We translated the complete Mexican Guidelines on Immunotherapy, GUIMIT, into English. This is submitted as online repository file. In the Addendum of this online file -last 2 pages- the reader can find DOI's that link to the original GUIMIT tables (most English version) in which source data for GUIMIT and the article's discussions can be found: clinical questions per chapter and the replies found in Main Reference Guidelines (EAACI, German, US, Japanese, depending on the subject). All these data are freely available and we managed to translate almost all into English.

Supporting information legends
eFILE: Full text, English version of GUIMIT 2019, Mexican Guideline on Immunotherapy. Guideline on the diagnosis of IgE-mediated allergic disease and immunotherapy following the ADAPTE approach.

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Abstract

Introduction: in Mexico allergists practice allergen immunotherapy (AIT) and immunotherapy with Hymenoptera venom (VIT) partially according to the European school, partially according to the American standards. In addition, both types of extracts (European and American) are commercially available. Moreover, for an adequate AIT/VIT an opportune diagnosis is crucial. Therefore, a national immunotherapy guideline, broad-based, up-to-date, that covers these topics and that explains the mechanisms of immunotherapy and future expectations (GUIMIT 2019) is needed.
Methods: with the participation of multiple groups of allergists at national level, including those from the training centers, the guideline document was developed according to the ADAPTE methodology, including the selection of main reference guidelines among the best guidelines available worldwide (according to the AGREE-II evaluation) , whose evidence forms the scientific basis for this document.
Results: GUIMIT emanates strong or weak (= suggestions) recommendations about practical issues directly related to *in vivo* or *in vitro* diagnosis of IgE mediated allergic diseases and the preparation and application of AIT / VIT and its adverse effects. It closes with a vision of AIT modalities for the future. All the statements were voted until consensus was found with > 80% approval.
Conclusion: with a wide and diverse group of AIT / VIT specialists, consensus was reached that might improve immunotherapy practice in Mexico.

Keywords: skin prick test, intradermal skin test, *in vitro* diagnosis of allergy, molecular allergy diagnosis, immunotherapy with allergens, subcutaneous immunotherapy, sublingual immunotherapy, immunotherapy with Hymenoptera venom, anaphylaxis, adrenaline, allergenic extract

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Introduction

Allergen or Hymenoptera venom immunotherapy (AIT and VIT) remain the only causative treatment for many of the allergic disorders to date. That's why it's one of the allergist's main tools. In 2011 the last national Mexican guideline focusing on this topic was published.(1) Since there have been several new developments in the field of both, subcutaneous (SCIT), as well as in sublingual immunotherapy (SLIT), but there has also been some further development in new administration routes.(2, 3) In addition, in our country new allergen extract suppliers have been able to register their products, thus increasing the options of standardized and high quality allergen extracts in Mexico, including new forms of allergens as will be reviewed in Chapters 4 and 8. Likewise, for the diagnostics of IgE-mediated pathologies there are now several new options in our country, specifically molecular allergy and the basophil activation test (BAT). Finally, in the 2011 guideline there were several aspects related to AIT and VIT that had not been included. That's why summer 2018 a group of allergists, experts in immunotherapy, met to start the development of the Update of the *Guía Mexicana de Inmunoterapia* (GUIMIT 2019), which final document is presented here. The GUIMIT 2019 document shall be valid for at least 3 and no more than 5 years, depending on new developments in the area. For the update, it can be expected that a methodology, similar to the current one, shall be employed.

Objectives of GUIMIT 2019, summary of the SCOPE document

The objective of GUIMIT 2019 is to establish recommendations and suggestions based on evidence-based medicine (MBE), following the grade system methodology and guidance of the ADAPTE document for the transculturization of guidelines, in order to homogenize both the diagnostic and immunotherapy part of the allergist's practice: when to order tests for the detection of immunoglobulin E (IgE) mediated allergy, *in vitro* and *in vivo,* how to perform skin testing and how to interpret, as well as everything related to the prescription, preparation and administration of allergen specific (AIT) and Hymenoptera venom (VIT) immunotherapy at up-to-date standards and of the best possible quality, within the national context. In the SCOPE document the objectives for GUIMIT 2019 were explicitly stated. The document shall cover AIT for allergic rhinitis, allergic conjunctivitis, allergic asthma, atopic dermatitis and latex allergy. GUIMIT shall not address food allergy. The aim is to enhance the quality of the allergy services, both in diagnostic and therapeutic procedures related to immunotherapy, to hereby improve the management of allergic patients of all ages and at all levels of health care still further. Thus, GUIMIT is directed to allergists practicing in hospitals and in private practice, as well as allergy fellows practicing in allergy training programs throughout the country. In the development process of GUIMIT 2019 the core group tried to unify criteria among all participating groups including allergists from both National allergy Colleges, experts from private practice and public health and health insurance hospitals, as well as representatives of all allergy training programs (see below). They were all involved in the development of the guideline right from the beginning, to facilitate the final endorsement of its content by all.

Several issues, considered of importance for the correct management of AIT and VIT, lack evidence. These were formulated as clinical statements and sent out just before the launch of GUIMIT to all members of both national allergy colleges, *Colegio Mexicano de Alergia e Inmunologia clínica* (CMICA) and *Colegio Mexicano de Pediatras Especialistas en Inmunologia clinica y alergia* (COMPEDIA), to obtain a broader consensus on these

aspects of AIT/VIT, but simultaneously to also create expectation of the guideline's launch and increase its visibility.
It is clear that this document can serve as guidance to informing clinical decisions, but at no time is it intended to replace the free decision-making of the physician in-charge.

Methodology

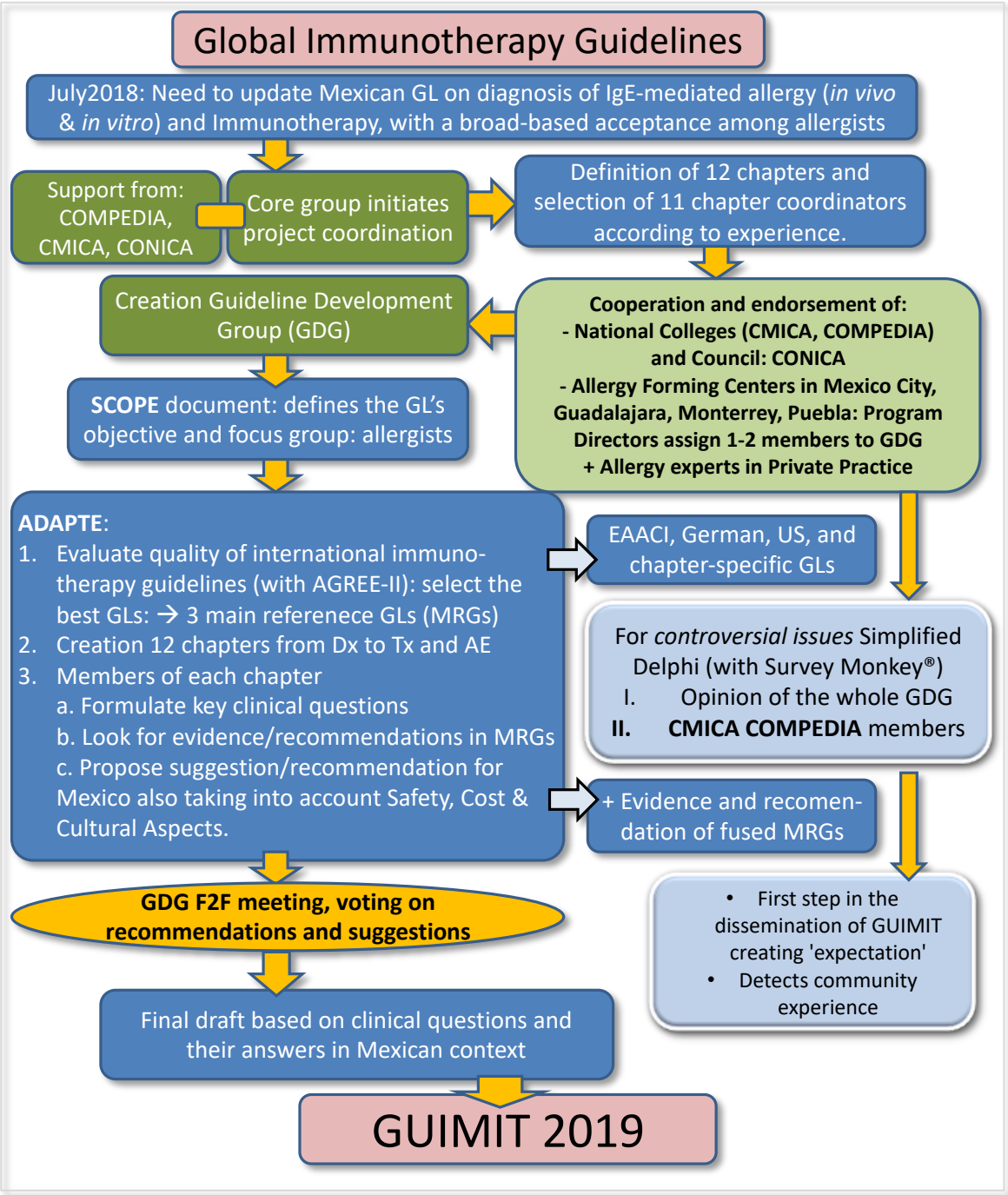
Guideline Development Group (GDG)

In the first step of the development of GUIMIT, the three main coordinators (DLL, JLP, NRP) defined the 10 chapters to be developed, after which one coordinator was assigned for each chapter, see figure A1. The two National Colleges of the specialty, CMICA and COMPEDIA), as well as the Mexican Board of Certification in Immunology and Allergy (CONICA) and all the Centers with an allergy training program in our country, were invited to collaborate, asking the College's Presidents and the Allergy Training Program Directors to assign one of their staff as a member of the guideline development group (GDG). In addition, each chapter coordinator was invited to select a few further collaborators. As such, the GDG includes allergists from all regions of the country, the public sector and the private sector. Some GDG members have been involved with the development of previous national guidelines and several core-group members have developed specific methodological skills related to the guideline development process (DLL, JALP, BRN, NRP).

ADAPTE and AGREE-II Methodology to select the Main Reference Guidelines (MRGs)

For the development of GUIMIT 2019 it was decided to follow the ADAPTE methodology, See Figure A1 . The first step in this methodology is to develop the guideline's objectives document, the *SCOPE* document. As soon as the objectives of the guideline are laid out in the *SCOPE* document, a literature search was conducted. However, as our objective was to transculturize high-quality international AIT guidelines, instead of focusing on original articles, here the search focused on guidelines that address the topics expressed in *SCOPE*. The next step was the quality assessment of the guidelines applying AGREE-II, the tool proposed by methodology experts from the McMaster University, Ontario, Canada to assess guideline quality.(4)
The tool qualifies 23 elements of clinical guidelines, grouped in the 6 domains of AGREE-II, related to the content of the guideline, the authors involved, the rigor of the methodology, its presentation, the declaration of conflict of interest and editorial independence, among others.
Each elements is graded from 1 to 7 on an ordinal Likert scale. The score of the elements is averaged per domain and then the score of the domains is averaged to obtain the total score of the guideline.(4) Therefor, AGREE-II is a recognized tool that allows the identification of the best guidelines worldwide, but also those guidelines most adaptable to the local reality. The thus selected guidelines will serve as the **main reference guidelines** (MRGs). Once the MRGs are selected the next step in the guideline development process is to formulate key clinical questions, based on the needs to be covered with the guideline (*SCOPE*) and the information found in the MRGs. Afterwards the MRGs are reviewed in search for replies to the questions. The pre-final step is to merge the evidence and level of recommendation of the MRGs per key clinical question to finally issue a local recommendation or suggestion, in this case for Mexico, taking also into account the cost and safety of the alternatives and the opportunities and obstacles in our country.

Figure A1



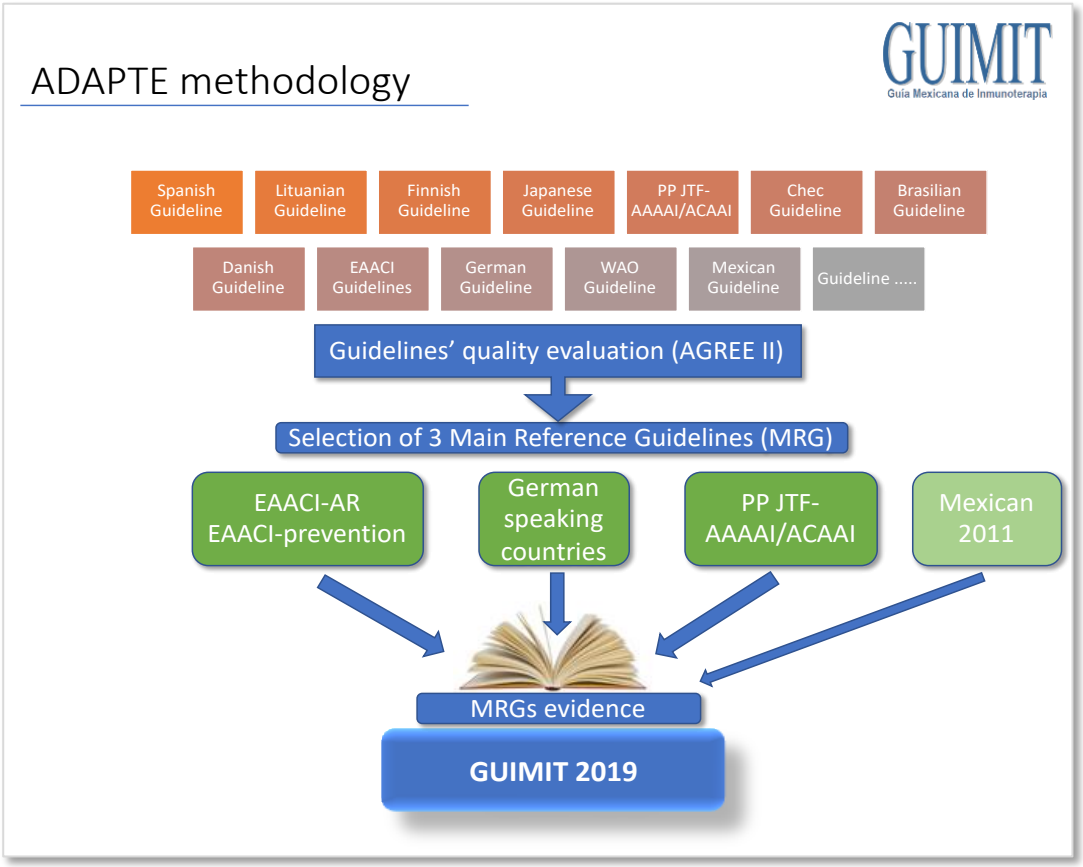
AE = adverse event; CMICA = *Colegio Mexicano de Inmunología Clínica y Alergia*; COMPEDIA = *Colegio Mexicano de Pediatras Especializados en Inmunología y Alergia*; CONICA = *Consejo Nacional de Inmunología Clínica y Alergia*; Dx = diagnosis; GDG = guideline development group; GL = guideline; GUIMIT = *Guía Mexicana de Inmunoterapia*; MRG = main reference guideline; Tx = treatment; US = United States of America

GUIMIT Methodology

This methodology was followed for GUIMIT, see figure A2. MEDLINE and Embase were searched from January 2008 to July 2018, using logical combinations of the following terms: [allerg* AND immunotherapy OR desensitization] AND [guideline OR practice parameter OR position paper OR statement OR consensus]. The collection of

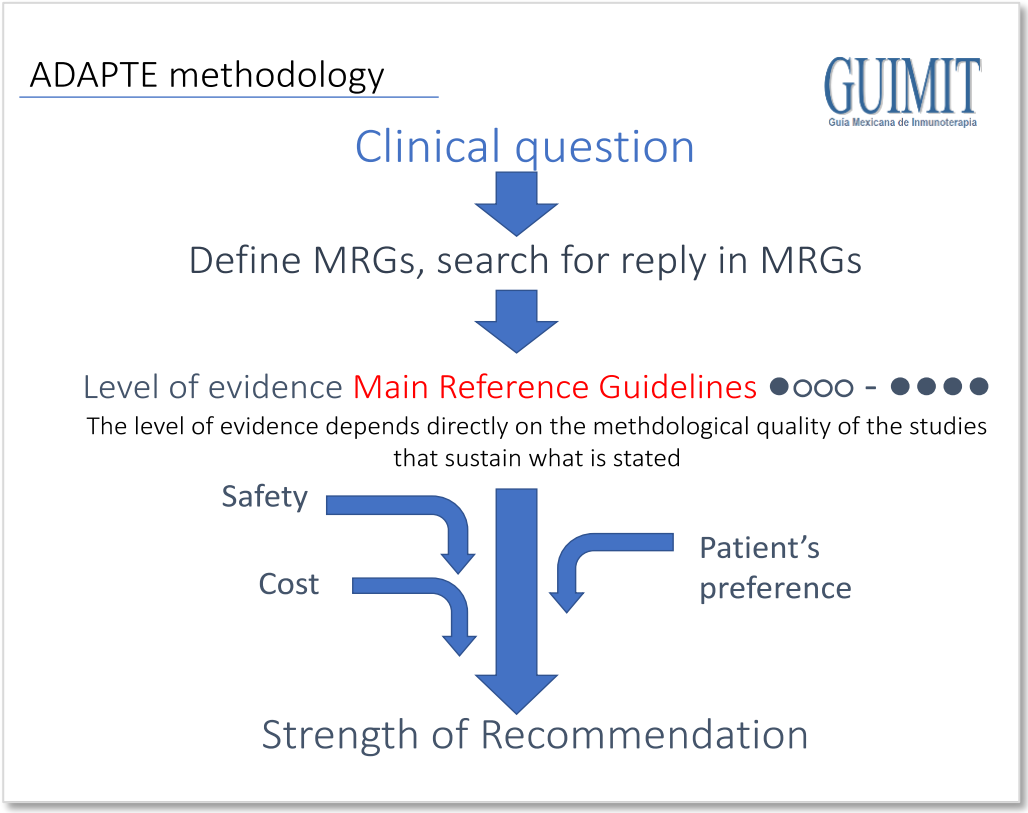
immunotherapy guidelines was cross-checked and completed with those identified in an active search by team members who contacted local and regional AIT experts to also identify articles published in the gray literature. All national, regional or global documents with guidelines for AIT were selected.

Figure A2. Selection of Main Reference Guidelines (MRGs) for GUIMIT



A publication was found in which all 1980-2016 immunotherapy guidelines were already qualified with AGREE-II.(5) GUIMIT members completed these evaluations with paired AGREE-II assessments by at least two core-group members of the guidelines published from 2016 till January 2019. So the best three guidelines were selected as MRGs: the guideline of the European Academy of Allergy and Clinical Immunology, rhinitis section (EAACI-RA, AGREE-II: 6.5/7)(6)and prevention section (EAACI-prevent, AGREE-II: 6.2/7),(7) the AIT guideline of German speaking countries (DGAKI, AGREE-II 6.0/7)(8) and the Joint Task Force of the American Academy of Allergy, Asthma and Immunology/ American College of Allergy, Asthma and Clinical Immunology Practice Parameters on AIT (JTF-AAAAI/ACAAI, AGREE-II: 4.6/7)(9)and surely we also based our document on the previous Mexican Immunotherapy Guideline from 2011 (AGREE-II 5.1/7).(1) For some chapters the information was not addressed in the MRGs. In these cases the chapter members selected their own specific MRGs following the same procedure with AGREE-II assessment as described above; this is manifested at the beginning of certain chapters (1.1, 1.2, 5 and 6).

Figure A3: From clinical question to recommendation or suggestion for Mexico.



MRGs = main reference guidelines

For each of the key clinical questions the level of evidence and recommendation was sought in the MRGs (Figure A3), tabulating the found results in large tables stating exactly on which page of the MRG the reply is mentioned. As such, Evidence Tables I were constructed for each of the chapters. Evidence Tables I are available online with the following links, see Addendum I. A link to Evidence Tables II, that contain the fusion of the evidence and fusion of the recommendations of the MRGs, as well as the level of recommendation that the GUIMIT experts proposed to issue for Mexico can be found in the same Addendum. During a two-day face-to-face meeting of all GDG members, end April 2019, all GUIMIT's recommendations/suggestions were voted on and the percentage of agreement was noted.

In a final step, the text of the guideline's manuscript was integrated in its final form, based largely on the texts of Evidence Tables II. The small text-boxes in the right-hand page margin, beside the texts, contain GUIMIT's recommendation or suggestion, the percentage of agreement among the GDG, as well as the fused evidence and recommendation of the MRGs.

Indirect level of evidence

When the main reference guideline didn't issue any level of evidence or recommendation on a certain aspect that we considered important, but at the same time the MRGs did refer to some studies that could contribute to create the level of evidence, GUIMIT experts went back to the source documents of the MRGs and issued the level of evidence and eventually the level of recommendation, using the scale of evidence levels of the Center for Evidence Based Medicine (CEBM), see Table A1.

Table A1

Recommen-dation	Evidence level		
A	Ia		SR (with homogeneity*) of RCTs.
A	Ib		Individual RCT (with narrow Confidence Interval"¡)
A	Ic		Efficacy demonstrated by clinical practice
B	or extrapolations from I	IIa	SR (with homogeneity*) of cohort studies
		IIb	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
		IIc	"Outcomes" Research; Ecological studies
B	or extrapolations from I	IIIa	SR (with homogeneity*) of case-control studies
		IIIb	Individual Case-Control Study
C	or extrapolations from II or III	IV	Case-series (and poor quality cohort and case-control studies§§)
D	or inconsistencies	V	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

RCT - randomized clinical trials; SR - Systematic Reviews;
* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
For a more accurate explanation of the other footnotes, see the original document.
Original version: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

Good practice points

There are details in all chapters that GUIMIT members consider important, but are not found in the MRGs nor in articles referenced in them. One example are very recent publications (as they were not yet referenced in the MRGs) or unpublished experience from local doctors. These are presented as 'good practice points', and have to be taken as such, without the strength of supporting evidence as opposed to the rest of the text where the quality of supporting evidence is clearly stated in the right-hand text margin.

Discussion points without solid evidence: community experience as modified Delphi

The core-group developing GUIMIT realized that there are details related to the topic of this guideline that are not found in the MRGs, nor in its referenced articles, or in more recent publications, but that were judged of importance for the elaboration of a good diagnostic process or a good AIT/VIT. Or, in some cases these are points of controversy and disagreement with what was recommended in the MRGs, because of the different reality in which medicine is practiced in Mexico. These are often details of clinical management. For these points it was decided to seek community experience among GUIMIT experts, through an anonymous electronic survey in a kind of Delphi process, but with one single round ('Simplified Delphi') of 30 clinical questions. Its results are also presented in some chapters; their full content shall be published elsewhere.

Results

Below are the chapters of the content of the guideline. Each chapter is structured as follows: it starts with a summary of the key clinical questions, their answer and the percentage of agreement between the GDG, the two most important questions submitted to the simplified Delphi process with their answer and the most outstanding ‘good practice points’ per the chapter. The other ones can be found in the text.

Chapter 1. Diagnostic tests

1.1. *In vivo* diagnostic tests (Table 1.1)

Table 1.1. Summary of *in vivo* diagnostic tests		
GUIMIT experts recommend or suggest according to evidence in the main reference guidelines *		Agreement
1.1.1 In patients with suspected allergic disease (rhinitis or allergic conjunctivitis, allergic asthma, venom allergy, some cases of atopic dermatitis, allergy to food or medication): are in vivo skin tests recommended to identify immediate, IgE mediated hypersensitivity?	Recommendation: Yes, as well as in some cases of acute urticaria associated with food allergy	100%
1.1.2 In children (including infants) and adults (including >65 years) with suspected IgE-mediated allergic disease, do SPTs confer greater accuracy, reproducibility, comfort and security than IDST?	Recommendation: Yes. SPTs are less sensitive, but more specific than ID tests; ID tests should not be done in small children	100%
1.1.3 As compared to tests to determine specific IgE in vitro in patients with suspected IgE-mediated allergic disease, in vivo SPT should be considered the first option to determine IgE sensitization and to guide AIT?	Recommendation: Yes. In vitro tests are complementary to SPT for most clinical scenarios (or first choice when SPT is contraindicated)	77%
1.1.4 In patients with suspected IgE-mediated allergic disease, is it adequate to have a specific panel of allergens to perform skin tests, in accordance with the geographical relevance of the region where the patient lives to increase diagnostic accuracy?	Recommendation: Yes	100%
1.1.5 In patients who are planning to perform skin tests for allergy, is it recommended to avoid or withdraw certain medications in order to avoid a probable pharmacological suppressive effect of the skin reaction? And, if so, for how long should medication be withheld before the procedure?	Recommendation: Yes**	100%
1.1.6 In patients who are planning to perform SPT, is it recommended to meet clinical criteria to procedure preparation in order to increase the safety profile of the procedure?	Recommendation: Yes***	100%
1.1.7 In patients who underwent skin tests, is it recommended to have a uniform criterion to prepare the test and interpret and record its results to avoid inadequate elucidations of the result and to, eventually, properly guide AIT?	Recommendation: Yes. Consider technique employed, manufacturer, extract concentration, device used and report results in millimeters	100%
1.1.8 In selected patients with allergic rhinitis or conjunctivitis and/or asthma, in addition to SPT, do specific nasal/ conjunctival/ bronchial challenge tests (respectively) increase the diagnostic accuracy for allergen selection to guide AIT?	Suggestion: Yes, as complementary tests in tertiary health care units	100%
1.1.9 In patients who are already using AIT, is it recommended to repeat skin tests as markers of treatment efficacy or in order to decide the duration of treatment?	Recommendation: No	100%

Consensus based on clinical experience of GUIMIT experts (Delphi simplified) ‡: evidence 1c	
1.1.10 Allergenic extracts based on mixtures with homologous groups (i.e. tree mix, pasture mix) can be used in order to make the skin test less invasive. If they are positive, should the AIT be prescribed with such mixtures?	No (33% suggest no and 31% recommend no)
1.1.11 Allergenic extracts based on mixtures with homologous groups (i.e. tree mix, pasture mix) can be used in order to make the skin test less invasive. If they are positive, should the clinician repeat the skin test in order to break down allergens from positive mixtures, to define which allergens use in the AIT?	There is no consensus (28% recommend yes, 24% suggests yes, 31% suggests no)

* The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1.
** But it depends on the medication (Table 1.3).
*** See table 1.2. ‡ Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM.
IgE = immunoglobulin E, SPT = skin prick test (by epicutaneous puncture), IDST= intradermal skin test, AIT = allergen immunotherapy.

1.1.1. Introduction

The effective treatment of allergic diseases relies on establishing an accurate and adequate diagnosis. Allergen immunotherapy (AIT) is indicated in patients with immunoglobulin E (IgE) mediated allergy as a cause of their symptoms and is currently the only causal treatment. The allergist shall select the allergens to be included in the AIT, guided by the proper identification of the likely causal allergen(s) based on the medical history, physical examination and confirmation of sensitization demonstrating the presence of allergen-specific IgE. For over 150 years, skin testing has been the preferred diagnostic procedure for most cases where the allergic component is suspected in order to assess IgE-mediated sensitization, even when some aspects could cause variability in the results, such as the device used, the type of extracts, skin color and administration technique. In this chapter, we review the clinical utility of skin tests, as well as some aspects that could increase their predictive value, not only to confirm allergic sensitization, but as a guide to the choice of the antiallergic treatment.

1.1.2. Selection of specific reference guidelines for this chapter

Considering the fact that diagnostic allergy tests were not included as a particular subject of study in any of the three official GUIMIT reference guidelines focused on AIT, in order to elaborate this chapter it was necessary to extract the evidence from three additional clinical guidelines (exclusively for this chapter), so a systematic research was conducted in the literature regarding the guidelines on *in vivo* diagnostic allergy testing, published over the past 12 years (because contemporary guidelines on this subject are scarce). The quality of these guidelines was further evaluated through the AGREE-II instrument, which was done in duplicate by two independent evaluators. Thus, the best qualified guidelines were the document of the European standards for allergy skin testing by the European Academy of Allergy and Clinical Immunology / Global Allergy and Asthma European Network of 2013, (10) the skin test guideline by the German Society of Allergology and Immunology Clinic of 2011(11) and the update of the United States' practice parameters published by the American Academy of Allergy, Asthma and Immunology / American College of Allergy,

Asthma and Clinical Immunology in 2008. (12) These guidelines became the reference for this chapter.

1.1.3. Skin tests as a tool to identify an immediate hypersensitivity

Skin prick tests (SPT) are a minimally invasive method with quickly available results and high reproducibility (when performed by trained personnel) to confirm IgE sensitization *in vivo*. SPTs are considered to have approximately 90% sensitivity and specificity and to have good correlation with nasal and bronchial challenge tests. During this procedure a small amount of allergen extract is applied on the skin of the forearms or back of the patient. Either through a percutaneous puncture or scratch (prick) with a fine needle that goes through the drop to the superficial part of the skin, deposition of a small amount of allergenic extract can be achieved, just below the epidermis. If there are sensitized mast cells with specific IgE on their surface, allergen recognition will cause them to release histamine, resulting in a rapid skin response with erythema followed by formation of a wheal, which is measured between 15 to 20 minutes after the skin penetration.

GUIMIT recommends SPT as the first line diagnostic tool to identify IgE-mediated sensitization in patients with rhinoconjunctivitis and allergic asthma, food allergy with a suspected type I reaction and in atopic dermatitis, associated with sensitization to food or aeroallergens and suggests SPT in the diagnostic work-up of suspected drug hypersensitivity reactions. SPTs can also be used in some cases of urticaria or acute angioedema (especially when associated with food sensitivity), although its usefulness in such cases is still controversial (European guidelines do not recommend them, but the American guideline does).

SPT indicated in ARC, asthma, AD, venom and food allergy
We recommend: Yes, 100%
Evidence: III, III, IV, III, IIb
Recommendation: C, C, D, C, B

Other *in vivo* tests useful to identify reactions with mechanisms other than IgE (for example, patch tests) can be used complementary as part of the diagnostic work-up, but they are not useful in deciding which allergens to use in AIT.

Drug allergy
We suggest Yes, 100%
Evidence: III
Recommendation C

1.1.4. *In vivo* skin tests: SPT versus intradermal skin test

GUIMIT recommends the SPTs over the intradermal skin tests (IDST). The IDST are applied by intracutaneous injection using 0.5 or 1.0 mL syringes applying a small amount of a highly diluted extract intradermally. They are more invasive, uncomfortable and painful, even though they use far more diluted allergen extracts compared to those used in the SPT (100 to 1000-fold more diluted than SPT, in smaller volumes, from 0.02 to 0.05 mL); although they are considered very sensitive, they are much less specific than the SPT and can frequently cause false-positive results and irritating reactions due to skin trauma. IDSTs as a diagnostic tool do not perform as well as SPTs, which decreases their potential utility as a tool to guide AIT. In addition, they require greater technical skill in their administration and have a higher risk of adverse reactions, including anaphylaxis and death. According to US data, between 2000 and 2008, six fatal outcomes were reported with IDSTs.

In favor of SPT versus IDST; We recommend: Yes, 100%
Evidence: IIa
Recommendation: C

IDSTs are read between 10 and 15 minutes after their completion. An advantage of the IDST is that they allow to evaluate late skin reactions, which appear six to 12 hours after administration, and on occasions are visible up to 24 hours later.

Despite the belief that skin reactivity could be lower in infants and in the elderly, GUIMIT recommends SPT in specific cases already could be performed from one month of age onward. On the other hand, IDSTs should be avoided in young children. GUIMIT suggests that, when possible, IDSTs should be limited to cases of insect venom hypersensitivity (in the case of previous negative SPT), reactions to some medications (especially to evaluate late reactions [> 24 hours]) and in adult patients with strong clinical suspicion of certain allergens and negative SPT.

SPT in adults> 65 years and in children <2 years
We recommend: Yes, 100%
Evidence: III, III
Recommendation: C, C

ID tests in adults> 65 years
We suggest: Yes, 100%
ID tests in children <2 years
We recommend: No, 100%
Evidence: IV, IV
Recommendation: D, / D

1.1.5. Skin tests versus *in vitro* specific IgE tests

Although the *in vitro* determination of allergen specific IgE in serum in its different variants is considered a useful and innovative diagnostic tool (see section 1.2), GUIMIT recommends that SPT (when performed by trained personnel, using appropriate techniques and extracts) to be considered as the first option to confirm IgE sensitization and to guide AIT. *In vitro* tests can be performed as a complement to SPT and are very useful in some specific cases (such as oral allergy syndrome or in search of causes of anaphylaxis, or high clinical suspicion of allergy with negative SPT) and are the first diagnostic option when there is a contraindication for SPT (Table 1.2). Among the advantages of SPT versus *in vitro* testing we can mention its lower cost, the immediacy and ease in its interpretation after the administration of the allergen on the skin (minutes versus days or weeks), its many options to test unusual allergens (some medications, fresh fruits and vegetables that are not available for *in vitro* testing, which usually are restricted to the available panel).

In favor of SPT versus in vitro tests
We recommend: Yes, 77%
Evidence: IIb
Recommendation: C

The concordance between specific *in vitro* IgE tests and SPT is variable, but it is estimated between 70 and 90%, although in general the serum tests are less specific than the SPT. In addition, in cases with very high serum IgE, *in vitro* tests often detect false positive IgE-specific reactions not relevant to the patient's clinical picture, which may cause diagnostic inaccuracy. To date, there are no comparative studies that have shown efficacy of AIT based solely on the results of *in vitro* tests. (13)

Table 1.2. Contraindications for allergy skin tests *in vivo* (by epicutaneous and/or intradermal puncture)

Active skin condition in the area to be tested (active eczema, dermographism, urticaria, etc.)
Poor or very weakened general condition
Recent or current consumption of medication that could affect the test results (Table 1.3)
Unstable or uncontrolled asthma
Suspicion of high risk of severe systemic reaction or having a history of recent anaphylaxis (in the last 4 to 6 weeks); if this is the case, it is recommended to avoid skin testing because a false-negative result can occur
Treatment with beta blockers, which constitute a relative contraindication to skin tests, considering their potential to pharmacodynamically affect the response to epinephrine, if required
Pregnancy (as a relative contraindication), considering the remote possibility of inducing a systemic allergic reaction that could induce uterine contractions or requiring epinephrine (which can cause constriction of the umbilical artery)

1.1.6. Allergens to be included in skin tests

In recent years, mapping studies of positive skin tests in different areas of Mexico have been carried out that allow us to have an understanding of the most prevalent aeroallergens, and it has been clearly demonstrated that house dust mite (*Dermatophagoides pteronyssinus*) is the most prevalent allergen in the country (>50%), independent from the geographical region.(14) Pollen exposure and sensitization patterns in Mexican patients are different from those reported in Europe and North America, so the panels for SPT suggested in GUIMIT's reference guidelines could not be totally suitable for Mexico. A multicentre study with blinded SPTs from 628 Mexican patients showed that, in addition to mites (56%), grass (especially *Cynodon dactylon*, 26%) and tree pollens (mainly *Fraxinus americana, Quercus ilex* and *Prosopis* sp, 22 to 24%) are the most frequent positive aeroallergens, with some variations depending on the specific geographical area. Among other allergens, cat (22%) and cockroach mixtures (*Blatella germanica* and *Periplaneta americana* [21%]) are the most prevalent ones. Positivity for weed pollen and fungi is less common (between 6 to 14%).(15)

Consequently, GUIMIT recommends that the SPT panel in Mexico should always include *Dermatophagoides* sp., grass pollens (mainly *Cynodon dactylon*), trees (including *Fraxinus americana, Quercus ilex* and *Prosopis* sp.), and other allergens (i.e. cat, dog and cockroach), pollens of weeds and intramural fungi (i.e. *Aspergillus fumigatus and/*or *Alternaria alternata*), and that the rest of the panel meets the criteria of the allergist, considering the region where the patient lives, restricting allergens with little regional presence and considering cross reactivity.

Good clinical practice: 100%

It is not possible to indicate how many allergens the SPT panel should include. However, based on data from a pan-European study that showed that with a panel of seven allergens a positive PCP was found in 35% of the cases and that adding more allergens the percentage only increased 1 to 2%,.(16) GUIMIT states that it is not necessary to test a very large number of allergens in the SPT and suggests that a standard panel in Mexico should include a maximum of 40 allergens.

Good clinical practice: 100%
Evidence 2a

The use of mixtures of extracts with homologous allergens (mixtures of various grasses, weeds, etc.) for SPT can be helpful for screening purposes, but they also can induce false-negative results. In these cases, especially for mixtures with three or more allergens, GUIMIT suggests to perform further tests with individual allergens (in cases with suggestive medical history) as a better indicator to guide AIT. Also, it is not recommended for AIT to be prepared based on results with such mixtures.

Good clinical practice: 100%

1.1.7. Medication withdrawal/avoiding prior to SPT

Taking into account the pharmacological suppressive effect of the cutaneous reaction and to increase the reliability of the test, GUIMIT recommends to withdraw and avoid some medications before performing SPT (table 1.3).

We recommend: Yes, 100%.
Evidence: IIb
Recommendation: C

Table 1.3 Effect of some common medications on the result of an allergy skin test and the recommended avoidance time

Medication	**Example**	**Action suggested or recommended by GUIMIT (level of evidence, grade of recommendation)**	**Avoidance time prior to the test**
First generation H1 antihistamines	Chlorpheniramine, diphenhydramine, hydroxyzine, meclizine and others	Recommendation: Avoid/withdraw (1c, B)	(~7 days)
Second generation H1 antihistamines	Fexofenadine, loratadine / desloratadine cetirizine / levocetirizine and others	Recommendation: Avoid/withdraw (1c,B)	(~7 days)*
Antidepressants with antihistamine effect	Tricyclic antidepressants (imipramine, amitriptyline, doxepin and others)	Recommendation: Avoid/withdraw (1c,B)	(~7 days)
H2 antihistamines	Ranitidine and others	Suggestion: Avoid/withdraw (2b,C)	(~1 day)
Leukotriene receptor antagonists	Montelukast, zafirlukast and others	Recommendation: Not to avoid/withdraw (1b,B)	Does not interfere
Systemic corticosteroids (<10 days)	Prednisolone or equivalent, <50 mg/day (adults) or <1 mg/kg (children)	Recommendation: Not to avoid/withdraw (2b,B)	Does not interfere
	Prednisolone or equivalent, >50 mg/day (adults) or >1 mg/kg (children)	Suggestion: Avoid/withdraw (2b,C)	(~3 days)**
Systemic cortico-steroids (>10 days)	Prednisolone or equivalent, minimum dose 10 mg/day	Suggestion: Avoid/withdraw (3,C)	(1 to 3 weeks)***
Topical (cutaneous) corticosteroids	Any potency (hydrocortisone, clobetasone, mometasone, betamethasone, i.e.)	Recommendation: Avoid/withdraw (1b,B)	(~7 days)
Topical (nasal and inhaled) corticosteroids, ophthalmic H1 antihistamines	Mometasone, budesonide, fluticasone, budesonide, olopatadine, ophthalmic azelastine and others	Recommendation: Not to avoid/withdraw (2b,B)	Does not interfere
Local anesthetics	Lidocaine/prilocaine combination	Suggestion: Not to avoid/withdraw‡ (2b,C)	Does not interfere
Topical calcineurin inhibitors	Tacrolimus, pimecrolimus	Recommendation: Avoid/withdraw (1c,B)	(~7 days)

* Ketotifen and astemizole are exceptions. It is recommended to suspend them ~30 days before the procedure.
** Consumption of systemic corticosteroids for up to 10 days prior the skin testing has very little potential to affect the results, and is only suggested to be discontinued (low evidence) if the daily dose is ≥ 50 mg (≥ 1 mg/kg in children) of Prednisolone (or equivalent).

*** Low evidence. GUIMIT suggests that they can be suspended considering the dose, duration of the treatment and the underlying disease, at the discretion of the allergist.
‡ Some local anesthetics, such as the lidocaine / prilocaine combination, although they possibly have the potential to delay the onset of erythema, apparently do not affect the wheal formation, so GUIMIT suggests not to avoid/withdraw them.

1.1.8. Preparation for skin testing

Trained staff and emergency team, 30min waiting time after SPT
We recommend: Yes, 100%.
Evidence: III
Recommendation: C

SPTs are generally safe and only rarely systemic allergic reactions can occur (i.e. rhinorrhea and, rarely, anaphylaxis); on the other hand, some fatal outcome reports have been reported with IDSTs (see section 1.1.4). Therefore, GUIMIT recommends in favour of having a staff with trained doctors and emergency equipment at the site where skin tests are performed. Serious reactions are usually immediate or start early on, so GUIMIT recommends to instruct the patient to wait at least 30 minutes in the health facility after tests. The risk increases when skin tests are performed for latex, drug or food allergies, and is much smaller with aeroallergen extracts.

Monitoring objective signs prior to SPT
We recommend: Yes 100%.
Evidence: IV
Recommendation: D

To perform a SPT, the allergic disease must be clinically controlled (for example, asthma without current symptoms). GUIMIT recommends using objective measures prior to the procedure to establish the degree of control of the allergic condition and as a baseline value in case of presenting a systemic reaction during or after skin testing. These measurements could include (but are not limited to) pulse oximetry, blood pressure and, in asthma, spirometry or peak expiratory flow. If there is a history of anaphylactic shock, GUIMIT suggests not to perform IDSTs; but if it is mandatory to carry them out, it is suggested to put up an IV line for vascular access prior to the procedure, although there is no solid data regarding its real utility. Eventually, the IDST could be done with gradual titration (starting with more diluted extracts). An increased level of serum tryptase is considered a risk factor for anaphylaxis.

Good clinical practice: 100%

Good clinical practice: 100%

In case of insect venom hypersensitivity, GUIMIT suggests delaying skin tests at least four to six weeks after the event, and even repeat it at intervals of three to six months, as there may be an early false-negative reaction. The GUIMIT working group also considers it important to highlight that patients in active treatment with beta blockers may be at higher risk in case of an anaphylactic reaction because of reduced response to epinephrine. (17)

Good clinical practice: 100%
Evidence: III

The stability and expiration date of allergenic extracts should be respected, and storage at a temperature of 2 to 8°C is recommended to maintain their stability.

Some ideal minimum requirements of the office where allergy skin testing is carried out are listed in chapter 7.

Good clinical practice: 100%

For preventive, legal-medical purposes GUIMIT recommends always obtaining written informed consent by the patient (or her/his parents if the patient is a minor), in compliance with the current regulations (see chapter 7).

1.1.9. Administration technique, interpretation and recording of results

Proficient staff and uniform criteria for SPT results registering & interpreting
We recommend: Yes, 100%, Evidence: IIb
Recommendation: C

The results of skin tests may vary depending on the administration technique, the skill of staff, the device used, the quality of allergenic extracts and the way that the results are recorded and interpreted. In order to achieve results with consistency and reliability, it is imperative that the staff person who administers the tests is properly trained and monitored by the allergy specialist, and preferably has passed a proficiency test (see chapter 7). A particular aspect in Mexico, evidenced in a comparative study, is that different allergenic extracts for SPTs used in the country showed great variation in their protein concentration,

due to the heterogeneous origin of the products and poor quality control in some manufacturers. GUIMIT suggests, whenever possible, using extracts with high stability, a uniform concentration and good quality control. (18) While different devices can be used for SPTs, GUIMIT experts recommend against the use of devices that produce a wheal of 3 mm or more in the negative control -or interpret their results with caution- given the high risk of false positive results. It is preferable to use a special device with a single metal tip (length 1 mm), given the lower trauma and better reproducibility compared to SPTs performed with devices that cause bleeding.

Good clinical practice: 100%
Evidence: IIb

We recommend: Yes, 100%
Evidence: III
Recommendation: C

There are also multi-tests (multi-tip devices) that allow several determinations simultaneously within one single administration. The choice of the device for SPTs depends on its availability, ease of use, safety, comfort for the patient, cost and technician's preference or experience.(19) The results of the SPT are read within 15 to 20 minutes, measuring the average size of the wheal and flare and reporting them in millimeters.

Every SPT must include a negative (usually 50% glycerin or saline solution with 4% phenol) and positive (e.g. 0.1% histamine phosphate) controls. Positive control is mandatory to avoid false-negative tests and is particularly useful as a reference when a wheal is not produced by any of the allergenic extracts. To consider a positive result, the major diameter of the SPT wheal produced by the allergenic extract should exceed the negative control wheal by 3 mm. The larger the skin reactions in the SPT, the greater the probability such allergen has clinical relevance. However, it is not possible to predict the severity of an allergic reaction based on the results of the SPT. The formation of pseudopods is always an indicator of a positive reaction.

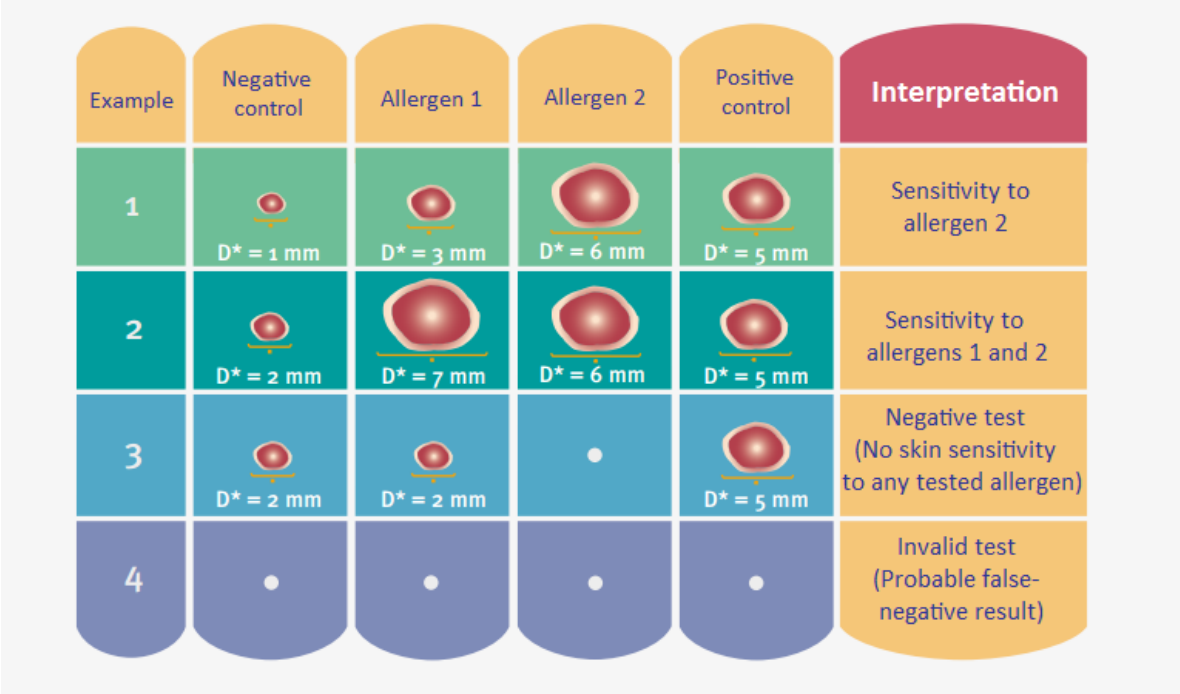


Figure 1.1. Recommended way to record the result of skin tests (four examples are shown). The result is obtained either by measuring the largest diameter of the wheal in millimeters, or by calculating the average diameter with the formula D + d / 2 (the mean value of the longest (D) and midpoint orthogonal (d) diameter of the wheal).
* D = longest diameter.
Source: GUIMIT 2011.(1)

The SPT is considered negative when no allergen extract, but the positive control, is capable of producing a wheal that exceeds the major diameter of the negative control for at least 3 mm. The test shall not be considered valid when neither the allergen extracts nor the positive control generates a wheal (Figure 1.1).
Another alternative method is to graduate the reactions into "crosses" (from 0 to 4+), although this method is less precise and too subjective.
It is important to point out that the lack of skin reactivity does not always mean that allergy is ruled out; if there is a reasonable diagnostic doubt, other complementary diagnostic methods could be indicated, without forgetting the premise that the clinical criteria will always rule above all diagnostic interpretations.

1.1.10. Provocation tests and other diagnostic techniques in respiratory allergy, complementary to skin testing

Some challenge tests with aeroallergens can increase the accuracy of the diagnosis with the purpose of guiding AIT, either to identify sensitization when specific skin or IgE tests are negative while the medical history is strongly suggestive, or to distinguish which allergen is relevant and which is not. In addition, such tests allow to investigate “new” potential allergens, monitor the effectiveness of the treatment and document occupational sensitivity. Nasal and conjunctival challenge tests are considered the gold standard to establish clinical sensitivity, and have shown good correlation with SPTs, helping to establish their degree of sensitivity and specificity.
However, there is a lack of clinical AIT trials that measure the change in response to specific nasal or bronchial challenges as a primary efficacy variable.
Conjunctival challenge tests are usually performed when there is suspicion of localized eye allergy, but in some cases, they can also be useful to investigate nasal allergy. The conjunctival challenge evaluates symptoms of itching or eye irritation by using objective measurements, including tear volume, the amount of mucus and bulbar or palpebral erythema. The nasal challenge tests are interpreted with subjective measurements (symptoms) and objective measurements of nasal airway resistance, number of sneezing and the measurement of inflammatory mediators in nasal secretions. The specific bronchial challenges (with allergens) provide an estimate of the clinical sensitivity of the lower airway.
GUIMIT recommends that respiratory challenge tests shall be performed by highly trained personnel in tertiary health care centers only.
Other complementary tests to evaluate airway inflammation (i.e., exhaled nitric oxide or condensed breath analysis) and the analysis of certain fluids (i.e., from nasal or bronchioalveolar aspirates) can help define phenotypes or predict severity, but they are not useful for guiding AIT. Similarly, challenge tests for food or occupational allergy have diagnostic value, but they are of little help in defining allergens for AIT.

As complement to SPT in tertiary care:
Nasal, conjunctival, bronchial challenge
We suggest: Yes, 100%
Evidence: IIa, IIa, III
Recommendation: B, B, C

1.1.11. Skin tests as markers of AIT efficacy

There is no evidence that a reduction in the size of the wheal in the SPT could be considered as a reliable marker of desensitization at the individual level. Furthermore, it has even been suggested that repeated use of in vivo tests could have the potential to induce new sensitizations.(20) Therefore, GUIMIT recommends against performing repeated skin tests during the process of AIT for the sole purpose of monitoring the

response to treatment or as a criterion to continue or eventually stop AIT, since this decision is taken considering firstly the clinical evolution of the patient. A possible exception is the AIT for insect venom, where it is actually suggested to repeat the skin tests every 3 to five years.

GUIMIT only suggests the repetition of skin testing in cases of clinical suspicion of new sensitization (i.e. when addressing a change in the type of exposure that causes symptoms), moving to a different region or country, or if the patient decides to change her/his allergist with previous skin tests done more than three years ago or with an incomplete report. A complete SPT report must contain the names of the allergens tested, the concentration of the extracts, the manufacturer, the technique and the device used, and the result must be reported in millimeters, in addition to the result of the negative and positive controls.

Good clinical practice: 100%

Chapter 1.2: IgE-mediated allergy diagnosis with *in vitro* studies

Table 1.4

SUMMARY Chapter 1.2: *In vitro* diagnosis		
GUIMIT experts recommend/suggest, taking into account evidence in MRG*		**Agreement**
1B.1 In patients with suspected allergy to aeroallergens, foods and Hymenoptera venom: Are there *in vitro* methods to identify an IgE-mediated hypersensitivity response? - Allergy to aeroallergen - Allergy to foods - Allergy to insect venom	 We recommend Yes We recommend Yes We recommend Yes	 100% 100% 100%
1B.2 In patients, both children and adults, with IgE-mediated allergy, which method is best suited for *in vitro* diagnosis? - ImmunoCAP - Immulite - RAST	 We recommend Yes We recommend Yes We recommend No.	100%
1B.3 In patients with IgE-mediated allergy, both children and adults: Is the basophil activation test (BAT) indicated for *ex vivo* diagnosis in patients with suspected allergic disease?	We suggest: Yes	100%
1B.4 In patients with IgE-mediated allergy, both children and adults, could molecular diagnosis increase diagnostic accuracy and thereby improve the accuracy of its management?	We suggest: Yes, see text for indications	100%
1B.5 In patients with IgE-mediated allergy, both children and adults: are there species-specific allergens for allergy diagnosis that might guide the formulation of AIT? Mites, trees, grass, weeds, molds, hymenoptera, epithelia?	We suggest: Yes for all options	100%
1B.6 In patients with IgE-mediated allergy, both children and adults, if there is no species-specific allergen involved: is positivity to only panallergens, an indication for AIT?	We suggest no	100%
Common clinical experience of GUIMIT experts (Simplified Delphi) ‡: evidence 1c		
In a patient with skin tests positive to 5 non-homologous pollens (= of different groups): Is it cost-effective to ask for		

molecular diagnosis to define the exact content of the proposed AIT?	Yes (37% recommended, 45% suggest)	
In a patient with a high suspicion of house dust mite allergy by clinical history, but a negative SPT: is *in vitro* diagnosis with ImmunoCAP indicated?	Yes (30% recommended, 52% suggest)	
Good practice points		
In patients with a clinical history highly compatible with allergy: Which screening method could be used for diagnosing allergy: - The total IgE? - Phadiatop?	 We suggest No We suggest Yes	 100% 100%
Can the results of different *in vitro* testing systems (InmunoCAP, Immulite, RAST, etc.) be compared?	We recommend: no	100%
Does the Basophil Activation Test (BAT) have advantages over nasal/bronchial challenge testing?.	We suggest: Yes Uses patient's basophiles, but without exposing him to invasive challenges.	100%

* Main reference guidelines. (2)The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for certain action (source tables 2). Links to these tables are found in Annex 1.
‡ Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM.
IgE = immunoglobulin E, SPT = skin prick test (by epicutaneous puncture), basophil activation test (BAT), AIT = allergen immunotherapy.

1.2.1 Introduction

Although the SPTs still maintain their place, historically recognized for over 100 years, as the first choice test for the diagnosis of IgE mediated allergic diseases(13), for decades specialists have sought alternative diagnostic methods. Initially due to the fact that SPT cannot be performed on all patients (see table 1.2) and because it is a diagnostic procedure not intended for non-allergists. However, with the evolution of knowledge and discoveries in this field, it has also become clear recently that the SPT not always reflects the absolute reality of the most important allergen(s) for the allergic patient. Therefore, in vitro tests, that first emerged as alternative tests for patients who could not be skin-tested, are becoming increasingly important in the comprehensive diagnostic approach of the allergic patient.(21)

In polysensitized patients, the SPT could identify the presence of reactivity to pan-allergens. Molecular diagnosis could can identify the specific allergen responsible for the allergy for those polysensitized patient and will help to select the specific allergen for AIT; Similarly, molecular diagnosis could be useful in patients with a positive history of allergy to Hymenoptera venom, but with ambiguous results in skin tests.

Another test that allows basophil activation to be measured without having to challenge the patient is the BAT (basophil activation test), which stimulates basophils ex vivo. In this section dedicated to in vitro tests, we will first review those tests using complete allergens and then the molecular diagnosis, patient selection and interpretation, including of those with pan-allergens, will be addressed.

1.2.2 Selection of specific guidelines for the chapter on *in-vitro* diagnosis

For the topic on diagnosis of IgE-mediated allergy with *in vitro* tests it was necessary to search for new reference guidelines, since this subject has not been addressed in the originally established reference-guidelines for GUIMIT. The researched literature focused on guidelines in the context of the diagnosis of Allergy, particularly on *in vitro* diagnosis and molecular diagnosis. Only three recent guidelines were found; these were evaluated with the AGREE-II methodology by two independent experts. The European Academy of Allergy and Clinical Immunology guideline on *in vitro* diagnosis obtained 2.7/7 points (39%),(22) the National Institute of Allergy and Infectious Diseases guideline 2.4/7 points (34%),(23) the one from the World Allergy Organization 3.58/7 (51%)(24) and the Hoffmann-BAT guideline 2.48/7 points (35%).(25) Although all obtained a relatively low score, the two selected main reference guidelines for this in vitro diagnostic chapter were the first two and the latter was specifically used for the basophil activation test.

We recommend 100%
ImmunoCAP: Yes
Immulite: Yes
Evidence: 2b
Recommendation: C

1.2.3 Existing methods for *in vitro* testing to identify an IgE-mediated hypersensitivity reaction

The use of serological tests for the detection of specific IgE is suggested in patients with suspected allergy to aeroallergens, food and insect venom.

We recommend yes 100%. Evidence: 2b
Recommendation: C

Total serum IgE was initially used as a screening method for the evaluation of the presence of IgE-mediated allergic disease. However, its positive and negative predictive values are low, because it can be high in non-allergic conditions, such as parasite infestation. Up to 50% of patients with allergic disease has total serum IgE levels in the normal range. Therefore, the total IgE value should not be used as a screening method for the diagnosis of allergy. Currently, there are methods such as Phadiatop that can serve as screening tool, because they confirm or exclude the presence of IgE-mediated sensitization to a group of the most common allergens.

Various *in vitro* techniques have been developed for the measurement of specific IgE, such as the Radio-Allergo-Sorbent-Test (RAST), the chemiluminescent immunoassay and the hydrophilic carrier polymer assay. The sensitivity of specific IgE for aeroallergens ranges from 60 to 80%, with a specificity of 90%, depending on the method used. An 80% sensitivity has been reported for the house dust mite in a skin test and 78.9%, for specific IgE by ImmunoCAP microarray, of which a concordance between both tests of 80.6% for aeroallergens was found.

In vitro tests for the diagnosis of food allergy help in decision making and complement the *in vivo* tests. The gold standard for diagnosis is the oral provocation test. For the diagnosis of IgE-mediated food allergy we suggest using specific IgE tests to assess food sensitization and correlate the results with the clinical history. This guide is focused on immunotherapy for aeroallergens, so it will not go deeper into this particular subject.

1.2.4 Methods for *in vitro* diagnosis: ImmunoCAP, Immulite and RAST

Serum specific IgE levels were originally measured using the RAST test, that uses radioactive reagents. More recently this test has been replaced by more sensitive tests that use fluorescent- and enzyme-labeled anti-IgE.

We recommend 100%
RAST No
Evidence: 2b
Recommendation: C

These methods are ImmunoCAP (Thermofisher Scientific / Phadia), IMMULITE (Siemens Healthcare Diagnostics) and HyTEC88 (Hycor Biomedical), which show good accuracy and

reproducibility; all three report up to the same quantification limit of 0.1 kUA / L. Automation has improved accuracy, reproducibility and linearity to a performance standard with a <15% coefficient of variation, a marker of excellence for clinical trials. The sensitivity and internal validity of in vitro tests vary according to the used technique, the most recommended being ImmunoCAP and IMMULITE. We recommend the RAST technique should no longer be used.

It is important to note that the results of these different test systems cannot be compared. Since they are not equivalent, and each has its own cut-off point.(23) IMMULITE overestimated all levels of specific IgE versus ImmunoCAP, between two and five times.(26) For this reason, if a specific IgE is to be monitored over time, the same method should always be used.(27)

Good practice point 100%

1.2.4.1 Possible indications for *in vitro* testing determining specific IgE

In vitro tests should be performed in those patients with a contraindication to perform skin tests (Table 1.2), such as patients with severe atopic dermatitis, dermographism, those who cannot stop antihistamines or have a serious pathology, such as unstable heart disease. An advantage of *in vitro* tests is that the intake of antiallergic medications does not interfere with the results. In addition, *in vitro* tests can be used as a supplement to SPT:

We recommend yes 100%. Evidence: 2b Recommendation: C

1) To more accurately determine the level of sensitization
2) To confirm sensitization after a positive SPT: in the European school AIT is frequently only prescribed to patients with both positive tests: SPT and *in vitro*. *
3) In a patient with a strong clinical suspicion of allergy to a certain allergen, but with negative SPT (a BAT or challenge test may be indicated).
4) In patients with multiple positive results in the SPT, to detect the presence of pan-allergens and thereby reduce the number of allergens necessary for AIT.

Good practice point 100%

Good practice point 100%

* Sporadically, stress can cause false positive skin reactivity.(28)

1.2.5 The Basophil Activation Test (BAT) in the diagnosis of allergy to aeroallergens

In IgE-mediated allergy, mast cells and basophils are sensitized by attaching IgE antibodies to the high affinity receptors on their surface.(29) Mast cells are found in the tissue, while basophils are easily accessible in the blood. By triggering basophils *ex-vivo* with decreasing concentrations of allergens, the lowest activation dose can be determined, corresponding to the sensitivity threshold of the basophils to the allergen, CD-sens. (6)

BAT is indicated if skin tests or serum allergen specific IgE are negative, but the clinical history is highly suggestive of allergy. In this test, the basophils are isolated from the patient's blood sample. *Ex-vivo*, the basophils are exposed to the tested allergen (s) and the concentration of basophil activation molecules (CD63 or CD203c) is measured. BAT has moderate sensitivity (50 to 85%), depending on the type of allergen, but with high specificity (85 to 100%). Thus, an *ex-vivo* exposure of the food, Hymenoptera venom or medication with the patient's basophils can be performed increasing the *in vitro* diagnostic profitability due to its high specificity.

We suggest yes 100%. Evidence: 2b Recommendation: C

The advantage of BAT is that there is no need to withhold antihistamine treatment. In addition, compared to nasal or bronchial provocation tests, the patient is not exposed to the allergens, making it useful and safer when this kind of tests are necessary for the diagnosis

Good practice point 100%

of allergic rhinitis, conjunctivitis or asthma, as well as food allergy. Experts still discuss its validity for drug allergies, since the test is not standardized and is highly dependent on the competence of the operator.(25)

1.2.6 Molecular diagnosis: utility in the exact determination of allergens

Molecular diagnosis does not identify the presence of specific IgE in the patient's serum to complete allergens, but to certain individual allergenic molecules (for example, not to *Phleum pratense*, but to Phl p 1, Phl p 2, Phl p 5, etc.). This is a useful tool to distinguish genuine sensitization from cross-reactive sensitization in polysensitized patients. The information obtained from molecular diagnosis could help the allergist who is facing a SPT with multiple positive pollen results (for example, simultaneous positivity to pollen from Birch, Ash, Ragweed and Bermuda grass) to determine the allergen(s) probably causative for the clinical symptoms and those positive due to cross-reactivity.
The advantages of the use of molecular allergy are the following: 1) it provides greater diagnostic accuracy, 2) it allows to distinguish the clinically relevant molecules, 3) in certain cases, it can provide information about the patient's prognosis
The disadvantages of molecular diagnosis are the need for large-scale multicenter studies based on different populations to evaluate sensitization patterns and the correct choice of the molecules to be analyzed in a specific region, the cost of the test and the need for a trained specialist in allergy for the correct interpretation of the results.

1.2.6.1. Indications for the use of molecular diagnosis

1. Polysensitized patients with unclear symptoms or who do not respond to treatment.
2. Patients in whom the clinical history and traditional methods of allergy diagnosis cannot identify the causal allergen.
3. Patients with multiple sensitizations to pollens in the skin test and who have an indication for AIT (30, 31)
4. There are some other indications for patients with Hymenoptera venom allergy (see Chapter 6) and food allergies, which are not an evaluative objective of this guideline.

We suggest yes 100%.
Evidence: 2a
Recommendation: B

AIT is a treatment that lasts three to five years. The identification of the primary allergen (s) is important to provide the best efficacy and safety to the patient. Studies have shown that 50% of SLIT or SCIT may be erroneously indicated when it's indication is based solely on results of the SPT.(30, 31)
The molecular diagnosis of allergy with single allergen or multiple allergen microarrays is a typical example of precision medicine (21, 32) that improves the specificity of the diagnosis of aeroallergen sensitization, especially in polysensitized patients; it can be applied in food allergy and it can even reveal the cause of unexplained anaphylaxis.(33)

1.2.7. Species-specific allergen molecules for aeroallergens: correct selection of extracts for AIT (Table 1.5)

Per allergen group we can mention the following species-specific allergenic molecules:

- *Mites*: the most common mites are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*; their main allergens are Der p 1 and Der p 2 (together identify 63 to 97% of sensitizations), as well as Der f 1 and Der f 2. Recent studies show that Der p 23, present on the surface of the fecal particles of the mite (airborne form of group 1 allergens of the mite) is highly allergenic.

We suggest yes 100%.
Evidence: 2a
Recommendation: B

- *Trees*: Cup a 1 is a marker of the *Cupressaceae* family, Bet v 1 is the major allergen of the pollen from trees of the *Fagales* family, Ole e 1 is the most common allergen in olive tree pollen sensitization and is used as a marker for cross-reactivity with ash tree pollen. Pla a 1 and Pla a 2 are the species-specific markers for sensitization to the plane tree.
- *Grasses*: the most important groups are those of the *Pooideae* and *Panicoideae* family, which may contain cross-reactivity proteins; while Phl p 1 is the main marker for grass allergy, other major allergens that could be used as markers are Phl p 5 and Phl p 2 (they serve when Phl p 1 is negative); in these pollens, cross-reactivity can be measured through the pan allergens Phl p 4, Phl p 7, Phl p 11 or Phl p 12 or through cross-reactivity carbohydrate determinants (CCD). In the *Panicoideae* family, species-specific allergens are Pas n 1, Sor h 1 and Cyn d 1.
- *Weeds*: the species-specific weed allergens that can be used are Amb a 1 (as *Ambrosia* marker), Art v 1 (as *Artemisia* marker) and both could cross with Art v 6 homologous to Amb a 1 (however, if Art v 1 is negative AIT is not required for *Artemisia*). The same applies to Art v 1 with Amb a 4 (but if Amb a 1 is negative, AIT for *Ambrosia* is not indicated). It should be mentioned that with the total extract, the patients would present SPT positivity to both, but detecting the species-specific allergenic molecules AIT will only be prescribed with the major allergen to which positivity is present. Par j 2 is a specific marker for Parietaria and Pla l 1 is used as a species-specific marker for plantain.
- *Fungi*: the species-specific allergen indicating AIT for *Alternaria* is Alt a 1. The hypersensitivity for *Aspergillus fumigatus* suggestive of a diagnosis of bronchopulmonary aspergillosis is determined by Asp f 2, Asp f 4 and Asp f 6, however, sensitization to Asp f 1 and Asp f 3 is associated with allergic asthma.
- *Epithelia*: Fel d 1 is the species-specific allergen for feline allergy. Positivity to lipocalins can cause positive SPT cross-reactivity to other animals (Fel d 4, Mus m 1, Equ c 1, Can f 1 and 2). Another allergen is Can f 5, the dog's prostatic kallikrein. This is associated with severe asthma. Specific allergy markers for feline/canine/equine are Fel d 1 / Can f 1 / Can f 2 / Can f 5 / Equ c 1.
- *Hymenoptera*: Bee and wasp sensitization. Hymenoptera allergens contain cross-reacting proteins, Api m 2, Ves v 2 (hyaluronidase), Api m 5, Ves v 3 (dipeptidyl peptidase), Api m 12, Ves v 6 (vitellogenins), which can be positive in SPT or specific IgE to whole allergen extracts. The species-specific molecular sensitization extracts for bees are Api m 1, Api m 3, Api m 4 and Api m 10 and for wasps, Ves v 1 and Ves v 5 (see Chapter 6)

Tablto 1B.2 Molecular allergy: species-specific and cross-reacting allergen molecules

Allergenic source	Allergen Specific Species (CM)	Possible utility for AIT	Reactivity	Profilin	Polcalcina	Ltp	Tropomyosin	Lipocalin	PR-10
Ambrosia	Amb to 1	Yes	Amb to 4 (Art v 1 Homologue)	Amb to 8	Amb to 9 Amb to 10	Amb to 6			
Artemis*	Art v 1 Art v 3	Yes	Art v 6 (Amb to 1 Homologue)	Art v 4	Art v 5	Art v 3			
Parietaria	Par j 2	Yes	Marker of LTP	Par j 3	Par j 4	Par j 1 Par j 2			
Salsola	Salt k 1	Yes		Salt k 4					
Chenopodium	Che to 1	Yes		Che to 2	Che to 3				
Phleum*	Phl p 1 Phl p 5	Yes	Smaller allergens that are often not present in sufficient amounts in the extract used for AIT.	Phl p 12	Phl p 7				
Birch*	Bet v 1	Yes	They have cross-reactivity with PR10 (Bet v 1 homologue) of other tree pollens or food	Bet v 2	Bet v 4				Bet v 1
Olive*	Ole e 1	Yes		Ole e 2	Ole e 3	Ole e 7 (Little cross-reactivity with other LTPs)			

Cipres	Cup to 1	Yes	They have cross-reactivity with Cry j 1						
Shadow Banana	Pla to 1 Pla to 2	Yes				Pla to 3			
Japanese cedar	Cry j 1	Yes							
Alder	Aln g 1	Yes	Cross-reactivity with PR10 (Bet v 1 Homologues)						Aln g 1
Mites*	Der p 1 Der p 2 Der f 1 Der f 2	Yes	Cross with other mites				Der p 10 (Behaves as pan-allergen cross with shrimp, cockroaches, nematodes) It is recognized by 81% of mites allergic.		
Cockroach*	Bla g 1 Bla g 2 Per a 1	Yes					Bla g 7 Per a 7	Bla g 4	
cat	Fel d 1	Yes	Fel d 2 (Cross with mammalian serum albumins)					Fel d 4	
Dog *	Can f 1	Yes	Can f 3 (Cross with mammalian serum albumins)					Can f 1 Can f 2	
Would alternate*	Alt to 1	Yes							
Aspergillus*	Asp f 1 Asp f 2 Asp f 3		Asp f 6 (Cross with other fungi)						
Cladosporium*	Cla h 8								
CCDs*	Phl p 4 MUXF3 Jug r 2								

The nomenclature of allergenic molecules is made under the Latin name of the family (genus and species). For example, allergens that begin with Art v correspond to Artemis. A number is attached to the name to designate the different allergens of the species (Art v 1, Art v 5, etc.) according to the order of identification of the allergen. LTP (Lipid Transporter Protein), CCDs (Cross-Reactivity Carbohydrate Determinants).

*Artemis: Art v 3 Possible crossover with other LTPs such as Pru p 3 and Cor to 8 and could intervene in pollen- weed feeding syndromes.
*Phleum: Phl p 2 Phl p 4 Phl p 6 Phl p 11 (No conclusive data for AIT indication)
*Abedul: It is associated with oral allergy syndrome, in Mexico it is a marker of awareness to Alnus.
*Olive: Marker of sensitization of Russian ash and olive tree. Ole e 9 (Immunotherapy Reaction Risk Marker)
*HDM: Der p 23 (Protein is highly allergenic is found on the fecal surface of the mite, which is the airborne form of der mites allergens p 1)
*Cockroach: Associated with pediatric-age asthma dependent on exposure.
*Dog: Can f 5 (Prostate dog kallikrein is associated with severe asthma)
*Alternaria: Risk factor for asthma in children and adults
*Aspergillus: Responsible for allergic bronchopulmonary aspergillosis (Asp f 2, Asp f 4, Asp f 6), Asp f 1 / Asp f 3 responsible for allergic asthma
*Cladosporium: Respiratory allergy responsible
*CCDs: Allergenic markers of CCDs in molecular diagnostics which are responsible multiple positive skin tests

1.2.8. Pan-allergens and the decision to provide or not AIT

Pan-allergens can be found in different species; Pan-allergen sensitized patients frequently show positivity to multiple specific cutaneous or IgE tests to extracts of complete allergens (polysensitized), because different extracts contain families of cross-reactive pan-allergens. In the analysis of GUIMIT experts of the molecular allergen diagnosis (Table 1.5), the question arose: should AIT be indicated in patients of any age with respiratory allergy, if there is no species-specific allergen involved, but if there is only pan-allergen positivity? GUIMIT experts suggests NO. Next, the pan allergen groups are reviewed.

We suggest not 100%.
Evidence: 2a
Recommendation: B

- *Polcalcins (calcium binding proteins [CBP])*: they are not present in food, they have high cross-reactivity among pollens of different families (grasses, trees and weeds), so they are markers of polysensitization. Their clinical importance is unknown, and

their positivity is not an indication for AIT. The molecular allergens for diagnosis of polycalcins are Bet v 4, Phl p 7, Art v 5, Che a 3.

- *Homologues of Bet v 1 (PR-10)*: associated with oral allergy syndrome. It has been suggested that AIT for birch pollen improves not only respiratory symptoms related to pollen, but also adverse food-related reactions. However, there is still no definitive evidence. These pan-allergens have high cross-reactivity among the group of *fagaleae* and food, especially *rosaceae*. Therefore, sensitization to Bet v 1 with oral symptoms, but without respiratory symptoms should not be considered an indication for AIT to birch pollen. The molecular diagnostic allergens are Bet v 1, Act d 8, Ara h 8, Pru p 1.
- *Respiratory lipid transfer proteins (LTP)*: are related to serious reactions when they are of food origin (fruits, nuts, vegetables and latex), since they resist heat and digestion. They can been found as major allergens (for example, Par j 1 [*Parietaria jaudica*]) and as minor allergens (Ole e 7 [olive]), related to severe asthma symptoms and increased risk of adverse reaction to AIT. The respiratory LTPs are Par j 1, Amb a 6, Art v 3, Ole e 7, Pla a 3.
- *Profilins*: profilins are recognized by 50% of patients sensitized to pollens and in 10 to 20% of those sensitized primarily to birch pollen. Their clinical importance as a respiratory allergen is variable. Symptoms related to profilin sensitization are those of oral allergy syndrome. Studies with palm profilin and conjunctival provocation tests with profilin have shown that it can act as an aeroallergen, however, positivity to profilin is not an indication for AIT. Molecular allergens of respiratory profilins are Bet v 2, Phl p 12. Aln g 2, Que a 2, Art v 4, Amb a 8, Par k 3, Ole e 2, Fra e 2, Cup s 8, Pho d 2.
- *Tropomyosins*: these pan-allergens are shared by arthropods, so they are responsible for cross-reactivity between mites, cockroaches, shellfish (shrimp) and parasites. The molecular diagnosis is more specific and has a high positive predictive value for diagnosis of shrimp allergy. Their positivity is not an indication for mite AIT. Allergens to assess tropomyosin sensitization are Der p 10, Bla g 7 and for shellfish, Pen a 1, Pan s 1, Oct v 1, Per v 1, Cha f 1.
- Cross reactive Carbohydrates Determinants (CCD): these are carbohydrates of cross-reacivity that can be found in complete extracts or specific IgE to extracts of whole allergens, but not in recombinant or purified allergens. Using extracts of whole allergens can produce positive skin tests to several allergens due to these carbohydrates. It has been shown that they have no clinical relevance in allergic patients. There is no indication for AIT in a patient who has only CCD positivity, without positivity to species-specific molecules.

In polysensitized patients (with multiple positivity in SPT), GUIMIT reminds the allergist to think of possible involvement of pan-allergens or CCDs, which requires the use of molecular diagnosis for greater diagnostic accuracy.

Good practice point 100%

We suggest that AIT be indicated in patients with food and respiratory allergies in whom a species-specific pan-allergen is involved (for example, birch: Bet v 1) and if the patient has associated respiratory symptoms. The decision to use AIT for cross-reacting inhalant allergens is not recommended when the main allergy is a food allergy, rather it should be prescribed when respiratory symptoms are present.(34)

Good practice point 100%

Chapter 2. Indications for subcutaneous and sublingual allergen-specific immunotherapy

Table 2.1

Table 2.1 Indications for the start of SCIT and SLIT
Clinical scenarios that apply to all patients related to the decision to start AIT: • Patients with verified sensitization related to clinical symptoms • Availability of high-quality allergen extracts • Patients in whom allergen avoidance is not possible or is inappropriate. Further...
It is recommended to indicate SCIT or SLIT in a patient with:
• Rhinitis or seasonal or perennial rhinoconjunctivitis
• Rhinitis, for reducing the risk of asthma
• Mild or moderate controlled asthma
• Asthma, in order to reduce symptoms, improve disease control, reduce medication use, reduce allergen-specific airway hyperresponsiveness and improve quality of life
• Respiratory allergy to mites, grass or tree pollen, for reducing disease symptoms and the need for medication
• Rhinitis with coexisting asthma
• Monosensitized respiratory allergy patients
• Polysensitized, but monoallergic respiratory allergy patients
• Older adults with respiratory allergy
It is suggested to indicate SCIT or SLIT in a patient with:
• Asthma, to reduce the risk of exacerbations and to reduce nonspecific airway hyperresponsiveness
• In respiratory allergy to cat or dog epithelium: to reduce symptoms and the need for medication
• Severe controlled asthma *
• Polysensitized and polyallergic patients with respiratory allergy
• Extrinsic atopic dermatitis with clinically relevant allergen **
• Children 2 to 5 years with respiratory allergy
*Weighing risk/benefit consider schedules with a higher safety profile and/or use of concomitant treatment (see chapter 10) **Evidence available mainly for mite allergy AIT = allergen immunotherapy, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy

Introduction

AIT is a long-term treatment that can bring substantial benefits for patients with respiratory allergy, both in symptomatology and use of medications; so far, it's the only treatment capable of modifying the natural history of allergic diseases.

The choice of the correct patient for the prescription of AIT will directly affect the effectiveness, as well as the patient's perception of their benefits; being a long-term treatment, it's crucial to identify the right time to start and the ideal patient for its use.

In this chapter we explain the recommendations and suggestions regarding the indications of AIT, both for SCIT and SLIT, as well as their contraindications (Table 2.1).

Use of AIT in children from 2 to 5 years of age

As in adults, both SCIT and SLIT have shown benefits in the reduction of symptoms and medications in children with respiratory allergy, so their administration in the pediatric population should be considered as having clear indications for its use.

The dilemma occurs in very young children, specifically between two to five years, in whom the available evidence is limited and the opinion in the different guidelines is controversial; the American and European schools suggest both use of SCIT and SLIT in children under five years old; however, they emphasize safety concerns in this age group. Especially the child's ability to identify and communicate systemic reactions might be reduced, which could delay their recognition and early management.

While it is important to consider that it is precisely at these ages where patients could obtain greater benefits from the early use of AIT, most of the effects attributed to it are extrapolations of clinical trials conducted in older patients or with mixed population, so the decision to initiate AIT, whether it is SCIT or SLIT, in this group should be made with caution and always customizing each case, weighing possible benefits and risks.

By consensus of Mexican experts, it was suggested to initiate AIT in children two to five years, always considering each case individually and taking into account that the security profile and the administration at home make SLIT a more attractive modality for young children and their caregivers.

We suggest yes, 85% SCIT // 97% SLIT
Evidence: 4/4
Recommendation: D/D

Use of AIT in the elderly

Age by itself does'nt preclude the use of AIT and starting AIT can be considered in the elderly, always assessing risks and benefits of its administration. While the presence of chronic diseases and the use of medication such as beta blockers, angiotensin converting enzyme inhibitors (ACE) and monoamine oxidase inhibitors is more common in the elderly, AIT (both SCIT and SLIT) can provide significant benefits with a reasonable security profile; so it should be considered in case of having an adequate indication and when comorbidities are controlled.

We recommend Yes, 100% for SCIT/SLIT
Evidence: 1b/1b
Recommendation: B/A

Multidisciplinary assessment is essential in these patients, since there are several diseases that could simulate respiratory allergy symptoms. So it is crucial to establish a correct diagnosis for this group of the population to perceive the benefits of AIT, as are a reduction in symptoms and medication use.

Indications for the use of SCIT and SLIT in children > 5 years and adults

Patient selection is essential to achieve the expected benefits with AIT. In general, three scenarios are recommended to consider the use of SCIT or SLIT:

Good clinical practice

- Patients with verified sensitization that correlate with clinical symptoms.
- Patients in whom allergen avoidance is not possible or is inappropriate
- Availability of high-quality allergen extracts.

2.4.1 Indications to recommend the onset of AIT (high evidence):

We recommend Yes, 100%
Evidences: 1b-2a
Recommendation: A-B

- Children and adults with seasonal rhinitis or rhinoconjunctivitis, for short- and long-term benefit.
- Children and adults with rhinitis or perennial rhinoconjunctivitis, for short- and long-term benefit
- Children and adults with asthma, for reducing symptoms, improving asthma control, reducing medication use, reducing specific airway hyperreactivity and improving quality of life.
- Children and adults with asthma and proven allergy to house dust mite, grass and tree pollen, for reducing medication use.
- Children and adults with mild or moderate controlled asthma, for reducing symptoms and medication use.
- Children and adults with monosensitized respiratory allergy.
- Monoallergic, polysensitized children and adults with respiratory allergy.
- Children and adults with rhinitis and coexisting asthma.
- Children and adults with respiratory allergy to mites, grass or tree pollen.

These recommendations are based on evidence presented in the reference guidelines and in separate studies reviewed for the specific age groups.

In general, evidence has been shown in favor of using AIT in children and adults with symptoms of respiratory allergy, either rhinitis, rhinoconjunctivitis, asthma or a combination of these, both with the aim of reducing symptoms and medication use, as well as to improve control of the disease and decrease the specific hyperreactivity of the respiratory tract. The scientific information in favor of AIT is especially strong in the case of monoallergic patients with symptoms related to mites and grass or tree pollen.

Specifically, in asthma it is recommended to start AIT only in those patients with mild or moderate and controlled disease, since the risk of adverse reactions increases considerably when the disease is severe or not under control.

We recommend if 100%
Evidence: 1b
Recommendation: A

2.4.2. Indications to suggest the onset of AIT (moderate or low evidence):

Some of the indications to suggest the onset of AIT in patients with aeroallergen allergy are (with comments below):

- Children and adults with asthma, for reducing asthma exacerbations.

- Children and adults with asthma, for reducing nonspecific airway hyperreactivity.
- Children and adults with asthma and proven allergy to cat or dog, aiming to reduce symptoms and medication use.
- Children and adults with moderate to severe, controlled asthma, for reducing symptoms and medication use.
- Polysensitized or polyallergic children and adults with respiratory allergy.
- Children and adults with atopic dermatitis.
- Children and adults with respiratory allergy to cat or dog.

In patients with moderate or severe asthma requiring AIT, the degree of control of the disease should be carefully evaluated, individually weighing the risks and benefits.

We suggest if 100%
SLIT: Evidence: 1b
Recommendation: A

We suggest starting AIT only when the disease is controlled, preferably with a ratio of the forced expiratory volume during the first second / forced vital capacity (FEV1 / FVC) > 70%, due to the increased susceptibility to present systemic adverse effects in this group of individuals. Although it was considered to suggest against the use of AIT, it is recognized that this therapeutic measure could be of great help for the long-term control of moderate-severe asthma, with potential benefits in reducing the use of medications and, even, of reducing severe exacerbations.(35) One could consider starting with the safest form of AIT: SLIT.

Because the evidence is less compelling in favor of the use of SLIT or SCIT in patients with proven allergy to animal dander, the decision to initiate AIT in these patients is considered a suggestion, according to the GUIMIT experts. However, this treatment may provide benefit in those patients.

We suggest if 100%
Evidence: 2a
Recommendation: B

The use of ITE in polysensitized or polyallergic patients has been controversial throughout the world, with the European school in favor of the use of monotherapy while the American school has proposed the possibility of performing allergen mixtures in AIT. Experience in Mexico shows that many of the patients are polysensitized with proven symptoms to multiple allergens, so we suggest starting AIT in this group of patients, prioritizing allergens related to the present symptoms and following the mixing rules of AIT preparation. In the simplified Delphi, based on the collective experience of Mexican experts, it was suggested to consider SCIT or SLIT with a mixture of four non-homologous allergens effective and safe.

We suggest if 100%
Simplified Delphi: Mex
Evidence: 1c
Recommended Mex: B

In patients with atopic dermatitis it is suggested to start AIT in patients with extrinsic atopic dermatitis and with clinically relevant aeroallergen, as it has been shown to be effective, especially in mite allergy.

2.4.3. Patients in whom it is not suggested or recommended to start AIT:

- In children and adults with rhinitis or seasonal rhinoconjunctivitis we suggest not to use the pre- and pre-co-seasonal modality.
- In children and adults with severe uncontrolled asthma we recommend not to start AIT in order to reduce symptoms and medication use

Although the reference guidelines recommend the use of pre-seasonal and pre-coseasonal SCIT in children and adults with seasonal rhinitis, most regions of Mexico have poorly marked seasonality, which makes the use of this SCIT and SLIT schedule not recommendable. However, there are exceptions for some parts in the North of the country, where there is clear seasonality.

We suggest not 100%.
Evidence: Yes 1b
Recommendation: Yes To Adults B Children

Although some reference guidelines suggest the onset of AIT in moderate or severe asthma to reduce symptoms, based on consistent results from individual studies, safety concerns in patients with severe asthma led to the suggestion to not start treatment in the Mexican population, especially when there is no control of the disease. This negative suggestion can change if the severity level drops and the disease is stable and controlled and in patients in whom adjuvant medication use is planned, as a strategy to improve the tolerance and safety profiles (See Chapter 10).

2.4.4. Clinical circumstances under which we suggest against starting AIT

Some clinical circumstances under which it is not recommended to start AIT are, among others:

- Children and adults with asthma, with the aim of improving PEF or FEV_1.
- Children and adults with asthma and fungal allergy, with the aim of reducing symptoms and the use of medication
- Children and adults with respiratory allergy and monosensitization to fungi
- Children and adults with respiratory allergy and monosensitization to cockroach

Due to the limited information found or inconsistent evidence, no recommendation can be made for or against the onset of AIT in patients with respiratory allergy and monosensitization to fungi and/or cockroach or in patients with asthma with the aim of improving pulmonary function tests.

No recommendation can be made in favor or against 100%
Evidence: 2b
Recommendation: B

Specifically, in fungi, there is a very limited number of studies that demonstrate its effectiveness, in addition to the fact that there is significant concern about the quality and safety of the extracts. The physician should take an individualized approach, assessing risks and benefits in cases that have a well-established indication and an adequate allergen (especially *Alternaria* and *Cladosporium*).

Contraindications for the use of AIT

Table 2.2. Comorbidities that contraindicate or limit the use of SCIT or SLIT

Table 2.2 Relative contraindications* for the use of SCIT or SLIT
Severe asthma
Start of AIT during pregnancy
Use of beta blockers
Use of immunosuppressants or immunomodulators
Diseases in which the use of epinephrine is contraindicated (chronic lung disease, with unstable angina, recent acute myocardial infarction, significant arrhythmia or uncontrolled hypertension)
Human immunodeficiency virus infection
Primary or secondary immunodeficiency
Autoimmune diseases
Cancer
Psychiatric disorders
Serious systemic reactions to AIT
Lack of treatment adherence
Oral lesions with loss of continuity of the oral mucosa in the specific case of SLIT

These are no contraindications for the use of SCIT or SLIT
Continued treatment instituted before starting pregnancy
Breastfeeding
Use of angiotensin converting enzyme inhibitors
Use of monoamine oxidase inhibitors

* any of these conditions in active, severe or out of control status become an absolute contraindication.

AIT is a treatment that, when well indicated, entails many benefits for patients, but it is important to consider that there are special situations in which its use is undesirable because there might be safety concerns.

It is very important to remember that allergic patients are not exempt from comorbidities and that at all times it will be preferred to initiate AIT in those patients in whom the underlying diseases are controlled, with or without treatment. In case of doubt we recommend a multidisciplinary approach, with the objective of determining whether AIT should be initiated or not and in what modality, always respecting the wishes of patients and family members.

GUIMIT experts are of the opinion that there are few absolute contraindications for starting SLIT or SCIT, under certain circumstances, some patients may benefit from their use. However, we highlight the importance of individualizing each case and weighing the risks against the benefits.

2.5.1. Relative contraindications for the use of AIT

Severe asthma.- Severe uncontrolled asthma for safety reasons is a contraindication (IC) for the use of AIT in both children and adults, since these patients are at a greater risk of presenting systemic reactions. Its use may be assessed in special cases, balancing risks against benefits. SLIT could be a good initial option. In cases in which it is planned to use adjuvant medication, as a strategy to improve tolerance and the safety profile of AIT (e.g. omalizumab or another biological), its use may be considered. (See Chapter 10)

Relative CI 100%
Evidence: 4
Recommendation: C

Initiation during pregnancy.- is a relative contraindication for starting AIT. Although retrospective studies suggest that there is no increase in the risk of prematurity or fetal abnormalities, due to safety concerns especially during the up-dosing phase we do not recommend starting AIT during pregnancy. The onset of AIT during pregnancy can be considered when the indication is a high-risk condition, such as anaphylaxis caused by Hymenoptera venom allergy.

Relative CI 100%
Evidence: 5
Recommendation: D

Use of beta-blockers.- treatment with beta-blockers is a contraindication for AIT, but not for VIT, although it is recommended to change to an alternative drug when possible. Co-treatment with beta-blockers in topical preparations it is a relative contraindication. Treatment with beta-blockers does not increase the frequency of anaphylaxis, however, there is less response to adrenaline, so it is not recommended to start immunotherapy unless there is a clear and necessary indication for its use (VIT) and always assessing risks against benefits.

Relative CI 100%
Evidence: 3b
Recommendation: B

Use of immunosuppressants and immunomodulators.- although specific data is lacking, it is logical to assume that treatment with immunosuppressants or immunomodulators can reduce the effectiveness of AIT, and the effect of AIT on the immune response of these patients is not yet fully known. It is recognized that the contraindication is hypothetical and that there are no studies that support this assertion.

Relative CI 100%
Evidence: 5
Recommendation: D

Diseases in which the use of adrenaline is contraindicated.- alternatives to AIT should be sought in patients with conditions that affect their ability to survive systemic allergic reactions, such as chronic lung disease, unstable angina, recent acute myocardial infarction, significant arrhythmia or uncontrolled hypertension. Its use will only be recommended in patients in whom a clear indication is evident and the risk to benefit ratio is favorable.

Relative CI 100%
Evidence: 5
Recommendation: D

Human immunodeficiency virus (HIV) infection.- Human immunodeficiency virus (HIV) infection: In patients with controlled HIV infection (highly active antiretroviral therapy, undetectable viral load and normal CD4 count) SCIT can be initiated since successful cases have been reported. In any case, risks and benefits must be assessed individually. One should not start AIT in HIV stage C.

Relative CI 100%
Evidence: 3b
Recommendation: B

Primary or secondary immunodeficiency.- AIT is contraindicated in patients with severe immunodeficiency. However, those with mild immunodeficiency and with a clear indication for AIT may benefit from AIT.

Relative CI 100%
Evidence: 5
Recommendation: D

Autoimmune diseases.- AIT can be initiated in patients with local and controlled autoimmune disease, although these types of entities in the period of clinical activity constitute a contraindication for the administration of AIT.

Relative CI 100%
Evidence: 5
Recommendation: D

Cancer.- the history of having suffered from cancer or having a stable neoplasia without the need for treatment are no contraindications per se to initiate AIT. However, AIT will be contraindicated in patients with active or symptomatic disease, and in those who are under treatment schedules with immunosuppressants to obtain or maintain therapeutic remission.

Relative CI 100%
Evidence: 5
Recommendation: D

Psychiatric disorders.- the presence of psychiatric disorders is a relative contraindication for the use of AIT, especially since identifying early symptoms and signs of serious adverse reactions could be more challenging in these patients. In addition, patients suffering from psychiatric disorders could be more prone to treatment mal-adherence..

Relative CI 100%
Evidence: 5
Recommendation: D

Serious systemic reactions (SR) to AIT.- the history of serious SR with SCIT is a clear risk factor for future serious SR. Although the start of treatment could be assessed under strict supervision, in those cases switching to SLIT could also be a consideration, respecting a updosing phase of at least one month.

Relative CI 100%
Evidence: 4
Recommendation: C

Lack of treatment adherence.- Lack of treatment adherence is a relative contraindication for the use of SCIT due to concerns concerning efficacy as well as safety.

Relative CI 100%
Evidence: 5
Recommendation: D

Active oral injuries.- Patients with chronic oral mucosal diseases are not specifically candidates for the use of ITSL until The improvement in injuries.

Relative CI 100%
Evidence: 5
Recommendation: D

2.5.2. AIT can be started or continued (these are not contraindications)

Continue during pregnancy.- AIT can be continued in women who get pregnant once the effective therapeutic dose of AIT has already been reached. We recommend against increasing the dose of AIT during pregnancy.

It's not a contra-indication (CI) 100%
Evidence: 5
Recommendation: D

Breastfeeding.- there is no evidence of an increased risk of initiating or continuing SCIT in general in the breastfeeding mother or the breast-fed child, so this is not a contraindication for its use.

It's not a CI, 100%
Evidence: 5
Recommendation: D

Use of ACE inhibitors - there is no contraindication for SCIT with aeroallergens in patients treated with this group of drugs, but it is a relative contraindication for VIT. There is also no evidence of an increased risk of local or systemic adverse reactions to AIT in patients using these medications. One exception could be one of the recently reported fatal cases in US, but apart from taking an ACE-inhibitor the patient had several other more serious complicating factors that most probably were the cause of the fatal outcome.

It's not a CI, 90%
Evidence: 3b
Recommendation: B

Use of monoamine oxidase inhibitors.- there is no contraindication for SCIT in patients treated with these agents. Although there is a theoretical risk of pharmaceutical interaction, the evidence in this regard is only supported by a case report.

It's not a CI 100%
Evidence: 5
Recommendation: D

In Chapter 9 we will discuss in more detail adverse events with the AIT and its management. In Chapters 4 and 5 we present the frequency of adverse events and how to increase the safety when administering SCIT.

2.6. AIT in preventing the onset of allergic diseases

Given the known propensity of atopic patients to present not only one but several allergic disorders, a recurring line of research is the use of AIT with the aim of preventing progression of already existing allergic diseases or of new sensitizations. There have been numerous efforts to answer this question. Specifically, it has been the initiative of the European Academy of Allergy, Asthma and Immunology to conduct a systematic review of all available information and come with recommendations regarding the use of AIT for this purpose..

Preventive AIT for asthma in AR
We recommend YES
Evidence: 1b
Recommendation: B

The experts of GUIMIT recommend the use of SCIT or SLIT in order to prevent the onset of asthma in patients with allergic rhinitis, since there is evidence in favor of a risk reduction, and it has been recognized as the only treatment capable of modifying the course of the disease. However, we do not recommend the use of AIT in sensitized patients in order to prevent further new sensitizations.

Preventing new sensitizations
We recommend NO 100%
Evidence: 1b
Recommendation: B

Finally, the current evidence does not allow issuing a recommendation in favor or against the use of AIT in children with atopic dermatitis to prevent the occurrence of other allergic manifestations.

Prevention in DA
Recommendation cannot be issued 97%
Evidence: 1b
Recommendation: B

Chapter 3. Mechanisms of action of allergen specific immunotherapy

Table 3.1

SUMMARY Chapter 3: Mechanisms of action of allergen specific immunotherapy		
GUIMIT experts answer the questions of this chapter, based on evidence from the most recent literature*		Agreement
Is there any scientific evidence to support the presence of immune changes during the desensitization phase?	Yes	100%
Do these immune changes have any clinical meaning?	Yes	100%
Is there any scientific evidence to support the presence of immune changes in the remission phase?	Yes	100%
Do these immune changes have any clinical meaning?	Yes	100%
Is there any scientific evidence to support the presence of immune changes in the tolerance phase?	Yes	100%
Do these immune changes have any clinical meaning?	Yes	100%
Are there any differences in the mechanisms of AIT using different routes of administration: subcutaneous, sublingual, epicutaneous or intralymphatic?	Yes	100%
Are there biomarkers to help monitor patients during AIT?	Yes	100%

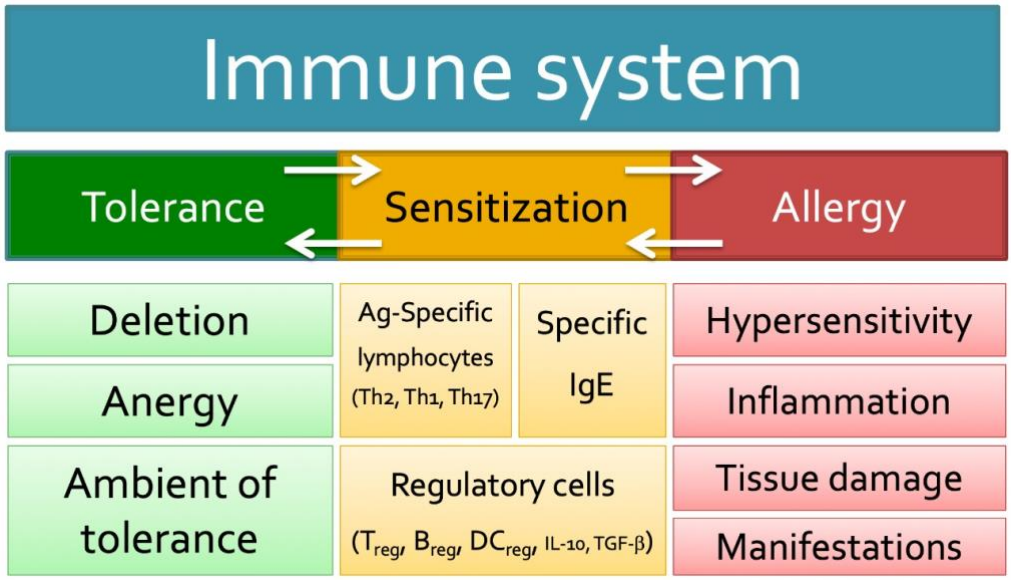
* Unlike other chapters here the clinical questions shall be answered in relation to what has been published more recently, since the reference guidelines do not delve into this topic. In addition, no recommendations are given, because of the very nature of the subject.

3.1. Introduction

Allergen specific immunotherapy (AIT) is so far the only treatment that can modify the natural history of allergic, IgE-mediated diseases and our knowledge of the mechanisms by which AIT can inhibit the allergic inflammatory response is steadily increasing.

During AIT treatment the immune system goes through different stages: from initial sensitization, followed by hypersensitivity and inflammation after contact with the allergen, through the desensitization phase where there is less reactivity towards the allergen to finally the remission phase where there is no longer an inflammatory response after exposure to the allergen. This non-responsiveness during remission, however, may be temporary, only while receiving treatment or till shortly after stopping AIT, until the tolerance phase has been reached, where the lack of an inflammatory response is permanent even though treatment has been discontinued (Table 1) (Figures 1 and 2). The objective of this chapter is to review the scientific evidence for the immune changes that occur at each of these stages during AIT treatment and what is its clinical significance we can expect in relation to the patient. We also describe the differences in mechanisms of action depending on the route of AIT administration and current knowledge about biomarkers for follow-up. (36-44)

Figure 3.1: Concepts related to tolerance, sensitization and allergy.



The immune system can learn to respond to an allergen (sensitization) with the activation of specific lymphocytes and the synthesis of specific IgE directed against allergen epitopes. This phase can be controlled by regulatory cells that induce a normal state of tolerance towards this allergen, but control can be lost by responding excessively to the allergen (hypersensitivity) causing inflammation, tissue damage and clinical manifestations.

3.2. Is there any scientific evidence to support the presence of immune changes during the desensitization phase?

Yes. The reactivity of mast cells and basophils decreases rapidly from the administration of the first doses of AIT onward. It has been found that this effect may be caused by an increase in type 2 inhibitor receptors for histamine (HR2) in different immune cells (mast cells, basophils, lymphocytes and eosinophils). Initially there is an increase in allergen-specific IgE and then a gradual decrease, as well as a gradual increase of other allergen-specific immunoglobulin isotypes: IgG1, IgG4 and IgA, which function as blockers of the allergic response to the allergen. These antibodies help to block allergens, forming an antigen-antibody reaction and thus prevent the binding of the allergen to IgE, thus preventing the activation not only of mast cells and basophils, but also of eosinophils, B lymphocytes and dendritic cells. The activity of type 2 innate lymphoid cells (ILC2) has also been found reduced during this stage of AIT treatment.

3.3. Do these immune changes have any clinical meaning?

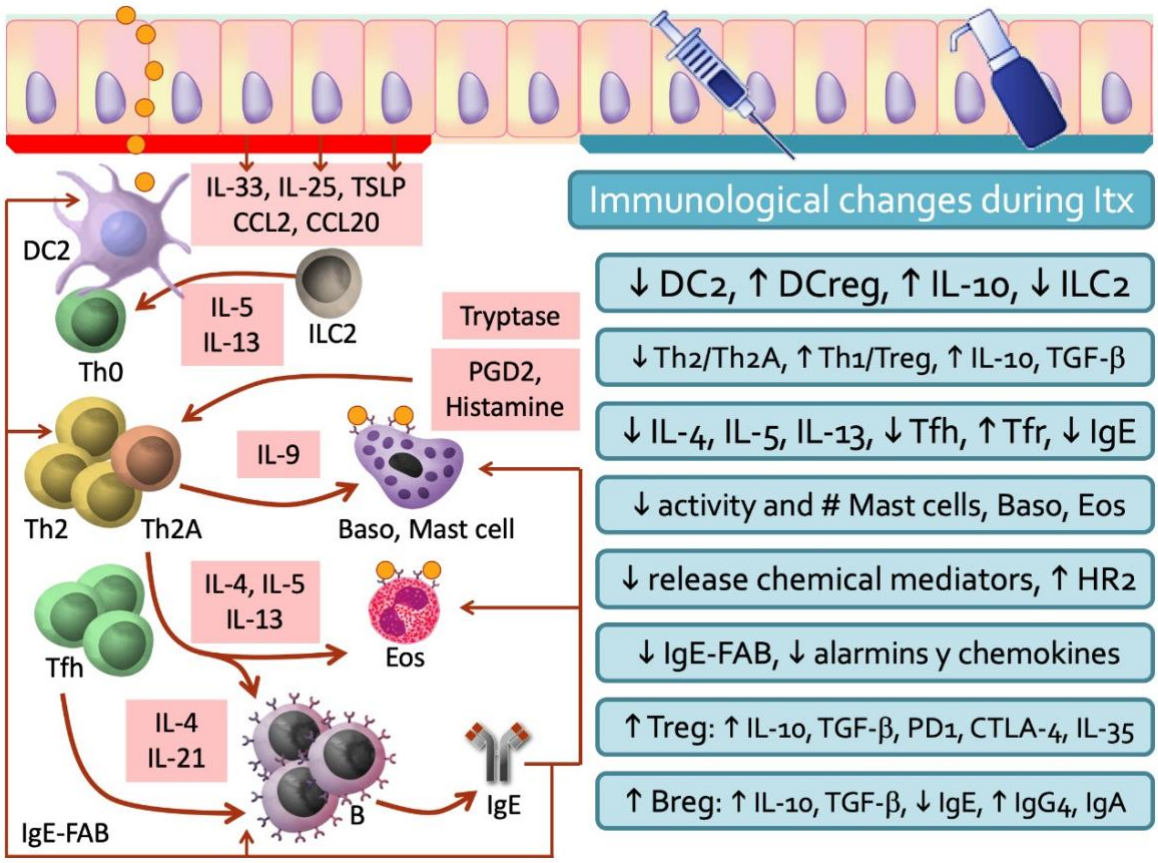
Yes. This rapid decrease in the reactivity of effector cells helps to avoid serious anaphylactic actions against accidental exposure to the allergen and this is the justification for the use of fast or ultra-fast immunotherapy schedules for different allergens.

3.4. Is there any scientific evidence to support the presence of immune changes in the remission phase? See Figure 2.

Yes. Immunotherapy induces the production of mediators such as Kynurenine and retinoic acid. Kynurenine is a metabolite of Tryptophan via indolamine 2,3 di-oxygenase

and like retinoic acid, the active metabolite of vitamin A, induces the expression of the transcription factor Foxp3 in T lymphocytes that mediates the production of regulatory cytokines such as interleukin 10 (IL-10), transformation growth factor beta (TGF-beta) and interleukins 27 and 35 (IL-27, IL-35), that attenuate local allergic inflammation. These mediators and cytokines also induce changes in antigen-presenting cells, especially in skin and mucosal dendritic cells, decreasing the expression of histocompatibility molecules (MHC-II) and co-activator molecules (CD80, CD86) for T cells, and increasing the production of IL-10 and TGF-beta, becoming tolerogenic or regulatory dendritic cells. Both cytokines (IL-10 and TGF-beta) have local anti-inflammatory effects and are able to inhibit the proliferation of T cells and induce the change of Th2, Th2A and B lymphocytes toward tolerogenic regulatory populations (T regulators and B regulators).

Figure 3. 2.



Exposure to repeated doses of the allergen in a genetically susceptible patient favors the release of alarmins and chemokines from the epithelium leading to the activation of type 2 innate lymphoid cells and type 2 dendritic cells that favors the change of Th0 naïve lymphocytes to Th2 and Th2A. These Th2/Th2A lymphocytes along with Tfh lymphocytes favor B cell activation and allergen-specific IgE synthesis. IgE binds to FC□RI and Fc□RII receptors on effector cells (mast cells, basophils, eosinophils) and on antigen presenting cells (DC), Th2/Th2A, and B lymphocytes to increase their activation on re-exposure to the allergen. This figure describes the main changes that occur during allergen immunotherapy blocking the allergic inflammation.

These locally released cytokines and mediators, attenuate the local activity of mast cells and the activation of other effector cells that contribute to the allergic inflammation, such as basophils and eosinophils. In addition, the release of IL-10 and TGF-beta, serves to reinforce the aforementioned production of IgG and IgA blocking antibodies. In particular

IgG4 subclasses play a very important role, as they can exchange heavy and light chains in their antigen binding fraction (Fab). This characteristic converts them into hetero-bi-valent antibodies (two different specificities) with moderate affinity to interact with the allergen, competing with IgE antibodies and blocking the inflammatory effect by binding to inhibitory receptors FcγRIIB (CD32) in both antigen presenting and effector cells in the allergic response. These inhibitory receptors have ITIM motifs (immunoreceptors with tyrosine-based inhibition motifs) which can inhibit cellular functions, as opposed to the ITAMs (immunoreceptors with tyrosine-based activation motifs).

3.5. Do these immune changes have any clinical meaning?

Yes. At this stage there is a sustained decrease in reactivity to the allergen that helps in reducing symptoms on allergen exposure. This lack of response occurs while on treatment, but when stopping AIT the remission is only temporary and may last just 2 to 24 weeks. Hence the importance of completing the treatment properly in order to reach the phase of long-term tolerance.

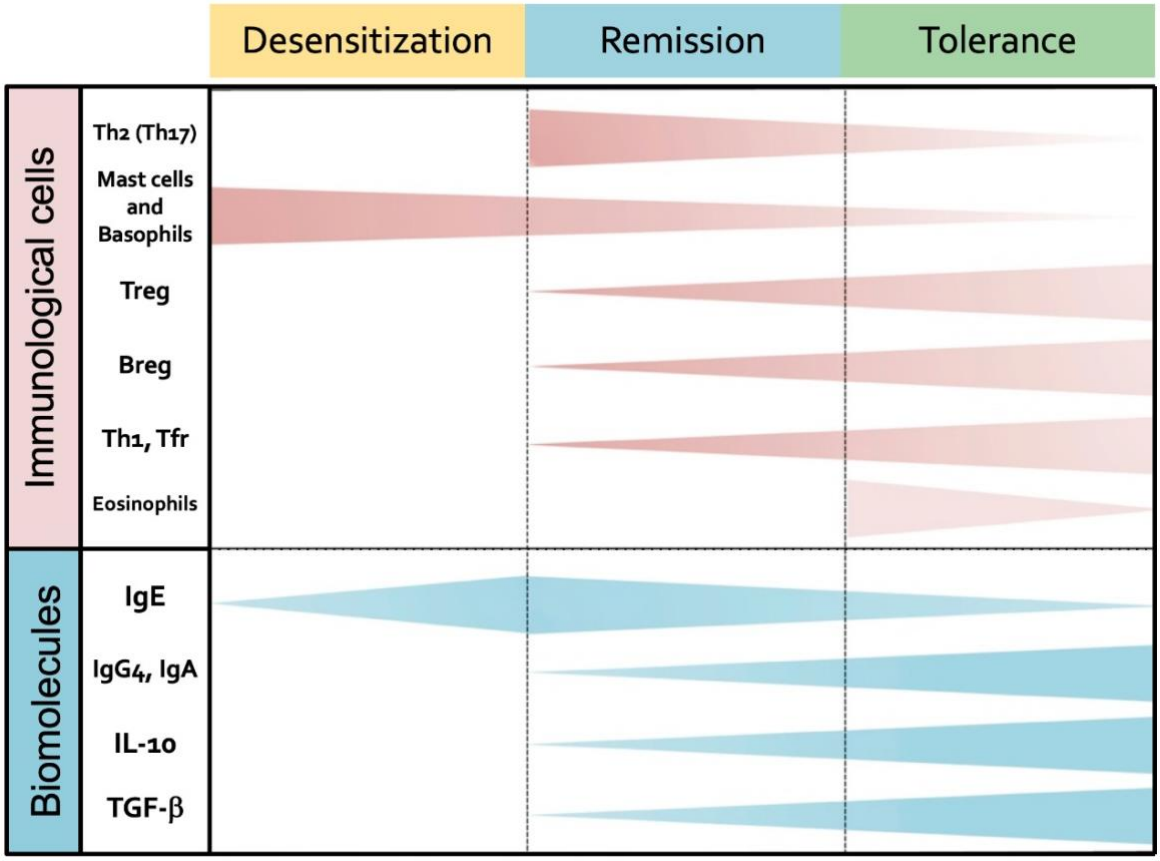
3.6. Is there any scientific evidence to support the presence of immune changes in the tolerance phase? See Figure 3.

Yes. Immune tolerance during immunotherapy has been found to be associated with induction of allergen-specific regulatory T cells (Tregs). Tregs express the transcription factor Foxp3 and produce regulatory cytokines, such as IL-10, IL-35 and TGF-beta. In addition to these cytokines, Tregs can inhibit the activity of antigen presenting and effector cells through other inhibitory molecules such as: PD-1 (programmed cell death protein 1), CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), adenosine receptors (CD39, CD73), IL-2 receptors (IL-2R or CD25) by sequestration of IL-2, thus maintaining the environment of tolerance towards the allergen. In this phase the allergen-specific regulatory B cells (Bregs) also contribute to the production of IL-10, TGF-beta and IL-35, in addition to the production of IgG4 and IgA, decreasing IgE synthesis. Long-term tolerance can occur through the persistence of these mechanisms and with the involvement of regulatory follicular T cells (Tfr) in an anergy-inducing reaction in lymph nodes (inhibition) and deletion (elimination) of allergen-specific Th2 lymphocyte cells.

3.7. Do these immune changes have any clinical meaning?

Yes. This phase may have permanent effects on the immune response even though treatment is discontinued and that is the ultimate goal of allergen specific immunotherapy.

Figure 3.3



Allergen immunotherapy has effects both on the level of activation/number of immune cells and on the production of different biomolecules. These immune effects occur at different rates and different moments during the treatment phases.

3.8. Are there any differences in the mechanisms of AIT using different routes of administration: subcutaneous, sublingual, epicutaneous or intralymphatic?

Yes. Some differences have been documented between the mechanisms of action of AIT, depending on the route of administration: subcutaneous (SCIT), sublingual (SLIT), oral (OIT), epicutaneous (EPIT) or intralymphatic (ILIT). The differences in the forms of immunotherapy depend on the place where their action is performed. In SCIT induction of desensitization, remission and tolerance mechanisms occurs in Langerhans cells in the skin and in the lymph nodes near the administration site (mainly axillary). While in SLIT, once the allergen has been captured, by the dendritic cells of the oral mucosa, it is transported to the regional lymph nodes, specifically to the Waldeyer's ring in the pharynx to induce the shift towards Th1 cells, as well as to Treg Foxp3+ lymphocytes, and also the activation of B cells for the production of local allergen-specific secretory IgA.

Contrary to what occurs in SLIT, in OIT the allergen is administered in an aqueous form or in capsules. It is swallowed immediately and mostly absorbed at the level of the intestinal mucosa, where it is captured by mucosal antigen presenting cells and carried towards the Peyer plaques in the intestine, where predominantly a polarization occurs towards Treg $Foxp3_+$ with IL-10 and TGF-beta production.

Epicutaneous immunotherapy (EPIT) has been attempted as an immunological method since the mid-20th century. It is currently applied through patches that contain the required allergen. They are stuck onto the skin for 24-48 hrs and applied daily or weekly. Applying the cover of the patch not only decreases the thickness of the corneal layer of the epidermis, but also activates keratinocytes to produce pro-inflammatory cytokines and to increase antigen penetration in the epidermis. This Ag is delivered to Langerhans cells that migrate to the regional lymph nodes by inducing activation of Treg LAP+ lymphocytes that can directly inhibit the activation of mast cells in the skin. Because the epidermis is not vascularized the risk of systemic effects or adverse reactions is also minimal.
Intralymphatic immunotherapy (ILIT) is given by direct injection of the allergen into the inguinal lymph nodes, guided by palpation or ultrasound. Once the allergen is injected into the lymph nodes, it is phagocytized by follicular dendritic cells and its peptides are presented in conjunction with histocompatibility molecules MHC-II to B cells in the clear area of the germinal center. These B cells are activated and differentiate into plasmablasts, plasma cells and memory B-cells; after this they leave the lymph node, through the efferent lymphatic vessels and secrete allergen-specific IgG4.
It has been observed that only intralymphatic immunization stimulates the production of the Th1-dependent IgG2a subclass, which is associated with better protection against allergen-induced anaphylaxis. Production of IgG1 and several cytokines such as IFN-alpha, IL-10 and IL-2 has also been described.

3.9. Are there any biomarkers to help monitor patients during immunotherapy?

Yes. The identification of potential biomarkers for the response to AIT and their validation is still a reason for study; biomarkers might help to improve the clinical selection and management of patients receiving such therapy. The biomarkers under study include molecular markers such as total IgE, specific IgE, specific IgE/Total IgE ratio, IgE inhibition tests such as the inhibition of the IgE mediated presentation of allergen to B-cells (IgE-facilitated antigen binding test = IgE-FAB), specific IgG4, and basophil activation tests (CD63, DAO). There are also quantitative cell markers such as the number or concentration of regulatory cells (DCreg, Treg, Breg), those of type 2 dendritic cells (DC2) and Th2a lymphocytes. Finally, also several cytokine patterns can be biomarkers (IL-4, IL-10, TGF-beta, IFN-gamma) or epigenetic markers of methylation or desacetylation of different genes promoting specific lymphocyte patterns.

Currently there are no validated and accepted biomarkers that can predict the clinical response to immunotherapy with a 100% reliability, but surely the better understanding of the pathophysiology of allergic diseases and the enhancement of the understanding of the underlying mechanisms of action of AIT inducing and maintaining a permanent state of tolerance, will contribute to improve AIT further in the near future.

Chapter 4: Subcutaneous immunotherapy (SCIT)

4.1 Introduction

SCIT has proven to be effective and safe as a causal treatment for those allergic diseases in which there exists an indication for AIT. In the AIT modality of subcutaneous administration (SCIT) there are two schools endorsed and applied in our country, which are the US and the European school. In this chapter we will compare both schools and give tips for good practice about their administration in México. As a summary we present in the following figure the highlights of both schools which we will develop in this chapter.

- Apply SCIT according to manufacturer's instructions
- Use standardized and possibly non-standardized products
- If grouped dose increase schedule
- Maintenance 4-6 weeks
- Do not mix non-counterparts
- Do not mix more than two homologous allergens
- Non-homologous allergens use 2 SCIT separately
- If using 100% polymerized mixtures of each allergen
- Yes seasonal pre-co schedule

Apply SCIT maximum effective dose tolerated
Use endorsed products
Use standardized and non-standardized
If you mix up to 4 allergens, use those which have low proteases levels
Maintenance doses every 15-30 days
No seasonal pre-co schedule

Chapter 4.2. SCIT: Dosage, maintenance vial preparation and administration schedules. US School

Table 4.2.1 SUMMARY Chapter 4.2. SCIT according to the US school		
GUIMIT experts recommend/suggest, taking into account evidence in MRG*		**Agreement**
4a.1. Is the efficacy and safety of this dependent on reaching the recommended therapeutic dose or – where appropriate – the maximum tolerated dose?	We recommend: Yes	100%
4a.2.a Is it advisable to start with an updosing phase and how long should it last? In Conventional SCIT	We recommend: YES 3-6 months	100%
4a.2.b Is it advisable to start with an updosing phase and how long should it last? In cluster, rush and ultra-rush schedules	Rush schedules are safer when conducted with modified or depot extracts. See 4.3: European school.	
4a.3.a. Is a time interval between each immunotherapy administration of 15-30 days advisable?	We recommend: YES	85%
4a.3.b Is the maintenance phase at least 3 years?	We recommend: YES	100%
4a.3.c Is the volume in vial for immunotherapy 3-5 ml?	We suggest: YES	100%
4a.4.a Is it advisable to mix taxonomically unrelated allergens?	We recommend: YES Consider proteases content. We suggest considering preparing separate vials	100%
4a.4b How many allergens could be mixed in one vial?	We recommend: consider selfdilution effect, see below	100%
4a.4c. Which allergens to mix and which not to mix	We recommend: Do not mix allergens with high protease content with low-content allergens	100%
4a.4d Can standardized allergens be mixed with non-standardized ones?	We recommend: YES	100%
4a.5.a Does in-office administration compared to home administration increase the safety profile?	We suggest: Yes	100%
4a.5.b it is advisable to get HR, RR, BP, Temperature, PO2% and peak-flowmetry before administration?	We suggest: Yes	100%
4a.5.c . Should a health status questionnaire be filled in prior to AIT administration?	We suggest: Yes	100%
4a.6.a Should SLIT administration be postponed in special conditions?	We recommend: Yes	100%
4a.6.a Should SCIT administration be postponed in special conditions?	We suggest: Yes Any condition that increases the risk of AIT adverse reactions	100%
4a.6.b Is there any condition under which a reduction of the scheduled dose should be considered?	We suggest: Yes Missed doses, increased contact with allergen, i.e.	100%

4a.7 What is the frequency of systemic adverse reactions in SCIT? a. Per all doses administered b. Per all patients c. Frequency of severe reactions? d. Frequency of severe reactions in a Mexican practice	a: 0.3% b: 3.7% c: 0.002% d: 0.3/dose, 1.6%/pats	100%
5.8 Considering the pre- and co-seasonal modality, compared to continuous schedules: could it be useful for Mexico?	We suggest: NO Although effective, Not applicable in Mexico	100%
Common clinical experience of GUIMIT experts (Simplified Delphi) **: evidence 1c		
Taking the precaution of keeping the effective maintenance dose and not mixing high with low protease allergens: is SCIT with up to 4 allergens mixed in a vial effective and safe?	Yes (59% recommends, 34% suggests). (Dilution limits the number of allergens that can be added to the maintenance concentrate if a therapeutic dose is to be administered).	
As for the duration of SCIT with aeroallergens, when initial improvement was slow (not until into the second year) should SCIT administration be continued for 5 years?	Yes (19% recommends, 56% suggests)	
According to the US school: SCIT with three allergens should be administered in a single vial with each of the allergens at fractional dose (one third of the usual dose).	100% suggests: NO 100% recommends including 100% of the therapeutic doses of each of the allergens included	

*MRG – Main Reference Guidelines. The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1

** Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM.

4.2.1 Efficacy

The efficacy of subcutaneous immunotherapy (SCIT) has been demonstrated in numerous meta-analysis based on double-blind, randomized, placebo-controlled studies in adults and children with allergic rhinitis, allergic asthma and hypersensitivity to insect venom showing a statistically significant reduction in the scale of symptoms, quality of life, and need for use of rescue medication. Because immunotherapy is the only available therapeutic resource focused on the underlying pathophysiological mechanism, (see chapter 3), it has a disease modifying effect on allergic conditions, is a personalized treatment tailored to each patient's needs, with a long term effect after discontinuation, and its efficacy is increased to the extent that the maximum tolerated dose or recommended therapeutic dose for each antigen included in the extract is reached. Therefore, low-dose immunotherapy is not effective. Although immunotherapy with high maintenance doses increases the possibility of clinical efficacy, it also increases the risk of systemic adverse reactions. Therefore, GUIMIT experts warn to proceed with caution specially in highly sensitive patients.

Adult 100% We Recommend Yes
Evidence: Ia
Recommendation: A

Child 100% We recommend Yes
Evidence: Ib
Recommendation: B

Good practice point 100%

4.2.2 Recommended therapeutic dose or maximum tolerated dose. (effective maintenance dose)

According to the U.S. school for AIT, the allergist prescribes and mixes the patient's allergen extract vial by selecting which allergens to add individually, assessing together the data

obtained from the clinical history, the correlation of exacerbation of symptoms with exposure to allergens, the seasonality of symptoms and the results of specific, *in vivo* and/or *in vitro* allergen specific-IgE tests. Although the selected allergens for AIT vary from patient to patient, we should ensure that the recommended therapeutic dose of each is maintained.

When prescribing or compounding an allergenic extract for AIT, we should in principle consider the need to administer a therapeutically effective dose of each of the indicated allergens. otherwise, we can administer ineffective immunotherapy in sub-therapeutic doses due by the dilution effect.

The maintenance concentrate can be obtained directly from the manufacturer, as is the case for the European extracts, the so called "patient named product" but these extracts are available in a lesser proportion in the US: non-dilutable extracts, to be injected directly into the patient according to the manufacturer's recommendations. Or, as is the frequent practice in the US, the maintenance concentrate can be prepared by the specialist who prepares the AIT under sanitary conditions, adding from the manufacturer's concentrate the necessary volume to the patient's vial to achieve the therapeutic dose of each individual allergen.

Suggest YES, 100%
Evidence: 2a
Recommendation: B

Table 1. Probably effective maintenance dose range and major allergen content in micrograms.

Allergenic extracts		
product Presentation	Therapeutic dose likely according to literature*	Mean of major allergen content mcg/mL (ALK-Abelló**)
D. pteronyssinus: 10,000 AU/mL	7 – 15 mcg der P1	Der p1+Der p2: 130
Major allergen content range EU allergen industry: Der P1 and Der P2: 8 – 538 mcg/mL		
D. farinae: 10,000 AU/mL	7 – 15 mcg der P1	Der f1 and f2: 140
Major allergen content range US allergen industry: Der f1 and Der f2: 48 - 216 mcg/mL		
Cat (hair, epithelium): 10000BAU	10 – 15 mcg/mL Fel d1	Fel d1: 40
Major allergen content range US allergen industry: 26 - 44 mcg/mL		
Cynodon d: 10,000 BAU/mL	¿? 300 - 1500BAU/mL	Cyn d1: 280
Major allergen content range US allergen industry: 125 – 449 mcg/mL		
Festuca e: 100,000 BAU/mL	10 – 20mcg Fes e 5	Fes e5: 160
Major allergen content range US allergen industry: 75 - 190 mcg/mL		
Dactylis g: 100,000 BAU/mL	10 – 20mcg Dac g 5	Dac mcg 5: 780
Major allergen content range US allergen industry: 294 - 940 mcg/mL		
Lolium p: 100,000BAU/mL	10 – 20mcg Lol p 5	Lol p 5: 440
Major allergen content range US allergen industry: 200 - 400 mc*g/mL*		
Poa prat: 100,000BAU/mL	10 – 20mcg Poa p 5	Poa p 5: 305
Major allergen content range US allergen industry: 118 – 421mcg/mL		
Phleum prat: 100,000BAU/mL	10 – 20mcg Phl p 5	Phl p 5: 675
Major allergen content range EU allergen industry: 354 – 1366mcg/mL		

*Maintenance dose range reported in scientific literature of controlled studies.
**Average major allergen values determined by ALK-Abelló with immunochemical methods (ELISA) and internal analytical reference standards.

According to analytical results there are considerable differences in the content of the major allergen in non-standardized extracts. Some attributed to differences in the allergen content of the source of the pollens. Although we would expect standardized extracts to show less variability between different lots, even in standardized products the major allergen protein content varies between companies in the US. (table 4.2).

The maintenance concentrate must be compounded in such a way that the dose considered to be therapeutically effective of each of its components is administered. The maintenance dose is considered at the therapeutically effective dose, which is the maximum tolerated dose without causing significant local or systemic adverse effects. Some patients reach the therapeutically effective dose, without necessarily reaching the projected effective dose. However, the maintenance dose should always fall within the clinically effective therapeutic range.

Table 4.3 Probably effective maintenance dose of standardized or non-standardized allergens. We recommend applying the general formula as an example (see text).

Origin	Standardization	Maintenance doses likely effective	Comments	
EU/ Mexico. Raw material imported into dry/freeze-dried US powder and reconstituted by Mexican companies	Not standardized 1:20, 1:10 p/v	Use general formula to obtain maintenance doses. Example: maintenance vial 2mL 1:200, 4 doses of 0.5cc once a month. V2=V1÷C1×C2 V2=2÷200×20=0.2cc V2= 0.2cc + 1.8cc diluent.	With this formula, effective maintenance doses of each of the allergens included can be obtained by monitoring the self-dilution effect.	
Mexico. Local raw material, local processing process	Not standardized 1:10 p/v	Same procedure: V2=V1÷C1×C2 – V2=2÷200×10=0.1cc V2= 0.1cc + 1.9 cc diluent.	The protein content of some allergens produced in Mexico is extremely low, impossible to achieve effective maintenance doses. (*)	
United States. Imported as a specialist-regulated diluted product that indicates immunotherapy **(Cox et, al. JACI;127.2011)**	Standardized AU, BAU: 10K – 100K/mL Not standardized w/v: 1:10, 1:20 NPU: 10K, 20K/mL	Use general formula for maintenance doses. Same formula for non-standardized, (invert mathematics) NPU and Standardized. Example: Maintenance vial 2mL, 1500AU 4 doses of 0.5cc 750AU/month. V2=V1×C1÷C2. V2= 2x1500÷10000. V2= 0.3cc +1.7cc diluent.	House dust mites D*f*, D*pt*	500 - 2000AU
			Cat (hair, skin)	1000-4000BAU
			Grass (pollen)	1000 - 4000BAU
			Cynodon	300 - 1500 BAU
			Ambrosia	1000 - 4000 AU
			Dog	?15mcg Can f1
			Pollen (non-standardized)	0.5cc 1:100 – 1:200 p/v
			Fungi	Maximum tolerated dose
			Hymenoptera	100 - 200mcg

V1 - final volume to be prepared; **C1** - Final concentration to be prepared; **V2** (unknown) - Volume required (manufacturer's concentrate) to reach the required dose and **C2** - Concentration of the extract (manufacturer's concentrate) to be used.

*Larenas-Linnemann D, Esch RE, Guidos-Fogelbach G, Rodriguez-Pérez N. A comparison of in vitro potency between European and Mexican allergens and US (CBER/FDA) reference extracts. Allergol Immunopathol (Madr). 2010 Jul-Aug;38(4):170-3.(45)

The maintenance dose is considered the maximum concentration of an individual allergen or mixture used as an effective therapeutic dose. However, some patients may not tolerate the maximum projected therapeutic dose due to extensive local reactions or systemic reactions; then the maintenance dose for that particular patient will be lower, except for immunotherapy with insect venom. For example, for *Dermatophagoides spp* the projected effective dose ranges between 500AU to 2000AU, but the maximum tolerated dose for a particular patient might only be 250AU. (table 4.3)

Good practice point
100%

Table 4.4

Calculation formula: mL of each allergen to be added to the patient's vial

$V_{Patient} \times C_{Patient} = V_{Manufacturer} \times C_{Manufacturer} \rightarrow V_{Manufacturer} = V_{patient} \times (C_{Patient} \div C_{manufacturer})$

$V_{Patient}$ - volume of the patient's vial to be prepared;
$C_{Patient}$ - concentration of the patient's vial to be prepared;
$V_{manufacturer}$ - (unknown) volume from manufacturer's concentrate to be added to the patient's vial to reach the required dose
$C_{manufacturer}$ - extract from the manufacturer (manufacturer's concentrate) to be used
(but reversed if concentrations such as 1:100 w/v are used, see below).

If using extracts expressing PNU, AU or BAU: $V_{manufacturer} = V_{patient} \times (C_{patient} \div C_{manufacturer})$

Example 1. Compounding SCIT for allergy to Dermatophagoides, you decide to give 500AU/dose as projected dosage. 0.5m/dose and prepare one vial with 10 doses.
Prepare 5mL ($V_{patient}$) 1000AU/mL ($C_{patient}$) from a concentrate of 10,000AU ($C_{manufacturer}$)
$V_{Manufacturer}? = V_{Patient} \times (C_{Patient} \div C_{Manufacturer})$: $5mL \times (1000AU \div 10{,}000AU) = 5 \times 0.1 = 0.5mL$.

Here we add 0.5mL from the manufacturer's concentrate to 4.5mL of diluent (or other allergens) to prepare your patient's 5mL vial with 1000AU/mL.
Each 0.5mL dose from this vial contains 500AU, thus meeting the projected dose for mites.

If *weight/volume* allergen extracts are used (w/v): $V_{manufacturer} = (V_{patient} \div C_{patient}) \times C_{manufacturer}$

Example 2. For SCIT for Ash pollen allergy, you decide to give a projected maintenance dose of 0.5mL 1:200 w/v and prepare a vial for 6 doses.
Prepare 3mL ($V_{patient}$) *1:200 w/v* ($C_{patient}$) *from a 1:10 w/v concentrate* ($c_{manufacturer}$).
$V_{Patient} = 3mL$; $C_{Patient}$ *1/200*; $C_{manufacturer}$ *1:10*; $V_{manufacturer}?$
$V_{manufacturer} = (V_{patient} \div C_{patient}) \times C_{manufacturer}$: $V_{manufacturer}$ (3mL ÷ 200) ×*10 (0.015* x 10 = 0.15).

Here we add 0.15mL from the manufacturer's concentrate to 2.85mL of diluent (or other allergens) to prepare your patient's 3mL bottle with 1:200 w/v. This complies with the projected dose requirements of 0.5mL of a concentration of 1:200 for non-standardized extracts.

All dilutions can be calculated using the following applicable general formula for standardized, non-standardized w/v or PNU available allergens: **V1 x C1 = V2 x C2**, where V1 - final volume to be prepared; C1 - Final concentration to be prepared; V2 (unknown) -

Volume required (manufacturer's concentrate) to reach the required dose and C2 - Concentration of the extract (manufacturer's concentrate) to be used, see table 4.4.

4.2.3 SCIT according to the US school: updosing (=dose increase) phase, administration schedule and duration

We recommend 100%
Conventional schedule
Evidence: 1
Recommendation: A

We suggest 100%
Evidence: not given
Recommendation: not given

Good practice point 100%

In the U.S. guidelines, a build-up phase is recommended for all SCIT schedules in order to reduce the incidence of side effects, especially systemic reactions. There is no fixed or unique schedule, but there are ranges of intervals, volume and total duration that are individualized according to the tolerance of each patient: 1 to 3 doses per week in a conventional SCIT schedule for a duration of 3 to 6 months. It usually starts with a dose 1000 or maximum 10,000 times lower than the maintenance dose, see table 4.5.
Cluster build-up schedules can be performed with aqueous allergens, but they are usually performed with modified allergens (polymerized) that reduce the risk of adver se events (Chapter 4.3).

Table 4.5 Preparation of vials for the dose increase phase: 1-3 administration per week in 6 increasing doses from 0.05mL to 0.5mL.

Vial number	Final concentration of compound vial vol/vol	Vial compounding technique			
		Original vial to take dose from. vol/vol	Volume (mL) to dilute from original vial	Diluent to add	Final volume (mL)
Maintenance	1:1	1:1	5.0	0.0	5
Vial 3	1:10	1:1	0.5	4.5	5
Vial 2	1:100	1:10	0.5	4.5	5
Vial 1	1:1000	1:100	0.5	4.5	5
In highly sensitive patients add an extra dilution					
Vial 0	1:10,000	1:1,000	0.5	4.5	5

The colors used are suggested for the cap of the vials. Thus, the red caped vial is maintenance and platinum caped vial the most diluted vial.
Adapted from: Larenas-Linnemann D, Ortega-Martell JA, Del Rio-Navarro B, Rodríguez-Perez N, et al. [Mexican clinical practice guidelines of immunotherapy 2011]. Rev Alerg Mex 2011; 58(1): 3-75 (1).

For cluster, rush and ultra-rush schedules the frequency of systemic reactions is higher compared to that of conventional SCIT. Therefore, GUIMIT experts insist that those schedules should only be carried out in specialized medical facilities with infrastructure for immediate attention of anaphylaxis. It is suggested to consider premedication with antihistamines, glucocorticoids, antileukotrienes or omalizumab, supported by studies showing a reduction on severity and frequency of systemic adverse reactions. Accelerated schedules are safer with modified or alum adsorbed extracts, see Chapter 4.3.

We recommend 85%
Evidence: I
Recommendation: B

Once the patient reaches the maintenance dose, the interval between injections can often be progressively increased, according to patient's tolerance, to an interval of 2 to 4 weeks for native inhalant allergens and up to 4 to 8 weeks for insect venom. Some subjects may do well with longer intervals between injections of maintenance doses.

Table 4.6. Cross-reactivity and representative allergens recommended for AIT.

Family/ Subfamily	**Scientific name**	**Common name**	Comments
Cupressaceae	*Juniperus ashei*	Mountain cedar	Strong cross-reaction between family due to marked homology of major allergens 1 and 2
Taxodioidea	*Cryptomeria japónica*	Japanese Cedar	
Pinaceae	*Pinus strobus*	White pine	No cross-reaction with *Cupressaceae* family
Poaceae	*Phleum pratense*	Timothy grass	Strong cross-reactivity due to marked homology between major allergen groups 1, 2, 3 and 5
Pooideae			Very low cross allergenicity between *Pooideae* due to the absence of groups 2 and 5 of major allergens
Cloridoideae	*Cynodon dactilis*	Bermuda Grass	
Panicoideae	*Sorghum halepense*	Johnson grass	
Sapindaceae	*Acer negundo* *Acer rubrum*	Boxelder Maple Red Maple	Disparity between *Acer Negundo* and Other *Acer*
Urticaceae	*Urtica dioica* *Parietaria jaudica*	Nettle Parietaria	Very low inter-allergenicity with other families
Betulaceae	*Betula verrucosa*	Silver birch	Strong cross-allergenicity between *Betulaceae* members by homology of groups 1 and 2 of major allergens
	Alnus glutinous	European Alder	
Fagaceae	*Quercus alba*	White oak	Strong cross-allergenicity between *Betulaceae* and *Fagaceae* by homology between groups 1 and 2 of major allergens
Amaranthaceae	*Amarantus retroflexus*	Pigweed	Strong cross-reactivity between species of *Amaranthus*
	Atriplex canescens	Saltbush	Strong cross-reactivity between species of *Atriplex*
Chenopodiaceae	*Kochia scoparia*	Burningbush	*Chenopodiaceae* show greater diversity and variable cross-reactivity
	Salsola pestifer	Russian Thistle	May possess unique allergens
Oleaceae	*European Olea*	Olive	Strong antigenic reactivity crossed between *Oleaceae* family by group 1 homology of major allergen
	Fraxinus exelcior	Ash white	Choosing local dominant allergens species
Asteraceae	*Ambrosia artemisifolia*	Short ragweed	Strong cross-reactivity between species of *Ambrosias*
	Ambrosia trifida	Giant Ragweed	Strong cross-reactivity between *Artemisia* species
	Artemisia vulgarias	Mugwort	Choosing local dominant species allergen
	Artemisia tridentata	Sagebrush	Minor or low cross antigenic reaction between *Ambrosia, artemisia and Xanthium*
	Iva xanthifolia	False ragweed	
	Xantum comunis	Coklebur	

Knowledge of allergenic interrelationships is crucial for the selection of extracts for aeroallergen immunotherapy. Cross allergenicity should be considered to achieve optimal doses of the main allergen causing symptoms and reduce the risk of adverse reactions by avoiding the simultaneous use of several allergens with high homology between the major allergen groups. Adapted from: Weber RW. J Allergy Clin Immunol 2008;122:219-21(46)

The decision to continue effective immunotherapy should generally be considered after 3 to 5 years of treatment. The severity of the disease, the speed of the patient's response, the sustained benefits of treatment and the convenience of treatment are all factors that should be considered to determine whether to continue or stop immunotherapy after that period of treatment.

We recommend 100%
Evidence: Ⅱ
Recommendation: B

One of the factors that can alter the potency of AIT, is the time that the allergens are kept in the vial, due to their tendency to adhere to vial glass' wall; that's why GUIMIT suggests to provide maintenance vials with 3 to 5 mL so they won't last for more than six months.

4.2.4 SCIT according to the US school: How to compound allergen extracts in poly-allergic patients.

According to the US guidelines on immunotherapy, mixing allergens is a common practice, bearing in mind that auto-dilution limits the number of allergens that can be added to the maintenance vial. When mixing, it should always be taken into account that for an effective AIT it is strongly recommended to reach the projected therapeutic dose for each of the constituents (see sections 4.2.1 and 4.2.2). Doing so, the number of allergens included in the extract should be limited to the maximum number of allergens that permit to maintain the clinically effective dose of each. That is why the knowledge of cross-reactivity between families and species of allergens is crucial. Considering cross-reactivity one should choose the locally most important one from among cross-reacting allergens for inclusion in the AIT vial (see table 4.6). Sometimes a patient can be positive to multiple allergens in the skin prick test, because they may have an allergy to a pan-allergen. GUIMIT suggests that if a patient has five or more positive reactions to pollens in the skin test, to consider confirming results by molecular diagnosis (see section 1.2.6).

We recommend 100%
Evidence: Ⅱ
Recommendation: B

We recommend 100%
Evidence: not issued
Recommendation: N.I.

Table 4.7. Combinations of allergenic extracts of compatibility
Low (⊗), moderate or *risky* (∅) or favorable (⊕) when mixed with insects, molds or *Dermatophagoides* mites. Adapted from: Esch RE. J Allergy Clin Immunol 2008;122:659-60.

Extracts with proteases				
Allergen	Insects	Molds	Mites	Comments
Insects	∅	⊕	⊕	Full-body extracts contain very high protease levels; endogenous proteases unless stored in glycerin 50%
Molds	⊕	⊕	⊕	Mold extracts do not appear to be affected by adverse effects of proteases
Mites	∅	∅	⊕	Dermatophagoides mites allergens resist mold and insect proteases if stored in glycerin >10%
Pollens	⊗	⊗	⊕	Allergenic pollen extracts are susceptible to adverse effects of insect proteases and molds; are compatible with mite extracts if stored in glycerin >10%
Cat dander/hair	⊕	⊕	⊕	Fel d 1 and other cat allergens are highly resistant to effects of insect and mold proteases
Dog dander/hair	⊕	∅	⊕	Dog allergens are susceptible to most mold extracts, but more stable when mixed with insects

Because the high variation in the content of the major allergen in the non-standardized extracts, ideally it is recommended to use standardized allergens if available. Standardized allergens can be mixed with non-standardized allergens when necessary.
It is strongly recommended never to mix allergens with high enzymatic activity (cockroach, molds, (dust mites of European origin) with allergens with low enzymatic activity (pollens, US dust mites) due to potential risk of degradation, (see Table 4.7)

We recommend 100%
Evidence: not issued
Recommendation: N.I.

Chapter 4.3 SCIT: Dosing, preparation of the maintenance bottle and administration schedules B. European School

Table 4.8 SUMMARY Chapter 4.3. SCIT according to the European school		
GUIMIT experts recommend/suggest, taking into account evidence in MRG*		**Agreement**
4.3.1. Is it advisable to start with an updosing phase and how long should it last? In cluster schedule	We recommend: Yes, 4 weeks	100%
4.3.2. Is it advisable to start with an updosing phase and how long should it last? Rush schedule	We recommend: YES, 1-3 days	100%
4.3.3. Is it advisable to start with an updosing phase and how long should it last? Ultra Rush schedule	We recommend: YES, 3.5-4 hours	100%
4.3.4 Is a time interval between each immunotherapy administration of 4-6 weeks advisable?	We recommend: YES	85%
4.3.5 What is the volume for the immunotherapy vial?	According to information provided by the manufacturer	100%
4.3.6 Can mixtures be made with unrelated allergens?	We suggest: No	100%
4.3.7 How many allergens could be mixed in one vial?	We recommend: No, eventually 2	100%
4.3.8 What allergens can be mix and which can't?	We recommend: No	100%
4.3.9 Can standardized allergens be mixed with non-standardized ones?	We recommend: No	100%
Common clinical experience of GUIMIT experts (Simplified Delphi) **: evidence 1c		
In the management of a patient with allergy to 2 non-homologous allergens (for example mite and grass pollen) with AIT according to the European school, should the SCIT be administered in two injections (one for each allergen) simultaneously, with 30 minutes of waiting after giving both injection?	Yes, 20% recommends, 30% suggests, 15% neutral	
SCIT with three allergens should be administered in a single vial with each of the allergens at fractional dose (one third of the usual dose)	100% suggests: No 100% recommends including 100% of the therapeutic dose of each allergen included	

*MRG – Main Reference Guidelines. The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1

** Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM

4.3.1 Efficacy and dosage of AIT according to the European school

We recommend 100%
Adults, Children
Evidence: Ia, Ib
Recommendation: A, B

The evidence of the efficacy of SCIT generated over the past two decades comes almost exclusively from studies conducted in Europe with European products from various manufacturers. However, there are other European manufacturers with little evidence.
In AIT according to the European school the extracts that the manufacturer delivers are final products, ready to be administered to the patient. In this way the European physician does not care about the dosage or how to prepare the vials. Moreover, the patient often picks up his vial at the pharmacy. The role of the allergist is to select the appropriate

extract(s) for AIT. Thus, immunotherapy will be applied according to the information and instructions given by the manufacturer of the product. Each product has its recommended therapeutic dose. It is important to have documentation and/or bibliography that guarantees the efficacy and safety of each product, given the heterogeneity between them.
At the moment the GUIMIT document is finished (June 2019) in Mexico we have standardized and finished products (ready to use) of European manufacture of the following brands: IPI, Inmunotek and some of ALK-Abelló.

4.3.2 SCIT according to the European school: updosing phase, administration schedule and AIT duration

The updosing phase for the SCIT according to the European school varies according to the manufacturer. Several already have accelerated updosing schedules, see below. During the maintenance phase the injections are administered at intervals of 4 to 8 weeks and the volume generally varies between 0.5 to 0.8mL, according to the manufacturer's instructions. GUIMIT recommends that the minimum duration of the SCIT be the same as in the US schedule of at least 3 years, as it has proven to be effective on the long term, even years after the completion of SCIT. With shorter schedules it has not been possible to demonstrate an efficacy beyond the administration time.

We recommend, 4-8s 100%.
Evidence: V
Recommendation: D

We recommend, 100%
Evidence: I
Recommendation: A

4.3.3 SCIT accelerated updosing schedules

Since updosing schedules with clustered administration are common in Europe, the reference guidelines (RGs) don't mention them directly, nor their level of evidence and recommendation. However, in the studies on which RGs are based to conclude levels of evidence and grades of recommendation, different updosing schedules with grouped administration are applied, using modified, standardized and ready-to-use products such as polymerized allergens, see Chapter 8.

We recommend 100%
Cluster, rush and ultra-rush schedules
Evidence: IV
Recommendation: C

Table 4.9 Dosage increase schedules with grouped administration schedules.

	Dosage per session	**Duration of dose-increase phase**
Conventional	1 to 3 shots per week	3 to 6 months
Cluster	2 or more shots per session with 30 min interval (weekly)	4 weeks
Rush	2 or more shots per session with intervals of 15 to 30min, daily	1 to 3 days
Ultra-rush	2 shots in 1 session, one day	3.5 to 4 hours

The advantage of cluster, rapid (*rush*) and (*ultra-rush)* schedules is that they allow one to reach the maximum dose more quickly, but especially with fewer office visits. In the cluster schedule, 2 to 3 doses are applied per visit at intervals of 30 minutes and on non-sequential days for a duration of 4 to 8 weeks; doses are applied every 15 to 60 minutes in rush immunotherapy to reach the maintenance dose in 1 to 3 days. In ultra-rush SCIT the maintenance dose is reached in 3.5 to 4 hours, see table 4.9.

Currently several manufacturers of SCIT in Europe already have studies and product instructions or even package inserts with updosing schedules with grouped administration.

In México it is suggested to apply them using modified products that have safety studies with this kind of schedule and taking all necessary precautions for the management of systemic reactions. When using accelerated updosing schedules it is suggested to pre-medicate with antihistamine to avoid or minimize local reactions. accelerated updosing schedules should always be apply under medical supervision and a minimum waiting time of 30 (some prefer 60) minutes after the last administration.

Good practice point
100%

4.3.4 SCIT according to the European school in poly-allergic patients

When administering SCIT with European extracts it is recommended to mix up to two allergens of the same family / biologically related. It is not recommended to make mixtures between allergens from unrelated families to avoid unnecessary reduction of allergen doses as well as avoid mixing allergens with high and low amounts of proteases to prevent enzymatic degradation. It is necessary to consider that in this type of immunotherapy finished products are used which, when mixed, are diluted, thus losing their standardization and the guarantee of efficacy given by the manufacturer. There are manufacturers who sell allergen mixtures in two ways: 100 mixtures, in which each allergen maintains its full concentration and diluted mixtures (for example when mixing 3 allergens, each one is 1/3 of its dose). GUIMIT experts express their preference for the 100 blends.

We suggest 100%
Adult, children
Evidence: I, I
Recommendation: A-B; B-C

In patients, poly-allergic to non-biologically related allergens, the European school suggests another solution: choose the two most clinically relevant allergens and apply them separately. Based on common clinical experience, GUIMIT experts suggest applying them simultaneously with a 30-minute post-administration waiting time.

Good practice point, see table 4.8

4.3.5 Pre and co-seasonal schedules of SCIT

Europe: Pre and co-seasonal schedules are those in which SCIT is applied only prior to/ and during the pollen season and is suspended outside the season. It is suggested that the dose increase phase be performed prior to the start of the pollen season to reduce the risk of adverse reactions that are seen more frequently when the updosing phase is administered during the season. During the co-seasonal phase it is possible in many cases to continue with the administration of the SCIT without reducing the maintenance dose. However, it is necessary to individualize the management plan for each patient prior to administration.

GUIMIT: Suggest: No
Agreement:100% in adults and children
Evidence: Yes Ia/ Children Ib

Both pre-and co-seasonal schedules are recommended for seasonal allergic rhinitis with a documented short-term benefit, but its long-term effect is doubtful.

In México we do not suggest applying this type of schedule because there is a prolonged pollination season and its long-term effect is doubtful. However, in México there are places where pollination seasons are not so prolonged and the seasons are more marked in which, with a correct assessment, these schedules could be applied

Good practice point , see table 4.8

Chapter 4.4 SCIT: safety and prevention of adverse events

In Chapter 9 we will discuss in more detail adverse events with AIT and their management. In the section below we present the frequency of adverse events and how to increase safety related to the administration of SCIT.

4.4.1 Frequency of local and systemic adverse reactions

With the administration of native extracts in the US, the frequency of local reactions (LR) is reported between 26 to 82% of patients and between 0.7 to 4% of injections. Regarding systemic reactions (SR), a prospective multicenter study in the US reported a frequency of 0.3% per injection and 3.7% per patient. With these same allergens and concentrations in México, in a retrospective case series we found an SR frequency of 1.6% per patient and 0.3% per injection.(1)(47) Another center reported 0.5 / 0.08% per patient / injection.(48) The frequency of SR in prospective / retrospective studies and surveys in Europe is reported from 2.1% (European survey) to 5.2% (Germany) of patients and about 0.06% (Germany) of injections.

Regarding serious or even fatal SR American colleagues have studied the issue in detail. The frequency of fatality varies between 1 per 2.5 to 4 million injections, with a reduction in frequency over the last decade.(49) The greatest risk factor for a fatal outcome was severe or uncontrolled asthma with FEV1 <70% at the time of administration (> 50% of cases), followed by activation of symptoms during the peak of the pollination season (25%), previous systemic reaction and start of a new bottle.(50) The Paul Ehrlich Institute reports SR between 0.002% to 0.0076% (2-7.6 / 100,000) of injections with native allergens in Europe, without fatalities. For allergoids the reports vary more: between 0.0005% and 0.1% systemic reactions. In a study on allergy safety Casasnovas M.et al. I report a series of three-year retrospective cases where 20 million doses of SCIT were applied with allergoids and 0.1% of the injections applied had a systemic reaction as well as that there was no fatal reaction.(51) Article referenced in volume 2 of the EAACI.

Local reactions (LR) largely depend on the maintenance dose administered. With optimal maintenance doses, see 4.2.1-2, it is very common to see mild LRs lasting less than 24 hours. On the contrary, with sub-optimal doses it is rare to see LR. Although LRs are low predictors of systemic reactions, large LRs - defined as larger than 2.5cm in diameter – and especially repetitive large LR are. Of the patients who presented SR 32% had presented severe LR compared to 8% of the control group without systemic reaction.

We suggest 100%
Evidence: 2a
Recommendation: B

4.4.2 Pre-SCIT administration care

Both in the US and in the European community, the recommendation to apply immunotherapy in medical units is based on the perception of faster and more efficient recognition and proper treatment of an anaphylactic reaction, and therefore, a lower risk of serious or fatal systemic reactions, assigning a greater risk to the practice of applying AIT at home. However, there is no comparative study of these 2 options that demonstrates an increase in risk with home administration; on the contrary, there is a retrospective report of more than 2 million administrations of AIT at home with a slow dose increase schedule and in low-risk patients that even showed less SR. (52)

We suggest: 100%
Evidence: IV
Recommendation: C-D

In conclusion, GUIMIT suggests that the SCIT be applied in a medical unit by trained medical personnel to treat serious systemic reactions with appropriate material and equipment for this purpose, see chapter 7. If such practice is not possible, administration in a doctor's office First-contact trained in treating anaphylaxis could be an alternative option. Finally, GUIMIT considers that it is also a valid position to administer at home, as long as the allergy specialist selects the patients with the highest risk of serious reactions and does not allow these patients to apply at home.

Good practice point
100%

4.4.2.1. Unequivocal identification of the patient and his bottle

Before applying the SCIT, two important safety points must be addressed.

- properly identify the patient's AIT bottle (s)
- determine the dose to be administered.

For the correct identification of any substance that will be applied to human beings, in this case immunotherapy with allergens, two identifiers are needed (for example patient name and date of birth or file number).(53)

Good practice point
100%

4.4.2.2 SCIT pre-administration patient assessment

This last point is directly related to the risk of an adverse reaction according to the detection of risk factors in the patient at the time of administration. Various circumstances can increase the frequency of systemic reactions and severe SR due to SCIT, see Table 4.10. (50, 54, 55) Above all, SCIT should not be applied in patients with uncontrolled asthma.

We suggest 100%
Evidence: Ⅳ
Recommendation: C-D

GUIMIT suggests taking baseline vital signs, peak-flow and using a short pre-administration standard questionnaire, see figure 4.2.

VS and Questionnaire:
We suggest 100%
Evidence: not issued
Recommendation: N.I.

If a risk factor for anaphylaxis is identified, the dose of immunotherapy should be reduced or its administration postponed. The best evidence that exists comes from a survey among a thousand certified allergists, see table 4.11.

Postpone/reduce doses:
We Suggest 100%
Evidence: III
Recommendation: C

Table 4.10

Risk factors for systemic reactions during SCIT
• Concomitant allergy symptoms and potential allergenic exposure
• Concomitant infection
• Mastocytosis
• Systemic reactions with previous SCIT
• Use of beta blockers
• Uncontrolled asthma or severe asthma
• High degree of allergen sensitization in SPT or by specific serum IgE
• Excess dose increase during the updosing phase
• Overdose of allergenic extract
• Not following recommendations for dose reduction when switching to a new batch
• High-impact exercise 1h before or within 2-3h after SCIT

*SR are not more frequent, but have poor response to adrenaline

Figure 4.2*

Before the administration of SCIT **Patient's Name:_____Date: _____**		
Vital signs	HR: _____/min RR: _____/min BP: ____/_____ (pulse oximetry): _____%	
Peak flow (asthma)	____ L/sec	
Brief questionnaire of good health	To increase safety regarding your allergen immunotherapy administrations, please answer the following questions. Our staff will review your answers and be able to notify your doctor if any questions arise regarding your administration today.	
	If you are pregnant, or if you have any new medical conditions, you should tell our staff before applying your vaccine. Please answer each question.	
	1. Are the name and date of birth on these vials correct?.	☐ Yes, ☐ No
	2. Was your asthma activated? Have you had any chest tightness, coughing, wheezing or shortness of breath this week?	☐ Yes, ☐ No
	3. Did you had eye or nose itching, sneezing, or nasal discharge this week?	☐ Yes, ☐ No
	4. Do you have a respiratory infection or any flu symptoms today?	☐ Yes, ☐ No
	5. Did you have any problems after the last shot: hives (urticaria), cough, wheezing or a local reaction of more than three fingers that lasted until the next day?	☐ Yes, ☐ No
	6. Are you taking new inhalers or medication, e.g. for high blood pressure? Please explain: _____	☐ Yes, ☐ No
	Was any action taken? Explain (if yes) _____ **Signature attending personnel: _____**	

** Questionnaire not validated but suggested by GUIMIT for orderly assessment of the patient prior to the administration of SCIT. Adapted from AAAAI website.

Table 4.11: When to postpone or reduce the dose of immunotherapy

Adjustments to the SCIT administration schedule	
Postpone doses - Exacerbation of asthma or FEV_1 or peakflow meter < 70% predicted - Acute exacerbation of allergy symptoms - Acute respiratory and non-respiratory infections	
Situation that requires dose reduction	**How to reduce doses**
- 1st shot of a new bottle	50%
- Large local reactions >25mm (more so, if the last until the next day)	Previous dose or reduce up to 50%
- Previous systemic reaction	Mild: previous dose Mod-severe: 1/10th dose
- Several systemic reactions	Evaluate if suspending SCIT is necessary
- Highly sensitized patients + seasonal exposure	50%
- Prolonged interval between doses (aqueous extracts)* 1) updosing phase. Time since last SCIT shot:	

○ < 2 weeks	Increase normally
○ 2-3 weeks	Repeat last dose
○ 3-4 weeks	Go one dose back
○ 4-5 weeks	Go 2 doses back
○ 6-8 weeks	Reboot from bottle 1
2) Maintenance phase. Time since last SCIT shot:	
○ < 5 weeks	Apply normally
○ 5-6 weeks	Go one dose back
○ 6-8 weeks	Go 2 doses back /50%
○ 2-3 months	Start vial from 0.05mL
○ 3-4 months	Previous bottle 0.05mL
○ > 4 months	Reboot from bottle 1
- Prolonged interval between doses (allergoid and/or adsorbed extracts) **:	Maintenance < 8 weeks: maintain normal dose (Details, see manufacturer recommendations)

* Based on the experience of about a thousand allergists members of the *American Academy of Allergy, Asthma and Immunology.* Adapted from: Larenas-Linnemann DE, Gupta P, Mithani S, Ponda P. Survey on immunotherapy practice patterns: dose, dose adjustments, and duration. Ann Allergy Asthma Immunol 2012; 108(5): 373-8

**Preferably continue normal or suspend. It is debatable whether reducing the AIT dose of European extracts results in loss of efficacy.

4.4.3 Post-administration care for SCIT

It is recommended that the patient waits 30 minutes after administration of SCIT since 80% of systemic reactions have been reported in that time span. It is also during the first 30 minutes when most serious reactions have occurred. In the last two decades there have no longer been fatal reaction that start > 30min post-administration.(49) SR grade I-II have been reported when there is a rapid absorption from the subcutaneous tissue into the systemic circulation. Therefore it is advisable not to exercise or take a hot bath 2 hours post-administration, and postpone performing extreme exercise for at least 3-4 hours.

Good practice point 100%

5 Chapter 5: Sublingual Immunotherapy

Table 5.1

SUMMARY Chapter 5: Sublingual Immunotherapy		
GUIMIT's experts recommend/suggest, taking into account evidence in MRG		**Agreement**
5.1.a For products, specifically sold for SLIT: Is there a probable effective maintenance dose?	We recommend: Yes	100%
5.1.b What is this probable effective SLIT maintenance dose?	We suggest: 5-50mcg of major allergen daily	100%
5.2.a For liquid SLIT products, prepared from vials with concentrate allergenic extract: Is there a probable effective maintenance dose, relative to the SCIT dose?	We suggest Yes	100%

5.2b For natural allergen extracts: what will this daily maintenance dose be -in relation to SCIT?	We suggest 50-200% of the monthly dose of SCIT	100%
5.3.a In the MAINTENANCE phase of SLIT: should the dose be administered daily for maximum efficiency?	We recommend: Yes	100%
5.3.b Is the duration of the maintenance phase minimum 3 years?	We recommend: Yes	100%
5.4.a In poly-allergic patients with indication for SLIT: Is it advisable to mix unrelated allergens?	neutral	100%
b. How many allergens maximum per bottle?	Suggest: 2 non-homologous allergens	100%
c. Which to mix and which not to mix?	We recommend: respect the biological content of proteases We suggest: consider preparing separate vials	100%
5.5 Is there evidence that adding adjuvants, e.g. bacterial products, can improve SLIT efficacy?	We suggest: Yes	100%
5.6.a Are there circumstances in which SLIT administration should be postponed?	We recommend: Yes	100%
5.6.b Are there circumstances in which SLIT dosing should be reduced?	We recommend: Yes	100%
5.7 What is the frequency of systemic adverse reactions due to SLIT? a. of all administered doses b. of all patients c. frequency of severe reactions?	a. 0.056% b. Local: 50-75%, systemic 0.08% c. severe 1.1% of patients	100%
5.8 The pre and co-seasonal mode, compared to continuous administration schedules: could it be a viable option for patients in Mexico?	Suggest: Yes effective, but No (no long-term effect)	100%
Joint clinical experience of GUIMIT experts (Delphi simplified): evidence 1c**		
Taking the precaution of maintaining the maintenance dose and not mixing allergens with high and low proteases: is SLIT with up to 4 allergens mixed in one vial effective and safe?	Yes (37% recommended, 45% suggest)	
In a patient who does not experience improvement after one year of SLIT: • Should SLIT be continued to see if the patient improves during the first part of his 2nd SLIT year? • Is it probable he/she shows improvement when switching to SCIT?	• No (29% recommends no, 51% suggests no) • Yes (11% recommends, 55% suggests)	
Points of good practice		
5.3.c The volume of the maintenance SLIT vial is 5-10mL?	We suggest Yes	100%

*MRG – Main Reference Guidelines. The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1

** Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM.

5.1 Introduction

High quality, DBPC studies, have clearly demonstrated the efficacy and safety of SCIT: EAACI-RA/WAO-SLIT guideline: evidence 1a with pollens and house dust mite; evidence for pet extracts and molds is less solid and for cockroach almost absent, see chapter 2. With this, SLIT presents a good treatment option of AIT for patients who cannot regularly come in for their SCIT shot or for those who prefer not to receive injections. In addition, SLIT has better safety than SCIT. So far no grade V reactions have been reported with SLIT and grade IV reactions are extremely rare (see chapter 9). Therefore, SLIT might also be an option for patients who do not tolerate SCIT. This point has been discussed internationally, because systemic adverse events have been documented when patients who had systemic adverse events with SCIT were switched to SLIT. Therefore, in this particular situation it is important to start SLIT with an appropriate build-up phase, as there are case reports in Europe showing that starting directly with the maximum SLIT dose - as is common practice in Europe for SLIT- is not well tolerated in this kind of patients.(56, 57) However, when using a build-up phase at the start of SLIT no problems were reported in 2 patients with anaphylaxis post-SCIT in the UK.

5.2 Selection of SLIT-specific main reference guidelines

For the sublingual immunotherapy (SLIT) chapter, two new main reference guidelines had to be sought, since one of our original main reference guidelines did not cover this modality (JTF AAAAI/ACAAI), and the other two had a very similar approach, since both reflect the concepts of the European school related to SLIT and also partially shared the same lead authors. Thus the authors of Chapter 5 relied on the quality evaluation according to AGREE-II of SLIT guidelines, published over the past ten years, to select the two SLIT guidelines with the best score as extra main reference guidelines for this chapter. In literature there already existed a publication with AGREE-II evaluations of several SLIT guidelines, but not of the most recent ones.((5)The most promising of the not analyzed SLIT guidelines was the JTF AAAAI-ACAAI-SLIT practice parameter 2017.(58)In the independent assessment according to AGREE-II of the newer guidelines by two experts, the JTF one achieved an average score of 3.15/7 points, which was too low to be selected as main reference guideline. Thus, the two best quality SLIT guidelines that were selected as additional main reference guidelines for this chapter were the WAO (40) and the Japanese SLIT guideline. (7)

5.3 SLIT dosage, frequency and duration

Studies in search of doses have shown that the efficacy of SLIT depends on the dose and possibly other factors as well. Thus, just as for SCIT, the efficacy of the SLIT is dose-dependent.

With the data analyzed below, it could be suggested that the daily dose of SLIT is possibly between 50-200% of the monthly dose of SCIT. In addition, it is very likely that the lower the volume of administration, the greater the trans-mucosal concentration gradient and possibly the greater its absorption (good practice point). This was demonstrated for the difference between the SLIT tablets: the bioavailability depends on the formulation and is higher for the lyophilized tablet vs. the compressed tablet.(59)

Suggest Yes, 100%
Evidence: indirect
Recommendation: not emitted.

We recommend Daily 100%
Evid: 1a, Rec: A

All main reference guidelines either explicitly mention that the administration of SLIT is daily or include DCPC studies that used such administration schedule.

During the first year of administration, there is already a reduction in symptoms and medication use with SLIT; an administration is recommended for at least 1 year for house dust mite, because it was proven effective at 12 months and the effect persisted one year later. For grass pollen it is recommended to administer for 3 years, because with this it has been possible to document a medium-term effect (2 to 5 years post-administration), which continues after immunotherapy has ended (EAACI-prevention; Japanese SLIT guideline). For the long-term effect, more than 5 years after completing AIT, the evidence is low. Two year SLIT administration failed to maintain the beneficial clinical effect one year after discontinuation,(60) confirming the need for a minimum duration of 3 years for SLIT, to obtain a beneficial effect after its termination.

We recommend minimum 3 yrs, 100% Evidence: 1b, Rec B

The main reference guidelines do not mention the volume of the bottle, but a volume between 5 to 10mL seems adequate, so that it can last 2-4 months.

Point of good practice 100%

Starting the maintenance phase 12 weeks before the pollination season gives a better therapeutic effect (Japanese SLIT guideline: Ia). SL immunotherapy with a pre-coseasonal schedule is an alternative for the management of seasonal rhinoconjunctivitis since it is effective for symptom reduction during its administration, it is safe and it reduces costs. However, it has not been possible to demonstrate the induction of tolerance with this type of schedule and has no long-term effect, so we do not suggest it for Mexico.

We suggest no, 100% Evidence Yes: Ⅱ Recommendation: B

5.4 SLIT dosage according to main reference guidelines and original studies referenced in them

One can only make assertions regarding the dose of SLIT relative to the monthly maintenance dose with SCIT, reviewing the doses documented as effective for SLIT in original studies referenced by the main reference guidelines. Thus, table 5.2 was constructed showing the effective doses found in high quality studies, expressed both in units used by the manufacturer, and in micrograms of major allergens. As the labtests used for the determination of micrograms of major allergen may vary, caution must be taken in comparing the results between manufacturers, see Chapter 8. Therefore, a comparison of the potency of extracts, all analyzed in the same laboratory has greater validity. There are some reports that used this method and that do allow direct comparison of potency between extracts, some referenced in the main reference guidelines.(61-65) These studies showed that there is great variation between the products on the market in Mexico(18); they also teach that the dose of the SLIT is not well defined in Europe either, since there is a great variation between the doses of the SLIT of the products of different manufacturers. In an attempt to give a range for the probably effective maintenance dose in SLIT, table 5.2 was created in relation to the recommended dose for SCIT.

We suggest, 100% Evidence: indirect Recommendation C

Table 5.2:
Clinically effective SLIT dosage in randomized dose-finding studies

Allergen	Sublingual immunotherapy					SCIT Monthly Dosage	SLIT/Monthly SCIT Daily Dosage
	Manufacturer	Tablet or liquid	Daily dose (manufacturer units)	Daily dose (mcg major allergen) 1*	Daily dose (expressed in (B)AU)		
Grass pollen (63, 66, 67)							

Phleum pratense	ALK-Abelló	Tabl	75,000 SQ-U	15mcg Phl p 5	6200 BAU	1000-4000 BAU[1]	1.5
5-grasses	Stallergènes	Tabl	300IR	25mcg Phl p 5	8200 BAU	1000-4000 BAU[1]	2
Tree pollen (68)							
3-trees [2]*	ALK-Abelló	Liquid 0.4ml	28.6 SQ-U	4.3mcg Bet v 1/ Aln g 1/ Cor to 1 (850,000 SQ-U per month)	No info	100,000 SQ-U	0.35
(69)**Weed polen** (69-72)							
Ambrosia	Greer	Liquid	48mcg Amb to 1[3]*	48mcg Amb to 1	No info	6-12mcg Amb to 1[1]	5
Ambrosia	ALK-Abelló	Tabl	12 Amb to 1 unit	12 Amb to 1 unit	No info	6-12mcg Amb to 1[1]	1-2
House dust mite(73, 74) **and for asthma** (24-27)							
Dpt+Df: 1:1:1:1	ALK-Abelló	Tabl	6 SQ HDM-10,000 JAU; 12 SQ HDM [4]*	6 SQ-U = 7.5mcg grp 1 and 7.5mcg group 2.	No info	500-2000AU[1] 7 Der p 1[2] Using ALK-US analysis: 1-8 Der p 1, Der f 1; 0.1-9 Der p 2, Der f 2	1 (range 1-7)
Dpt+Df: 1:1	Stallergènes	Tabl	300IR	16mcg Der p 1 68mcg Der f 1 (=84 grp 1)	(Some calculated: 15,000 AU) [5]*	500-2000AU[1] 7 Der p 1[2] Using InBio analysis: 4-10 Der p 1, Der f 1; 0.65-7 Der p 2, Der f 2	8 (range 8-20)

1* Source: publications in indexed journals or Package insert
2* 3-Tree pollen – *Betula verrucosa*, *Corylus* Hazelnut and *Alnus glutinosa*
3* 94% received this dose. Those who did not tolerate continued with the lower dose of 18mcg Amb to 1 daily.
4* the dose chosen for marketing in Europe is 12 SQ-U (for greater efficacy in secondary parameters in dose search study) and in Japan 6 SQ-U/10,000 JAU.
5* https://www.aaaai.org/ask-the-expert/allergen-immunotherapy-IR-units
1. AAAAI/ACAAI JTF 2011
2. Haugaard 1993(75) (referred to in AAAAI/ACAAI JTF 2011)

Dpt = *Dermatphagoides pteronyssinus*; Df - *Dermatphagoides farinae*; 1:1:1:1 = equal amounts of Der p 1: Der p 2: Der f 1: Der p 2; 1:1 = equal amounts of Der p 1: Der f 1, no group 2 is mentioned; IR = index of reactivity; JAU = Japanese allergy units; SQ-U = standard quality unit

5.5 Maintenance phase: argumentation of how to compare the daily dose of SLIT with the monthly dose of SCIT

The EAACI-RA and German guidelines observe that the meta-analyzes have shown considerable heterogeneity in the level of efficacy between different products and different doses for SLIT. As a result, they issue the recommendation: if available, it is recommended to use products with evidence of documented efficacy in clinical studies. GUIMIT experts note that part of the heterogeneity in clinical studies is also due to multiple differences in study design, in the population studied and in the exact definition of efficacy parameters.(76)

We suggest, 100%
Evidence: 1a
Recommendation A

At the time of the development of GUIMIT in Mexico we only have a few allergens and products for SLIT whose efficacy has been proven in clinical studies, partly because several of our most prevalent allergens are considered of minor importance in Europe. Fortunately, however, the main reference guidelines do consider the situation of these 'orphan' allergens (= with few European patients allergic to them and consequently without financial resources to conduct clinical studies) and consider it acceptable to give AIT without solid clinical documentation. Likewise, the EAACI-prevent guideline does allow us to assume the existence of a class effect: by demonstrating that AIT works for a certain allergen, it most probably also do so for a different one. Interestingly, the dose that is finally effective for SLIT with grass pollen is in the same dose range for very different products and from different manufacturers: 75,000 SQ-U, containing 15mcg Phl p 5 and 300IR containing 25mcg Phl p 5. For the rapidly dissolving tablet (ALK-Abelló) a very similar dose was found as the most effective dose for the house dust mite (6 SQ-U containing 15mcg total major allergen groups 1 and 2), but the ideal dose for the slower dissolving tablet was somewhat higher (300IR = 80mcg total major allergen groups 1 and 2). This could be considered the top dose, because it yielded better results than 500IR in both a European study(73) and Japan.(77) Effective doses between 4.5-48mcg of the major allergen have been reported for tree and ragweed pollen, see table 5.2. Although this indicates a variation of a factor of 10, it is still in the same range of micrograms in which the recommended monthly dose for SCIT is found (6-12mcg Amb at 1). Therefore, GUIMIT suggests that the daily effective dose of SLIT is possibly between 50-200% of the monthly dose of SCIT.

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5.6 SLIT with extracts available in Mexico

Analyzing the evidence in main reference guidelines in the context of the extracts available in Mexico the GUIMIT experts observe that:

1) All main reference guidelines recommend using products with documented evidence in clinical studies.
2) In Mexico we only have one tablet variant for SLIT (liophilyzed)
3) En Mexico we do not have extracts for SLIT with clinical documentation of efficacy considered solid by the main reference guidelines.
4) The proven effective daily dose range for SLIT does not have too high a variation, see Table 5.2. It appears to be close to the monthly dose considered effective for SCIT (5-20mcg of the major allergen)

5) En Mexico we have standardized and non-standardized, highly concentrated extracts, but we also have much more diluted extracts.(18, 64, 78)
6) Only natural extracts for SLIT can be used, extrapolation to doses used for SCIT with adsorbed extracts may not be valid.

Point of good practice
100%

For SLIT with standardized extracts **GUIMIT recommends**:

1) For allergens available in Mexico as standardized extracts for SLIT, which have clinical documentation of efficacy: it is preferable to use these extracts (this holds true for this moment or for in the future)
2) For these allergens, use the manufacturer's recommended dose

For SLIT with non-standardized extracts **GUIMIT suggests**:

1) For allergens only available as not standardized extracts and/or without dose-response studies consider a minimum daily dose for SLIT between 50-200% of the monthly dose of SCIT.
2) Consider that a smaller volume (<0.4ml) is likely to be more effective than a larger volume (1ml).
3) To prepare SLIT only use concentrate vials with high allergen concentration (e.g. 1:10 p/v).

5.7 Updosing phase

The main reference guidelines do not mention a dose increase phase, since most products marketed nowadays for SLIT with tablets in Europe and US are given directly at the maximum dose. With this practice local reactions have been reported in the first few weeks in 40-75% of patients. GUIMIT experts consider that an updosing phase of maximum one month is preferable, to improve safety on the one hand, but also to not delay too much in reaching the effective dose on the other. At this stage one could start with a dose 1/1000 times the maintenance dose, with increase every third day.

5.8 SLIT in poly-allergic patients

The different guidelines so far only recommend the use of mono-SLIT because they lack DCPC studies with poly-SLIT in polysensitized patients, probably because only mono-SLIT is sold in European countries as a finished product, whether in liquid form or as tablets. So, no main reference guideline mentions how many allergens can be mixed in SLIT. There is sufficient evidence to prove efficacy using mono-SLIT, and in the original articles cited in the main reference guidelines there is some evidence for duo-SLIT in a single bottle(79) or in separate jars(80, 81) (evidence 2a and 1b). Otherwise, SLIT with ten allergens seems to be ineffective in provocation studies. However, so far there is no evidence for SLIT with between 3 to 9 extracts. On the other hand, it has been shown that SLIT with multi-allergen is safe, although efficacy is discussed (WAO-SLIT).

For a poly-sensitized patient who is poly-allergic to biologically related homologous allergens, the main reference guidelines recommend maximum mixing of two homologous allergens. The German Guideline does not recommend mixtures, arguing that when the extracts are mixed they are diluted and that there may be degradation due to the presence of proteases. These two arguments do not apply to the SLIT with natural extracts as they are prepared in Mexico: there should be no dilutional effect if the SLIT is prepared from concentrate vials from the US with adequate calculation of the maintenance dose of each of its components. In addition, protein degradation, due to the proteases present in some

Suggest Yes, 100%
Evidence: 1b-2a
Recommendation: A

extracts, is minimized by avoiding mixing allergens with high protease content with those of low protease content (see Chapter 4). In our country the allergists formulate immunotherapy and have symptom scores, to evaluate in patients the efficacy and safety of the SLIT. When adding more than one allergen, the allergist has to adhere to the rules of allergen mixtures. In this sense, there is no major difference mixing standardized extracts or non-standardized ones, because standardizing an extract does not change its composition. To increase efficacy, we suggest mixing only those allergens, relevant in the clinical history. The more reduced the number of allergens in the immunotherapy, the greater its effectiveness.

Good practice point 100%

Point of good practice 100%

'Do not mix' does apply for IT that is sold in Mexico made with European extracts, since it is sold as a finished product with no intention of being manipulated/diluted.

5.9 Adding adjuvants to the SLIT vial

Some SLIT preparations include adjuvants aiming to extend the therapeutic effect by modulating the immune response and / or improving the safety profile. Probiotics have been investigated as adjuvants for SLIT in mouse models and have improved tolerance induction (p65) (35)

Suggest Yes, 100%
Evidence: not stated
Recommendation: not emitted

Without mentioning directly the bacterial vaccine, the Japanese SLIT guideline does explain its possible mechanism of action, stimulating immunoregulation: the oral mucosa contains myeloid dendritic cells (mDC) that contain abundant Toll-like receptors 2 and 4 (TLR-2 and 4) on its surface, that are activated by bacterial products. Their activation stimulates the expression of co-stimulatory molecules B7H1 (PD-L1) and B7H3 and the production and release of IL-10. mDC also stimulate Treg cells. GUIMIT suggests using bacterial products in patients who, in addition to allergic diseases, have recurrent respiratory tract infections, but does not suggest using this type of products in all AIT.

Good practice point 100%

5.10 SLIT safety: adverse events, when to postpone and when to reduce dose

In general, SLIT is considered safe and well tolerated. The frequency of severe adverse reactions was 1.1% of the treated patients. With SLIT according to the European schedule, without an updosing phase, 40-75% of the patients present with local adverse reactions, especially in the oral mucosa (oral pruritus or dysesthesia, edema of the oral mucosa, irritation of the pharynx) or abdominal pain. Four to 8% of the patients who use tablet SLIT interrupt treatment due to intense local reactions.

We always recommend applying the first dose of SLIT in the office with a 30-minute waiting period and we suggest applying the first dose of each new vial under supervision. We also recommend postponing the administration of SLIT or reducing its dose under certain conditions, see table 5.3. After one or more serious systemic reactions with SLIT the physician and the patient should discuss whether it is worthwhile to continue with its administration.

We recommend 100%
Evidence: not issued
Recommendation: D

Table 5.3

Adjustments of the SLIT administration schedule under certain conditions

Postpone administration	**For how many days?**
Exacerbation of asthma or uncontrolled asthma: SLIT will be restarted. (Rec B)	Once asthma is controlled
Severe asthma	As soon as the level of severity reduces
Activated allergy symptoms (increased risk of adverse event)	5-7 days
During an acute upper respiratory infection (in patients with asthma)	3-5 days
Acute gastroenteritis	3-5 days
SLIT should be postponed when there are lesions in the oral cavity, after: i. Dental extraction ii. Oral cavity surgery iii. After a tooth has fallen out iv. Ulcer or injury of the oral mucosa	7 days
Reduce doses	At what dose?
After a period without administration (7 days).	1 drop
When systemic symptoms develop after administration*	1 drop
Reboot from bottle 1	
After 3 weeks without administration	1 drop (bottle 1)
Suspend SLIT	
As eosinophilic esophagitis develops	Stop indefinitely

*The Japanese guideline suggests that in these cases you may eventually switch to the administration-spit method (especially in case of gastrointestinal adverse reactions)

We recommend 100%
Evidence: III-V
Recommendation: C-D

We recommend 100%
Evidence: III-V
Recommendation: C-D

Point of good practice
100%

Chapter 6: Hymenoptera Venom Immunotherapy (VIT) and other insects

Table 6.1

SUMMARY Chapter 6: Hymenoptera Venom Immunotherapy (VIT) and other insects			
GUIMIT experts recommend / suggest, taking into account evidence in main reference guidelines (MRG)			Agreement
Which are the indications for specific immunotherapy with Hymenoptera venom?			
6.1a	Patients with a history of systemic reaction (SR) to a Hymenoptera sting and with demonstrable evidence of clinically relevant specific IgE antibodies.	We recommend: Yes	100%
6.1b	Patients older than 16 years with a history of a limited systemic reaction to the skin and demonstrable evidence of clinically relevant specific IgE antibodies.	We recommend: Yes	100%
6.1c	Adults and children with a history of a systemic reaction to the imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.	We recommend: Yes	100%
6.1d	Adult patients who experience frequent and disabling large local reactions.	We suggest: Yes	100%
6.2 In patients with an indication for VIT, but under special conditions, is Hymenoptera venom immunotherapy recommended?			
6.2a	Stable cardiovascular disease	We suggest: Yes	100%
6.2b	Beta - blockers and ACEIs use.	We suggest: Yes	100%
6.2c	Stable malignancies or in remission	We suggest: Yes	100%
6.2d	Multiorgan autoimmune disease	We suggest: until patient is in remission / controlled	100%
6.2e	Start during Pregnancy	We suggest: Yes	100%
6.2f	Continue during pregnancy	We recommend: Yes	100%
6.2g	Mastocytosis	We recommend: Yes	100%
6.3 which is the recommended maintenance dose for specific immunotherapy with Hymenoptera venom? - Hymenoptera venom (dose for every insect´s venom) - Whole body of fire ants		We recommend: 100mcg We recommend 0.5mL of 1: 100 w / v	100% 100%
6.4 What should be the characteristics of the allergenic extract for Hymenoptera venom to start VIT? - Flying Hymenoptera? - Fire Ant?		- We recommend standardized venom extract - We suggest full body extract	100%
6.5 Is the duration of the maintenance phase of the VIT a minimum of 3 to 5 years?		We recommend: Yes, at least	100%
6.6 Does premedication with antihistamines before VIT decrease the frequency of local or systemic reactions?		We recommend: Yes	100%
Common clinical experience of GUIMIT experts (Delphi simplified) **: evidence 1c			

After 5 years of VIT, without systemic reaction in the last 3 years and with negativity in skin and serological tests: should VIT be suspended?	Yes (37% recommend, 43% suggest)
In a patient with systemic mastocytosis, VIT is never suspended, but it is applied at intervals of every 6-8 weeks.	Yes (13% recommend, 55% suggest)

* The level of evidence and recommendation was sought in each of the main reference guidelines MRG (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1.
** Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM

6.1 Introduction

The frequency of adverse reactions in people with the Hymenoptera venom allergy in our country is increasing. Specially, in the northern states of our country, where the red fire ant is endemic, but it is present in the entire country. Among the different family members of the order *Hymenoptera,* the most relevant genera are *Apidae* (honeybee, bumblebee), *Vespidae* (wasp and hornet) and *Formicidae* (fire ant). Although they are members of the same order or even within the same family, each of these species has its own species specific venom.

Therefore, it is very important to identify the culprit insect, considering its geographical distribution. Adverse reactions can be large local reactions (> 10cm, lasting> 24 hours to 7 days) or systemic reactions (SR).(82) SR occur in 0.4-0.8% of the children and in up to 4% of the adults. Anaphylactic reactions are more common in men under 20(83), are the cause of 10% of all anaphylaxis cases that occur in emergency departments and in the US, 40-50 fatal cases are reported per year. Currently there are no Mexican statistics with respect to *Hymenoptera* sting reactions. It has been demonstrated that VIT reduces the risk of anaphylaxis in subsequent stings from 40-60% to less than 5%.(82)

This chapter will present the indications for VIT administration, even in patients with other coexisting pathologies. Venom extract characteristics are described, as well as dosage and administration schedules, proposed premedication and finally the discussion on the decision to terminate or continue VIT.

6.2 Indications for the administration of VIT

After the initial management of a patient with a *Hymenoptera* sting reaction, the physician should decide whether there exists an indication for VIT, see figure 6.1 . Patient selection for VIT should be based on the patient's medical history and demonstrable evidence of specific IgE antibodies by skin tests (by prick and intradermal) or *in vitro* tests . There exists high level evidence for the recommendation of venom immunotherapy in adults with a SR, regardless of its severity. Patients under 16 years of age who have a history of only cutaneous symptoms due to *Hymenoptera* stings generally do not require VIT, although depending on the risk of exposure, in some cases their indication may be justified. According to the European guidelines, there is sufficient evidence to indicate VIT in children for large local reactions (LLR) (evidence III , rec. B), unlike in adults in whom large local reactions rarely predispose to a subsequent SR. We conclude that patients under 16 years of age with a history of only skin symptoms due to *Hymenoptera* stings, usually do not require VIT, while GUIMIT suggest “yes” for some specific cases of LLR .

Figure 6.1

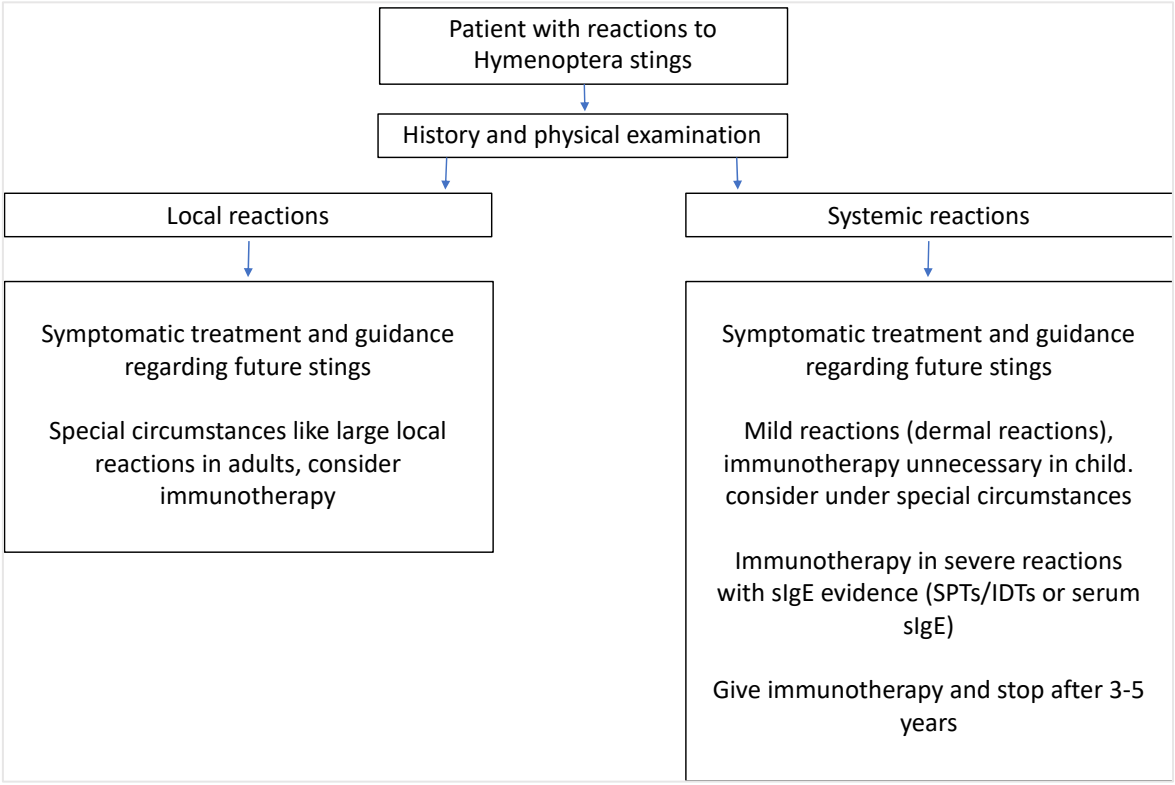


Fig 6.1. Process of attention and indication of venom immunotherapy (VIT) in cases of allergic reactions due to Hymenoptera stings

Indications for VIT

1. Adults and children with a history of a systemic reaction to bee or vespid stings and who have demonstrable evidence of specific IgE antibodies to the culprit insect.
2. Patients older than 16 years of age with a history of a mild systemic reaction (limited to the skin) due to a bee or vespid sting and with demonstrable evidence of specific IgE antibodies for the culprit insect.
3. Adults and children with a history of systemic reactions due to an imported fire ant sting and who have demonstrable evidence of specific IgE antibodies for this insect.
4. Adult patients and children who experience frequent and disabling LLR due to *Hymenoptera* stings and who have demonstrable evidence of specific IgE antibodies to the insect involved.

We recommend yes for 1-3; 100%
Evidence: I
Recommendation: A

Suggestion Yes, 100%
Evidence: adult: IIa
Recommendation: B

We recommend measuring baseline serum tryptase in all patients, candidates for VIT, since an increased level of baseline serum tryptase in patients with moderate to severe anaphylaxis induced by *Hymenoptera* stings, could be related to a mast cells disorder, associated with an increased risk of anaphylaxis during future stings . (Rec. B)

6.3. Indications for VIT in patients with other medical conditions

The special medical conditions referred to in this section are not *per se* a contraindication to VIT, although the evidence in reference guidelines is weak. A published report, that includes a collective experience of almost a thousand allergists members of the American

Academy of Allergy, Asthma and Immunology, increases the level of evidence.(84) In all cases, the patient should be informed about possible risks. The risk-benefit analysis must be carefully weighed from an individual standpoint. The patient´s preferences and other treating physicians should be incorporated into the medical decision-making process to decide on the VIT indication.

In patients with cardiovascular diseases, neoplasms or autoimmune diseases, the indication of VIT is suggested as long as these conditions are stable and controlled or in remission.

In patients receiving beta-blockers or ACEIs , it is recommended to consider other pharmacological alternatives for cardiovascular treatment. If this is not possible, we suggest the administration of the VIT with caution and close monitoring (some physicians tell their patient to withhold the ACEI on the day of administration).

In relation to pregnancy, it is generally recommended to apply the same guidelines as established for aeroallergen immunotherapy. It is suggested to start immunotherapy during pregnancy only if the severity of the reactions and the high risk of suffering a new sting event justify it. If during VIT, pregnancy occurs, it is recommended to continue with VIT shots, always evaluating the individual risk-benefit.

In cases of mastocytosis, even if there is a greater risk of SR due to VIT, we recommended to initiate VIT, considering the risk of exposure to future sting events. When indicating VIT, we recommend to make sure that the patient always carries epinephrine, as well as a written action plan.

GUIMIT suggests (evidence V, recommendation D) to administer VIT in patients with:
a) Stable cardiovascular disease
b) Use of beta - blockers and ACEIs
c) Stable malignancies or in remission
d) Multi - organ autoimmune disease
e) Start during pregnancy
f) Continue during pregnancy (recommendation)
g) Mastocytosis (recommendation).

We suggest 100%
Evidence: V (1c),
Recommendation: D (B)

6.4 Demonstration of specific IgE against Hymenoptera venom

For demonstration of specific IgE against *Hymenoptera* venom we have skin test (ST) and serological tests . More recently, the utility of the basophil activation test (BAT) has been suggested for diagnosis (see Chapter 1.2) .

The decision to perform a ST for *Hymenoptera* venom allergy should be based on the patient's medical history. In case of a SR to the sting, the patient is considered a candidate for the test. The STs should be deferred 3 to 6 weeks after a SR, due to false negative results that may occur transiently during this period. Bee and vespid venom STs typically start with an epicutaneous puncture SPT using a venom concentration of 1 mcg / mL. If the result of this test is negative, intradermal ST (IDST) should be performed, starting with a

concentration of 0.001 to 0.01 mcg / mL. If the results are negative at these concentrations, IDSTs are continued with progressive increases of 10 times the concentration until a positive response occurs or a maximum concentration of 1 mcg / mL is reached. In the case of ST for fire ants, whole body extract is used and started with a prick test using a 1: 100 w/v dilution. If this test is negative, IDST should be performed, starting with a 1: 1,000,000 w/v dilution, with increases of 10 times the concentration until a positive response occurs or a maximum concentration of 1: 1,000 w /v is reached. A test is considered positive when a 3 to 5 mm wheal larger than the negative control is generated, after 15 to 20 minutes waiting time.

Although STs are preferred because of their greater sensitivity, *in vitro* tests can be performed for the detection of specific serum IgE (ImmunoCAP). *In vitro* tests are useful if the results of the STs are negative, despite the existence of an evident history of SR due to a Hymenoptera sting. It is generally recommended to start VIT In patients with a history of a SR and a negative result to ST but a positive result to the *in vitro* test.

Although the diagnostic approach with ST and/or *in vitro testing* is sufficient enough to indicate treatment in most patients, cases of anaphylaxis but negative venom-specific IgE tests and those with multiple sensitization, constitute a special diagnostic challenge. The potential use of molecular diagnostic tests with recombinant allergens can improve diagnosis and facilitate the identification of specific sensitizations in cases of cross-reactivity between venoms of different families, genera or species of *Hymenoptera*. *Api m 1* (bee) as well as *Ves v 1* and *Ves v 5* (yellow jacket); and *Pol d 5* (*Polistes* wasp) recombinant allergens are currently available for molecular diagnostic tests.

6.5 VIT dose

Based on evidence from the main RGs, we recommend starting VIT with a dose of 1 mcg and increasing to a maintenance dose of at least 100 mcg (recommendation B). In patients who have experienced systemic reactions by insect sting for which they are receiving immunotherapy while being on a maintenance dose of 100 mcg (especially in the case of bee venom allergy), we recommend increasing the maintenance dose up to 200 mcg per injection, as this dose has proven to be effective in achieving protection in these cases. In children, the efficacy of 50 mcg of venom as a maintenance dose (recommendation C) is controversial.

We recommend 100%
Hymenoptera:
Evidence: II, Recom .: B
Ant:
Evidence: III, Recom .: C

For immunotherapy with imported fire ant, a maintenance dose of 0.5 ml of 1:100 w/v extract of *Solenopsis invicta* or a mixture extract of *S. invicta* and *Solenopsis richteri* is recommended.

There is a risk of anaphylaxis during administration of VIT, especially in patients with mastocytosis. Recommendations listed on Table 6.2 are intended to reduce the risk of adverse reactions.

Table 6.2.

Table 6.2 Recommendations to reduce the risk of adverse reactions due to immunotherapy (IT) for Hymenoptera venom allergy
1. Verify that the patient's name on the extract and the patient's chart are correct before the administration of each injection
2. Keep the patient under observation for at least 30 minutes after the administration of each injection.
3. Ensure that coexisting allergic diseases (such as asthma) are under control before administration.
4. Consider the use of depot extracts instead of aqueous ones, if available.
5. Consider the administration of omalizumab in patients who have repeated systemic reactions during VIT.
6. Consider modifications in the updosing of VIT in patients presenting systemic reactions.
7. Ensure that patients at higher risk carry epinephrine with an action plan for administration .
8. Determine the basal level of serum tryptase before the start of venom immunotherapy.
9. Consider pre medication with 2nd generation H1 antihistamines and / or montelukast.
10. Consider alternative medications in patients receiving beta blockers or angiotensin converting enzyme inhibitors.

6.6 Recommended characteristic for the allergen extract for specific Hymenoptera venom immunotherapy (VIT)

Extracts of bee venom, yellow jacket and white-faced hornet are available for diagnostic tests and treatment. *Hymenoptera* venoms are standardized extracts. Commercially, in our country non -standardized bee and wasp extracts (whole body) are available. GUIMIT recommends the use of standardized purified venom extracts, that must be imported through trading houses. With the use of the latter type of extracts evidence has shown a lower rate of local and systemic adverse events, as well as greater efficacy.

We recommend yes
100% Evidence: I,
Recommendation: B

In the case of imported fire ant sting allergy, the use of a whole body extract is recommended, considering that it is currently the only one commercially available. Since these types of extracts are not standardized, each new vial should be started with caution, similar to the procedures for aeroallergen immunotherapy, see Chapter 4.

6.7 Duration of maintenance phase of VIT

A minimum period of three years of treatment with VIT is recommended before considering discontinuation. Expert reports recommend extending VIT up to five years. However, there is no consensus on the evidence for the dichotomous definition of 3 or 5 years. For this reason, we recommend that patients who start VIT continue it for 3 to 5 years, identifying each case, according to risk factors (potential risk of frequent exposure to bites, systemic reactions during immunotherapy), response to immunotherapy (evidence of sting events in the course of treatment without presenting systemic reactions; negativity of skin tests, or significant reduction in specific serum IgE levels) and patient preferences.

We recommend yes
100% Evidence: IV,
Recommendation: C

We recommend yes
100% Evidence: III,
Recommendation: C

We recommend maintaining immunotherapy for a period longer than 5 years, and even for an indefinite period, in patients with high-risk factors, such as serious life-threatening

reactions before immunotherapy, severe systemic reaction during immunotherapy, baseline high serum tryptase and mastocytosis (recommendation C).

6.8 Does pre - medication with antihistamines reduce the occurrence of local or systemic reactions during VIT?

There are high levels of evidence and recommendation for premedication with antihistamines at each dose of immunotherapy with hymenoptera venom. Second generation non sedating H1 antihistamines are medications that have been shown to reduce the incidence of mild local and systemic reactions, but not anaphylaxis. See Chapter 4AB . Case reports have shown the likely usefulness of premedication with montelukast. We recommend the use of the second generation H1 antihistamines as a premedication in the immunotherapy with *Hymenoptera* venom.

We recommend yes 100%, Evidence: I, Recommendation: A

In case of repeated systemic adverse events during the updosing phase, prior treatment with omalizumab may be recommended, see Chapter 10 .

6.9 Allergy to other insects

Adverse reactions to venom or insect sting/bite other than Hymenoptera has been documented, but in general, they are only isolated case reports or case series and most reactions are mild to moderate(LLR or SR). Skeeter syndrome, an allergic reaction to mosquito salivary proteins, is characterized by extensive local symptoms and systemic symptoms that include vomiting and malaise, is an exception.(85) However, cases of mosquito bite reactions are increasing, without we have to date, purified extracts for diagnosis. Simons FE, et al, found that one of their major allergens is Aed at 3. (86) At the moment STs with whole body extract are suggested for diagnosis. Although there are case reports of SRs in patients with allergic reactions to mosquito bites, it is still considered an experimental treatment.

Chapter7: Conditions for skin testing and for immunotherapy preparation and administration in hospital setting and in private practice

Table 7.1

SUMMARY Chapter 7: Conditions for skin testing and preparing and applying immunotherapy in hospital setting and in private practice		
GUIMIT experts recommend/suggest, taking into account evidence in Main Reference Guidelines*		**Agreement**
7.1 The allergist is ultimately responsible for indicating, performing and interpreting skin tests and prescribing the composition of immunotherapy.	We recommend yes	90%
7.2 Do there exist any minimum requirements and materials needed to perform skin tests and prepare and give immunotherapy? • Physical area of preparation/administration • Availability of crash cart or adrenaline • Staff who perform it with training and protection	We suggest yes (and some suggestions are given for the ideal situation)	100%
7.3 Is it better to administer AIT/VIT in the hospital's office or allergy service, but may there be exceptions?	We recommend yes	100%
7.4 How does COFEPRIS catalogue immunotherapy	XX	XX
7.5 Can guidelines be given of how allergens need to be stored with respect to: a) Expiration date b) Concentration control c) Temperature control d) Biological mean life after diluting (see also chapter 8)	We suggest yes	100%
Common clinical experience of GUIMIT experts (Simplified Delphi): evidence 1c**		
One of the minimum Hospital and Private Practice requirements (outside the hospital environment) for SCIT administration is to have the crash cart available.	Yes (68% recommended, 23% suggest)	
One of the minimum requirements in Hospital and Private practice for the personnel preparing SCIT and for the personnel administering it is to wear gloves	Yes (25% recommended, 39% suggest, 33% neutral)	
Good practice points		
For the area where AIT/VIT is prepared: 1) A plastic screen can be placed between the preparation area and the face of the staff. 2) If there is a possibility, place a HEPA filter in the area	Yes	100%
Have a pre-filled syringe - protected from light- with the appropriate epinephrine dose for the patient in case of home administration (and in the skin test/AIT area)	Yes	100%

* The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1.

** Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM..

7.1 Introduction

*MRG – Main Reference Guidelines. The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1
** Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM.

The practice of Allergy in Mexico takes place both in the private environment and at community health care level in hospitals of second and third level such as the *Instituto Mexicano del Seguro Social* (IMSS) and the *Instituto de Servicios de Seguridad Social de los Trabajadores del Estado* (ISSSTE). Both branches deliver out-patient (ambulatory) and in-patient services. Each environment has its own insights, so it will be impossible to give strict guidelines to be applied in each of them. In addition, each hospital has its own rules and/or the standards of the group to which it belongs. Therefore, the instructions found in the main reference guidelines, can only help to give a guidance to each group. Mexican specialists in Allergy and Clinical Immunology have adapted to their clinical practice what they have learned in training centers, coupled with everyday experience and exchanges of ideas in national and international forums.
Therefore, there was a need to propose ideas, agreed upon amongst the members of the broad development group of the GUIMIT guideline, based on ideas expressed in the main reference guides, but contextualized in the experience and learning of the Mexican allergist.
So far, the subject of this chapter has not been formally addressed in national publications nor had it been considered in the previous Mexican immunotherapy guidelines 2011.(1) However, the GUIMIT experts decided to include it in the *SCOPE* document containing the objectives of this guideline, in an effort to give suggestions on how to enhance the quality and safety of the daily practice of AIT.
We offer here a proposal on the appropriate minimum conditions under which our specialty's specific procedures should be conducted in relation to the topics of GUIMIT: skin testing and the preparation and administration of AIT and VIT. The recommendations and suggestions embodied in this chapter are the result of the consensus of GUIMIT experts, sometimes strengthened by the evidence in the main reference guidelines. Unlike other chapters, most of the points on which a recommendation is issued, originate from the consensus of the members of GUIMIT, even without have evidence in the main reference guidelines.

7.2 The Allergist responsible for skin testing and AIT/VIT

GUIMIT experts consider that the Allergist is the responsible for indicating, performing and interpreting skin tests and prescribing the composition of AIT/VIT. We suggest primary health care workers or other specialists should refer patients with suspected allergy to the allergist, for evaluation and an eventual decision by the allergist to perform allergy diagnostic procedures, see Table 7.2.

Table 7.2

When to Refer to the Allergist, also see AIT indications Chapter 2
Frequent respiratory events, especially if they are fever-free
Respiratory events and skin symptoms suggestive of allergy
Life-threatening asthma crisis: mandatory reference to the allergist or pulmonologist
Moderate or severe persistent asthma
Recurring episodes of acute asthma (2 or more over a 6-month period)
Need for high dose inhaled steroids or more than 2 systemic corticosteroid bursts in the previous year
Chronic or recurrent conjunctivitis without infection
Food allergy*
Uncertain diagnosis or atypical presentation of respiratory symptoms, skin disease or suspected anaphylaxis

*It is important to confirm this suspition given the high frequency of under- and over diagnosis, which often results in the decision to avoid foods unnecessarily.

We recommend 100%
No Evidence available
Recommendation main guidelines: not available

The main reference guidelines have a low level of evidence and recommendation related to the responsibilities of each medical specialty in relation to the allergic patient, because they have different realities that do not apply to our country. GUIMIT recommends that in order for the physician to be considered to have the competence, necessary skills to employ the correct diagnosic approach to allergic diseases and to be able to prescribe and administer AIT/VIT, he should comply with the requirements set out in the Single Medical Specialization Plan (PUEM) for both Allergy and Clinical Immunology as well as for Allergy and Pediatric Clinical Immunology (http://www.sidep.fmposgrado.unam.mx:8080/fmposgrado/programs/allergy.pdf and http://www.sidep.fmposgrado.unam.mx:8080/fmposgrado/programas/alergiaped.pdf), as well as be certified by the *Consejo Nacional de Inmunologia Clinica y Alergia* (*CONICA*). The updated directory of certified Allergists can always be found at: http://www.conica.org.mx/directorio.php

7.3 Nursing equipment or diagnostic testing support

In the event of nursing or support staff to perform procedures or prepare AIT, the allergist should monitor their performance and skills and provide them with appropriate preparation and training. This is why this specialist should be physically close to the area of diagnostic procedures and AIT/VIT administration. For staff who apply skin prick tests (SPT), it is desirable that proficiency tests are performed regularly to demonstrate their ability to perform SPTs with a technique that results in inter-test variability within acceptable limits.

7.4 Administration of AIT/VIT outside the allergist's office

The alllergist is responsible for the administration of AIT/VIT, but he can train a physician to continue the administration of the AIT for logistical reasons. There are circumstances under which home administration may become the only viable alternative; in these cases, home administration will be preferred in patients whose clinical profile assumes low risk for systemic reactions. GUIMIT suggest one of the latter two options (see the end of this

chapter), as long as written instructions are given on how to apply the shots and what to do in case of an adverse reaction; also, the allergist should monitor that the instructions have been understood and executed by direct interrogation during follow-up consultations with the patient. Failure to follow the instructions indicated by the allergist, frees him from liability in case of an adverse event. VIT shall not be applied at home.

7.5 Informed consent and assent

GUIMIT recommends obtaining informed consent, prior to diagnostic and therapeutic procedures in the office or in the hospital. On the Mexican College's (CMICA) and CONICA's websites, certified physicians can find links to access electronic formats for informed consent for SPT, administration of AIT, as well as formats for such procedures.

7.6 Minimum required and optimal performances for performing skin tests and preparing AIT/VIT

The JTF AAAAI/ACAAI guidelines consider the issue of the physical area only in the preparation of AIT, but they do not make recommendations regarding the area of administration of skin tests. The other guidelines do not mention a procedure. GUIMIT experts recommend the minimum requirements for in-office materials or at the Allergy Department of the Hospital: they are listed in table 7.3. More details in Chapters 4 and 6.

Recommendation 100%; Evidence: Ⅳ Recommendation: D

Table 7.3

Minimum materials needed and requirements for performing SPT/ ID testing *
* Wear a robe * Wear gloves for hygiene and to avoid causing sensitization in personnel * Adrenaline availability (check expiration date) and syringes * 2nd generation oral antihistamine * Fast-acting inhaled bronchodilator (via metered dose inhaler or nebulizer and mask) * Close access to the emergency department or crash cart availability. * Refrigerator proximity to keep the cold chain between tests for diagnostic extracts

STEP - Skin tests by epicutaneous puncture; IDST- intradermal skin test
* A complete list should not be considered but also suggestions for the material needed to perform PST/IDST (alcohol swabs, lancets, syringes, allergens, vials for dilution, etc.).

As an ideal condition for applying SPT/ID testing GUIMIT suggests that the office has a work area with adequate lighting, preferably daylight. The protection of the personnel performing the tests is useful to avoid sensitization, and should include a mouth covering mask, a gown and use of a hair cap and/or beard protection. The gloves must be talc-free and ideally under latex-free-conditions, resistant to 70% isopropyl alcohol. It is suggested to have a crash cart in case it is necessary to manage anaphylaxis in patients undergoing *in vivo* diagnostic tests, taking special caution when performing interdermal skin testing or

We suggest: If 100% No Evidence available No Recommendation available

in patients with suspected food, latex, medication or hymenoptera venom, as the risk of a system reaction related to the procedure will be higher, see Chapter 1A.

In addition, GUIMIT experts recommend having the minimum materials and requirements required for AIT/VIT preparation mentioned in Table 7.4.

Table 7.4

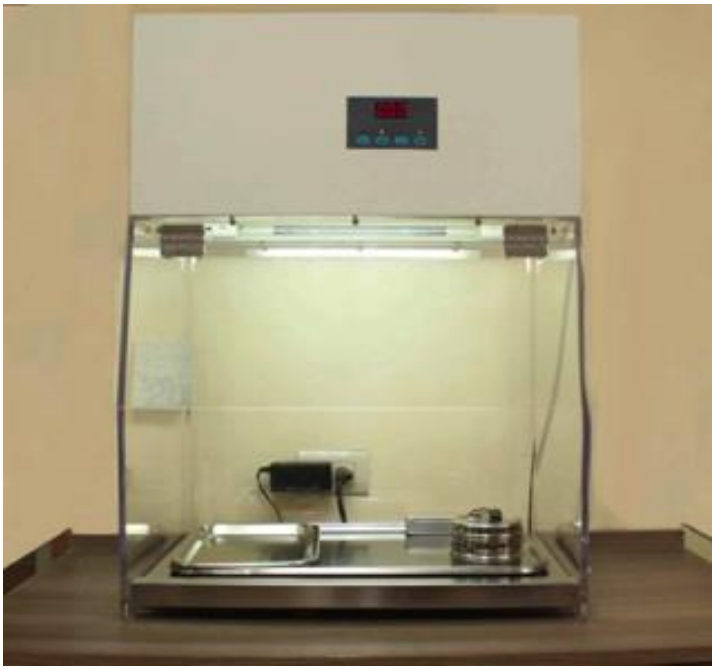
Material and minimum requirements indispensable for AIT/VIT preparation*
• Use of mouth covering masks • Wear a gown to protect street wear • Wear gloves • Proper lighting • Prepare in an area free of exposure to pollutants • Clean the preparation area with antiseptic • Quiet place, preferrably isolated: avoid constant entry-exit of personnel during preparation.

* This should not be considered to be a complete list, but more as a complementary list on top of the material needed to prepare the AIT/VIT (vials, alcohol swabs, syringes, etc.).

Similar as for the SPT administration, as part of the ideal set of materials needed for AIT/VIT preparation GUIMIT suggests that the staff preparing it should use a mouth covering mask, a disposable gown and cap for hair and /or protection of beard hair, both to protect themselves from sensitization and to avoid contamination. The gloves must be without powder, latex-free and isopropyl alcohol-resistant. Under ideal conditions AIT/VIT should be prepared in an area with a laminar flow bell, see Figure 7.1.

We suggest: Yes 100%
No Evidence available
No Recommendation available

Figure 7.1: Laminar Flow Bell in a Private Practice Setting in an isolated area, with restricted movement of persons.



BYKG Air segregation equipment, Model: BYKG-I, pattern: laminar airflow, input power 160W, Mains: 110V, 60HZ, ex-factory date: 2014-06. Courtesy Dr. Roberto Osorio

Good practice point
100%

If a Laminar Flow Bell is not available, a plastic screen can be placed between the preparation area and the face of the staff preparing the AIT/VIT. If there is a possibility, a HEPA air purifier filter *(High efficiency particulate air)* should be placed in the AIT/VIT preparation area.

GUIMIT experts recommend the following materials and minimum requirements regarding AIT administration, see Table 7.5. For details regarding other procedures please refer to Chapters 4 and 6.

Table 7.5

Minimum Material Requirements for AIT/VIT Administration*
• Manage in an area with adequate lighting • Adrenaline availability (restock and consider expiration date) and syringes • 2nd generation oral antihistamine • Short-acting inhaled bronchodilator (in metered dose inhaler or with nebulizer and a mask) • Close access to emergency department or crash cart availability. • Close proximity to refrigerator to assure cold chain for AIT/VIT vials

* This should not be considered to be a complete list, but more as a complementary list on top of the material needed to administer AIT/VIT (peakflow meter, alcohol swabs, syringes, etc.).

GUIMIT suggests to take a peak flow measurement in asthmatic patients before AIT/VIT administration as an ideal procedure, see chapters 4.2 and 4.3, and to have a pulse oximeter sensor and a crash cart in the area where the AIT/VIT is administered, especially in Private Practice.
To ensure the cold chain of allergenic extracts for skin testing and AIT/VIT, GUIMIT experts make the following suggestions regarding the refrigerator (Table 7.6).

Table 7.6

Tips to Keep the Cold Chain
• To have an exclusive refrigerator for biological material and AIT/VIT, for the storage of allergens. Temperature should be kept between +2º and +8ºC. • Place warnings on the outside of the refrigerator: DO NOT OPEN AND DO NOT DISCONNECT, as well as a phone number and an electronic address of the person in charge for the area and the allergist in case of an emergency. • To have a maximum and minimum temperature logs *(Electronic Measuring Instrument Testo®)* from thermometers • The fridge should preferably be connected to an emergency (portable) generator • Defrost the refrigerator every 6 to 12 months, as indicated by the manufacturer, or when the frost in the freezer is thicker than 5mm.

7.5 Office administration of SCIT/VIT is preferred over administration at home (home administration might be considered for low-risk cases)

The main reference guidelines refer to the requirements regarding patient´s condition prior to administration of AIT; these are widely discussed in section 4.4.2 and chapters 6 and 9. The vast majority of complications occur within the first 30 minutes after administration of SCIT or VIT, and even with the first dose of SLIT.

Therefore, **GUIMIT recommends**:

- Administer SCIT at the Doctor's office, if possible.
- Always administer VIT in a Doctor's office (treating allergist or referral)
- Observe the patient in the office for at least 30 minutes after the SCIT or VIT shot.

Recommendation 100%; Evidence: Ⅲ Recommendation: C/D

GUIMIT also suggests:

- If for logistical reasons SCIT cannot be administered in the physician's office, SCIT/VIT could be administred in another medical unit or eventually at the patient's home. In this case:
- Precise and clear written indications shall be given concerning:
  - The administration schedule
  - In asthmatic patients, peak flow measurements should be taken before SCIT and specific indications should be given of when to postpone administration (critical PEF value).
  - Basic clinical safety rules (do not apply with fever, acute asthma exacerbation, recent physical exercise, etc.)
  - The adverse reactions (AR) that may occur
  - What to do in case and AR presents or in case of an emergency.
- In case of home administration it is advisable to provide indications to the patient regarding adrenaline, with a pre-filled dose in accordance with her/his weight, see paragraph below.

After administration of SCIT with rush or ultra-rush schedule, patients will be medically monitored throughout the procedure and at least 1 hour after administration of the last dose.

Every allergy clinic that is not in a hospital environment must have a crash cart. Offices in hospital areas should ensure quick access to the emergency department after intramuscular adrenaline administration, if necessary (see Chapter 9).

A point of good clinical practice is to have a pre-loaded syringe with 0.3 and 0.5mL of adrenaline ready before starting skin testing or administring SCIT/VIT. Pre-filled syringes with adrenaline must always be protected against light (to prevent drug degradation) and to keep it at environmental temperature of 25ºC or less.

Good Clinical Practice 100%

7.6 Standards required by COFEPRIS for AIT Management

The *Comision Federal para la Proteccion de Riesgos Sanitarios* (COFEPRIS) classifies AIT as a class 2 medical device: "auxiliary in the treatment of allergy". AIT is not considered a biological vaccine since its function is not prophylactic/preventive, but as previously mentioned, it is an auxiliary in the treatment of allergy and an allergy treatment aid. (https://www.gob.mx/promexico/acciones-y-programas/dispositivos-medicos-26794). A list of sanitary registrations of medical devices granted during 2012, with some allergens, can

be found in: https://www.gob.mx/cms/uploads/attachment/file/305188/reg_dm_2012.pdf. There are no more updated lists available to public access.

7.7 Storage of Allergenic extracts in the Office

We suggest 100%;
Evidence: Ⅲ
Recommendation: C

We recommend to follow the manufacturer's recommendations carefully. Aqueous and glycerinated extracts should be stored at 4ºC to reduce loss of potency. Lyophilized extracts, prior to reconstitution, can be stored at room temperature. For storage details and expiration of different degrees of dilution of allergenic extracts, see Chapter 8.

8 Chapter 8: Allergen Extracts

Table 8.1

SUMMARY Chapter 8. Allergen extracts		
GUIMIT experts recommend/suggest, taking into account evidence in MRG*		**Agreement**
8.1a. Do the following types of allergen extracts have clinical efficacy?		
i. Natural aqueous extracts with 0.4% Phenol	We recommend: Yes	100%
ii. Glycerinated natural extracts (50% glycerin)	We recommend: Yes	100%
iii. Natural adsorbed extracts (Alum, tyrosine)	We recommend: Yes	100%
iv. Chemically modified extracts (depigmented, allergoids, recombinants, peptides)	We recommend: Yes	100%
8.1b Should the quality of an allergen extract be measured by the following parameters?		
i. Purity and composition (Der group 1 and 2, etc.) (qualitative)	We recommend: Yes	100%
ii. Concentration (quantitative)	We recommend: Yes	100%
8.1c The following are a way of expressing potency of an extract, indicating which are considered standardization tests (Stand). In order of less accurate → more accurate**		
In vitro	Weight/volume	X
	Protein nitrogen units (PNU)	X
	Total IgE binding capacity (ELISA inhibition)	Stand
	Micrograms of major allergen, including radio-immunodiffusion.	Stand
In vivo	ID50EAL (EU)	Stand
	Puncture skin test (Europe)	Stand
8.1d Are there specific conditions for the storage of allergenic extracts? iii. Freeze-dried: ambient temperature iv. Aqueous, glycerinated and vials of reconstituted freeze-dried extracts: 4ºC	We recommend: Yes (see Refrigerator temperature, Chapter 7)	100%
8.2 Is there an adequate concentration for an extract for diagnostic purposes?	We suggest: Yes	100%
8.3 Is there an adequate concentration for an extract for therapeutic purposes?	We recommend: Yes	100%
8.5a Is there a dose-response ratio and therefore is there a defined maintenance dose in SCIT? (see Chapter 4)	We recommend: Yes	100%
8.5b Is there a dose-response ratio and therefore is there a defined maintenance dose in SLIT? (see Chapter 5)	We suggest: Yes	100%
8.8 Can certain adjuvants be added to immunotherapy to increase its efficacy?	We recommend: Yes	91%
Consensus based on clinical experience of GUIMIT experts (Delphi simplified) ‡: evidence 1c		
With the concentrations as given by the manufacturers, one cannot compare potency between extracts from different manufacturers. So, when switching an allergen from one manufacturer to another, for example Dermatophagoides from manufacturer A to manufacturer B, one shall have to restart from vial 1.	Yes (26%recommended yes, 36% suggested yes)	
Considering the clinical scenario of the above question, if the extracts are analyzed simultaneously with the same technique (in one and the same laboratory or in a SPT in the same patient): can the concentrations and/or potency of AIT products produced by different manufacturers be compared?	Yes (13%recommend yes, 40% suggest yes)	
Points of Good Clinical Practice		

8.1b. Once efficacy has been proven for the extract of certain allergen, can this be extrapolated to another allergen of the same group (i.e. one tree pollen to another tree pollen), comparable in concentration and quality?	Yes	100%
8.6 Are there interchangeable doses between extracts from different manufacturers (equivalent dose)?	No	97%
8.7 Is the quality of immunotherapy affected by the type of diluent used?	Yes	100%

(the number of the subsections refer to the original order of key clinical questions)
MRG – Main Reference Guidelines
* The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1.
**Not voted, as this fact is not disputable.
‡ Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM.

8.1 Introduction

Allergen extracts exist in different forms. Historically, aqueous extracts of natural allergens have been used, containing 10% glycerin and 0.4% phenol as a preservative. For concentrated vials, from which vials are diluted to make the patient's vial, the solvent contains 50% glycerin to improve allergen stability and extend the shelf life of the extract. However, for SC application a patient generally tolerates no more than 15% glycerin concentration in the vial. That's why the diluent contains 10% glycerin, just as the 'ready-to-use' extracts from European manufacturers.

Since 1980´s the search for safer choices for SCIT in Europe, the aqueous formulations were changed for depot formulations, in which the natural allergen is adsorbed to a molecule such as alum, tyrosine or glutaraldehyde. Other researchers focused on changing the natural allergen to a less allergenic form, without losing its immunogenic potency. This is how the modified extracts were developed: allergoids and depigmented extracts. According to the European school SCIT almost exclusively uses adsorbed extracts, several of them allergoids, while the US school exclusively uses natural aqueous extracts for SCIT. Finally, in the era of Biotechnology, recombinant extracts and peptides were developed, which will be review in Chapter 10.

The qualitative and quantitative quality (potency) of an extract is crucial for its clinical efficacy and safety. The second part of this chapter will review how potency is expressed.

There are two schools for SCIT administration, (for further reference see Chapter 4). The European school manages products marketed as ready-to-use. Therefore, guidelines from Europe don't detail the concentrations of the extracts to be administered and don't recommend mixture of extracts, which -if European extracts are being used- could result in dilution of the final product. On the contrary, the American school uses concentrated commercial bulk extracts, made to be diluted in order to prepare the patient's vial. This chapter reviews which concentrations the vial should have in the maintenance phase of SCIT according to the US school and also which parameters were taken into account to establish the appropriate dose for this phase. For liquid SLIT, natural aqueous extracts are administered. Thus, in principle it should be possible to calculate doses in relation to SCIT made with the same type of extracts, reviewing doses used in clinical trials showing efficacy. We here suggest a concentration range to prepare SLIT based on these calculations.

Finally, there are adjuvants that can be added to immunotherapy in order to increase the effectiveness, decrease adverse events and improve the immunogenic response. We've reviewed these options too.
Many aspects of this chapter are unaddressed in the Main Reference Guidelines.

8.2. Types of allergenic extracts with proven clinical efficacy

For SCIT, unmodified allergens are used in aqueous form or physically adsorbed to alum or tyrosine (depot extracts). But for SCIT also chemically modified allergens (e.g. allergoids) can be used, which in turn may or may not be adsorbed. Allergen extracts for SLIT are presented in two forms: natural or modified allergens; these can be offered as solutions or as tablets.

8.2.1 Regarding SCIT

Aqueous allergen extracts are the most commonly used in Mexico as well as in United States. There exists less more recent evidence for AIT with this kind of allergen extract, whereas most of their evidence dates from past millennium (evidence 1b). It is exactly the opposite for adsorbed and/or modified extracts used by European colleagues, for which there is a wealth of recent evidence of their clinical efficacy in the Main Reference Guidelines (evidence 1a). The Main Reference Guideline EAACI-AR was informed by several meta-analyses of a comprehensive review of up-to-date evidence.(6) They demonstrated a moderate effect size for SCIT with a standardized mean difference (SMD) of -0.65 (87). In a subgroup analysis there was a greater benefit for AIT with perennial (SMD) -0.91 versus seasonal (SMD -0.37) allergens. The 61 clinical trials included in this SCIT meta-analysis used various extracts: adsorbed to alum or tyrosine, polymerized with glutaraldehyde, allergoids and depigmented extracts or a combination of them. Therefore, although experience abounds, there are few studies with SCIT with natural extracts. In Mexico we already have allergoid extracts commercially available from Inmunotek.

SCIT: efficacy evidence
Aqueous: 1b
Glycerinated 50%: xx
Adsorbed: 1a
Modified: 1a-1b
All: Recommend A (recombinants and peptides: B)

8.2.2. Regarding SLIT

Meta-analysis by Dhami et al showed a moderate effect size for SLIT efficacy with a SMD of -0.48. Compared with SCIT, most studies with SLIT used natural extracts, either in liquid or in tablet form. Efficacy has been shown for both forms in SLIT meta-analysis, (improvement in symptoms: SMD -0.42 and -0.53, respectively).(87)

SLIT: efficacy evidence
Aqueous: 1a
Glycerinated 50%: 1a
Adsorbed: xx
Modified: 2a
All: Recommend A

For a review of efficacy see Chapter 2, 4 and 5 and for other chemically modified extracts, such as recombinants or peptides, see Chapter 10, focused on the future of AIT, because they have not yet been approved in our country.

8.3. Measuring the quality of an extract: purity, composition and concentration

The Main Reference Guidelines do not mention details about the quality of an extract. They only mention that standardized products should be used, because potency may vary considerably in non-standardized extracts (JTF-AAAAI/ACAAI)(9). The composition of extracts, even if they come from the same source of allergens, may vary between manufacturers, by variation in the manufacturing processes. Therefore, although MRG mention that in selected cases the existence of a class effect could be assumed (extrapolating efficacy demonstrated with one product to another similar product), MRG

express their preference for the use of standardized extracts for which efficacy has been demonstrated in clinical studies (EAACI-RA, DGAKI) (6, 8).

The quality of an allergen extract depends not only on quantitative parameters (the total IgE binding capacity or the major allergen concentration), but also on qualitative parameters; the latter includes the purity of the extract. for example: pollens from other grass or trees should not be present in a *Phleum pratense* extract, or that all the allergenic molecules of importance in dust mite extract must be present, for example from group 1 and 2 allergens (and lately 23) (88) as ALK-Abelló Europe has shown.(65) Therefore, the potency of an extract only partially reflects its quality.

Good clinical practice 100%

8.4. Methods to Measure the Potency of an Extract and Standardization

The data in this subsection is solid knowledge, so no evidence was sought in the Main Reference Guidelines nor were the issues voted on.

8.4.1. *In vitro* standardization

There are four ways to express the potency of an *extract in vitro.* The first two are not considered standardization tests.

i. Non-standardized extracts are measured by weight/volume that expresses weight in grams per volume in milliliters. Thus, the potency of 1:10 indicates that to 1 gram of dry allergen (e.g. *Ambrosia*) 10 mL of buffer solution was added for allergen extraction.
ii. Another expression for the concentration of an extract is PNU, where 1 PNU is equal to 0.01 grams of protein nitrogen unit. This is one step closer to the true potency of the extract, as the protein unit contains the allergen fraction of the extract. Even so, this measure is not considered standardization, because there are also multiple non-allergenic proteins.
iii. Mite and pollen extracts are standardized according to their total IgE binding capacity, which is the capacity of the extract to bind IgE present in a standard serum pool of allergic patients, as measured with ELISA inhibition.
iv. In Europe *in vitro* standardization is generally based on the determination of the concentration of one or more major allergens (micrograms of major allergen (Recommendation A). Each manufacturer uses its own tests and reagents for such determination (some acquired from the same supplier, INDOOR Biotechnologies). In the US only two extracts are standardized based on the content of the major allergen, as measured by radial immunodiffusion (RID): ambrosia (Amb 1) and cat (Fel d 1). For SCIT a monthly maintenance dose of between 5 and 20 mcg of the major allergen is recommended.

In the US, the Food & Drug Administration (FDA) regulates extract quality centrally and issues reference reagents all allergen manufacturers use in the above-mentioned tests (ELISA and RID). For dog epithelium there are no assays standardized by the FDA.

8.4.2. In *vivo* standardization

i. *In vivo* allergen standardization in the US is based on the potency of allergenic extracts using quantitative methods in intradermal skin tests and reported as Allergy Units (Bioequivalents) (BAU and AU). This quantitative method used for determination of potency of extracts by skin tests is known as intradermal dilution

for 50 mm sum of erythema (ID50EAL). The ID50EAL method prepares several half-log dilutions of a reference candidate and injects 0.05 mL intradermally into 15 or 20 'highly sensitive' allergic subjects." The dilution resulting in an erythema in which the sum of the largest and perpendicular diameter equals 50 mm is considered the target (D50). The average of the D50 dilutions of the tested subjects is assigned as the BAU/mL value.(89) The potency of subsequent batches shall be determined *in vitro* with the extract tested *in vivo* as a reference.

ii. Standardization in Europe is done through skin prick tests versus codeine control or versus histamine control. Each manufacturer has its own standards and reference extracts.

8.5. Conditions for Storage of Allergen Extracts

The Main Reference Guidelines (MRGs) mention that allergen extracts need to be refrigerated, while others can be kept at room temperature. Extracts should be stored according to manufacturer´s recommendations; in general storage at 4ºC is recommended to prevent loss of potency. The potency of concentrated immunotherapy extracts (1:1 v/v up to 1:10 v/v) when kept at 4ºC is relatively constant and allows extracts to be used until the expiry date, present on the manufacturer's label. Less concentrated extracts are sensitive to the effects of temperature and may not maintain their potency. Mixing allergens into mixtures can decrease potency loss over time, because additional allergens can prevent allergen proteins from sticking to the vial´s glass wall. The expiration date of any dilution must not exceed the expiration of the constituent added with the earliest expiration date. Studies in ambrosia at 1:10 v/v dilution demonstrated stability for 12 months. Dust mite and cat at 1:10 and 1:100 v/v also remain stable for 12 months. (personal communication during immunotherapy committee meeting of tests run by US manufacturers)

We suggest 100%;
Evidence: Ⅲ
Recommendation: C

We suggest that freeze-dried allergens can be kept at room temperature until the expiry date. Once reconstituted it is suggested to keep them refrigerated and to remove them from the refrigerator only for short periods of time to preserve the expiration date, recommended by the manufacturer. For the 1:1000 weight/volume dilutions a 6-months' period is recommended as expiration date and for dilutions higher than 1:10,000 weight/volume an expiration date of 3 months is recommended. There is no availability of human serum albumin for immunotherapy in México, that might enhance maintenance of potency by reducing glass-adherence of proteins. Glycerin 50% is a good stabilizing agent, but could be painful in concentrations over 10%.

8.6. Is there an appropriate concentration for a diagnostic extract?

The MRGs do not specify the concentration of extracts for diagnostic purposes for skin prick tests (SPT), only for intradermal tests (IDT). Ideally, for SPT, allergen extracts should be used that have been standardized on the content of major and minor allergen determinants, that have batch-to-batch consistency and skin prick test results should be comparable when using the same extracts from different manufacturers.

We suggest: Yes, 100%
No Evidence
Recommendation:

The allergen extracts used for SPT and available in Mexico can be found in Table 8.2.

For ID testing the recommended potency of extracts is 1:1000 w/v or 1-10 (B)AU/mL, i.e. 100 to 1,000 times more diluted than the concentration used for SPT. For ID testing with

Hymenoptera venom it is recommended to start with a concentration of 1:1,000,000 w/v, see Chapter 6.

Good clinical practice 100%

Table 8.2. Concentration of diagnostic extracts commercially available in Mexico

Manufacturer/Marketing Holder	Allergenic extract	Concentration (per mL)
ALK-Abelló US	*Standardized* Pollens (*Bermuda, Phleum, Festuca, Lolium, Ambrosia*) Mites *Non-standardized:* Pollens Mites Fungi	 10,000 or 100,000 BAU 10,000 AU 1:20 w/v 1:20 w/v 1:10 and 1:20 w/v; 10,000, 20,000 PNU
Inmunotek	*Standardized* Dust mite (Dpt, Df, Blomia) Fungi (Alternaria, Cladosporium, Aspergillus, Fusarium, Mucor, Penicillium) Epithelium (cat, dog, horse) Insects (Blatella, red ant) Pollens *(Bermuda, Phleum, Festuca, Lolium, Ambrosia, Trees,* etc.)	 100 HEP, 100 HEP, 150mcg 25mcg (3mcg Alt to 1) 50 HEP, 10mcg Can f 1, 50mcg 1000mcg, 500mcg 50-100 HEP, 500 HEP trees
IPI-ASAC	*Standardized* Pollens (xxxxx) Dpt and Df cat *Non-standardized:* Dog Fungi *Periplaneta*	 UBE, depending on the allergen 58,500 BEU and 20,175 BEU 94,500 BEU 10,000 PNU 10,178 PNU 5,000 PNU
Alerquim	All extracts	1:20 w/v

BEU: bioequivalent units, PNU: protein nitrogen units, w/v: weight/volume.
Source: information obtained from each of the manufacturers.

8.7. Is there an Adequate Concentration for an Extract for treatment?

There are two phases of AIT administration: the build-up phase and the maintenance phase, when the patient receives an effective therapeutic treatment. The starting dose of immunotherapy is 1,000 to 10,000 times lower than the maintenance dose (JTF-AAAAI/ACAAI y GUIMIT 2011) (1, 9). For highly sensitive patients, the starting dose may even be lower.

8.7.1. Vial concentration for SCIT according to US practice parameters

For SCIT, according to the U.S. school, if the effective maintenance dose suggested for *Dermatophagoides* is 500-2000 AU (see Chapter 4A) and the volume of each shot is 0.5mL, the preparation of the maintenance vial should be such to reach a concentration of 1000-4000 AU/mL, see table 8.3.

We recommend
Yes, 100%
Evid: 1a, Rec: A

Assuming that the maintenance dose of SLIT will be 2 drops (0.1mL), in table 8.3 concentrations for the maintenance vial are suggested.

Table 8.3 Concentration for maintenance vial, with SCIT according to the U.S. school and proposal for maintenance vial for SLIT.

Allergen	Projected dose for SCIT maintenance	SCIT maintenance vial concentration*	SLIT maintenance vial concentration**
Dermatophagoides sp.	500-2000 AU	1000-4000 AU/mL	2500-10,000 AU/mL
Bermuda or Timothy grass pollen	1000-4000 BAU	2000-8000 BAU/mL	5,000-20,000 BAU/mL
PNU non-standardized extracts	3000-5000 PNU	6000-10,000 PNU/mL	15,000-60,000 PNU/mL
w/v non-standardized extracts	0.5mL from 1:100 to 1:200 w/v	1:100 to 1:200 w/v	1:50 w/v

* 0.5mL per dose.
** 2 drops/sprays daily dose (0.1mL)

8.7.2. Vial Concentration for SCIT according to the European guidelines

For SCIT according to the European school, in relation to standardized extracts, a range between 5 and 20 mcg of the major allergen is the recommended maintenance dose for inhaled allergens and 100 mcg for Hymenoptera venom. Depending on the volume projected to inject the manufacturer adjusts the concentration of the vial, because in this variant – as previously explained in Chapter 4B– the product is sold as a terminated ready-to-use preparation.

8.7.3. Vial concentration for SLIT

The allergen dose for SLIT should be considerably higher than for SCIT. Initial data suggested between 5-375 times, still showing uncertainty and great variation in this parameter. A detailed analysis of more recent SLIT data suggests that the effective daily dose of SLIT could range from 0.5 to 2 times the monthly dose of SCIT, see Chapter 5. However, there is controversy related to comparing dosages like this, because the efficacy of SLIT also depends on the vehicle and the volume administered. It has been suggested that the minimum daily dose of major allergen for SLIT should be 5 mcg daily (consensus of non-Mexican experts).

8.8. Commercially Available Allergen Extracts in Mexico by Manufacturer

The extracts available in Mexico are:

1. Extracts from U.S. Suppliers: Standardized and Non-Standardized (ALK-Abelló)
2. Extracts from European Supplier: Standardized and non-standardized (ALK-Abelló, Inmunotek, IPI-ASAC)
3. National extracts, imported as freeze-dried products from the United States and conditioned for sale locally, without standardization (Alerquim).
4. National extracts, principally produced from local bulk extracts, without standardization (Allergomex, Rocel).

National extract manufacturers report to have a pending registration number with extension for Good Manufacturing Practices, while their extracts do have a sanitary registration from the Department of Health (SSA). The European manufacturers with products available on

the Mexican market and with registration from COFEPRIS (Federal Commission for the Protection of Health Risks) at the moment of the publication of GUIMIT are ALK-Abelló, Inmunotek and IPI-ASAC.

8.9. Is there a defined dose-response ratio and therefore a maintenance dose in SCIT?

We recommend
Yes, 100%
Evid: 1b, Rec: A

In the case of European extracts, the maintenance dose in SCIT has been defined in accordance with the manufacturer's recommendations; European guidelines refer that due to the heterogeneity of clinical trials a universal maintenance dose for all extracts cannot be established. Therefore, each has a different maintenance dose. The commercially available vial provides the therapeutic dose established by the manufacturer, therefore, its mixture could have a dilutional effect. In the event the physician does want to mix allergens, an adjustment should be made to the number of monthly administrations or two doses should be administered each session to achieve the effective monthly dose.

However, in the case of the national Mexican and US schools, where the allergist, knowledgeable in AIT, prepares the vial formulation and its administration schedule, there are known dosing intervals that have shown clinical efficacy per group of allergens (aeroallergens versus VIT). See Chapter 4 and 5.

Regarding national and US extracts, the maintenance concentrate should be formulated to provide a dose considered therapeutically effective. This vial is defined as *maintenance concentrate* (which is defined according to its dilution factor as 1:1 v/v). This concentration should provide a projected effective dose which is the objective of the maintenance phase of SCIT. The effective dose used in clinical trials is based on standardized extract dosage ranges; for non-standardized allergens, the effective dose should be estimated and individualized (See dose table, Chapter 4.2). Some subjects will not tolerate the projected effective dose and may experience clinical benefits with lower doses, just to the limit of what they tolerate without systemic adverse reactions. Therefore, the maintenance dose is the one that provides therapeutic effect without local or systemic adverse events and shall not always be the dose that was initially calculated as a projected effective dose; however, very low doses are ineffective, for example, dilutions of 1:1,000,000, 1:100,000 or 1:10,000 (v/v). This reinforces the fact that AIT should always be individualized, taking into account that administration of a higher maintenance dose increases the likelihood of clinical effectiveness, however, it also increases the risk of adverse systemic reactions. (Recommendation Grade A).

Good Clinical Practice 100%

When mixing extracts the dilutional effect should always be considered, which definitely influences AIT's efficacy and limits the number of allergens that can be include in the vial. It is possible to maintain the appropriate dose for each allergen when the mixture is made from highly concentrated vials to allow for preparation: 10,000 or 100,000 (B) AU/ml for standardized vials and 1:10 or 1:20 w/v for non-standardized ones.

If the mixture is made from a concentrated vial from the manufacturer having a lower concentration (e.g. 1,000 (B) AU/ml or 1/100 w/v), it should be considered to increase the volume taken from that low-concentrated vial to prepare the appropriate maintenance concentration and/or increase the number of monthly applications to try to achieve the projected monthly effective dose.

Good Clinical Practice 100%

8.10. Is there a defined dose-response ratio and therefore a maintenance dose in SLIT?

The maintenance dose for SLIT has been defined according to the recommendations of each manufacturer for their extracts marketed in Europe and the US; these are pollens (tablets/ liquid) and dust mites (tablets/liquid). Because the extracts used in clinical trials are produced by different manufactures and each one has different potency units, comparison between the different sublingual products in relation to their potency is difficult and it is impossible to set a universal dose for each of the extracts. On the other hand, the amount of allergen administered has been quantified and a dose range of antigenic determinants has been established with some of the most prevalent therapeutic extracts (*Phleum pratensis* and *Betula verrucosa*); considering these findings it can be inferred that the monthly maintenance dose in SLIT should be much higher than the subcutaneous one. See Chapter 5 for further details.

We suggest Yes, 100%
No Evidence
No

8.11. Are there interchangeable doses between extracts from different manufacturers (equivalent doses)?

None of the main reference guidelines comments on interchangeable doses between the different manufacturers, nor the possibility of establishing equivalences between the therapeutic doses of standardized and non-standardized allergens, despite having the knowledge of effective doses for SCIT for multiple allergens, which are in relation to the amount of major allergen (5 – 20 mcg per injection).

Because there are variations between different manufacturers in the amount of major allergen in both standardized and non-standardized extracts, in general it is recommended to not consider the possibility of interchangeability or dose equivalence. In case there is a need to change provider, it will be necessary to restart treatment from the build-up phase to avoid potentially serious side effects. An exception could be comparing the potencies of the extracts of the old and the new provider simultaneously in the same lab or with SPT in the same patient, which would allow us to deduce how the potency compares between both extracts [only applicable with natural allergens] (GUIMIT in a simplified Delphi: We suggest yes).

Good Clinical Practice No 100%

Good Clinical Practice Yes 100%

8.12. Is the quality of immunotherapy affected by the type of diluent used?

Diluents used in immunotherapy play an essential role in the extract's preservation and efficacy. Phenol is used for its antibacterial and preservative properties; however, it does not stabilize proteins, allowing their denaturation and loss of potency.

50% glycerin and human serum albumin (HSA) have a stabilizing and preservative effect due to inhibition of enzymes with proteolytic activity present in some extracts. They have been shown to be effective in preserving solutions even with high dilutions, compared to normal saline or glycerin 10% as diluents. It is recommended to add 0.03% HSA to avoid adsorption of the allergen on the inner surface of the vial in higher dilutions, as well as to prevent the deleterious effect of phenol on extracts. No additional effect has been shown on the extract concentration at increasing concentrations of HSA, (information obtained from the manufacturer). In México, HSA is not available for the preparation of immunotherapy. The albumin available in the local market is not meant for this purpose.

Good Clinical Practice Yes 100%

However, there is HSA contained in the solvent vials of freeze-dried extracts, marketed by some European manufacturers in Mexico.

Freeze-dried extracts should be reconstituted with 50% glycerin or HSA for preservation (solvent), while the preparation of SCIT vials for the patient should not contain more than 10% glycerin. Higher concentrations cause injection site irritation and pain. For SLIT, higher concentrations of glycerin (up to 50%) can be used.

Good Clinical Practice Yes:

8.13. Can certain adjuvants be added to immunotherapy to increase its efficacy?

8.13.1. Aluminum hydroxide

Aluminum hydroxide has been widely used as a first option adjuvant, because adherence to allergen molecules generates a cluster that functions as a slow-release reservoir, suppressing the peak of the allergen concentration in the systemic circulation and therefore reducing the possibility of systemic adverse events. Furthermore, interactions with innate and adaptive immunity have been attributed to adjuvants, thus enhancing AIT immunogenicity. However, in some patients alum has been linked to acute inflammation at the site of administration and in rare cases it might cause a chronic local inflammation resulting in a granuloma; this is probably due to a contact dermatitis reaction or even vasculitis. In case of presenting any type of adverse local reaction it is recommended to change to extracts free of this adjuvant.

We suggest Yes, 100%
No Evidence

8.13.2. Toll Like Receptor Agonists

Some bacterial products are Toll Like Receptor (TLR) agonists; they have been used as adjuvants with immunomodulatory properties. Monophosphoryl lipid A (MPL-A), derived from Salmonella *minnesota* lipopolysaccharides, a TLR-4 agonist, stimulates Th1 cell response along with its cytokine pattern. In some studies, it has been mixed with grass pollen showing efficacy in phase III studies. (grade A for adults, grade B for children). TOLAMBA, is the fusion of a TRL-9 agonist, (oligodeoxynucleotide CpG) to the major determinant of ambrosia (Amb a 1). CpG promotes an anti-inflammatory effect mediated by elements of the innate immune system, as well as the production of regulatory cytokines that eventually support the isotype switch from IgE to IgG4. It has been tested in conventional and accelerated AIT schedules proving to be safe and effective. (Recommendation Grade A). In Mexico, such products are not yet available.

8.13.3. Omalizumab

Concomitant administration of the anti-IgE monoclonal antibody, Omalizumab, has been shown to be effective in inducing tolerance and decreasing adverse effects in conventional and accelerated schedules of AIT and VIT, see Chapter 10.

We suggest Yes, 100%
Evidence: 1b

8.13.4. Bacterial vaccine

Polivalent or monovalent bacterial extracts, which are obtained from the most common pathogenic strains, improve the activity of natural killer (NK) cells, stimulate the production of TNF-α, IL12, IFN-γ in mononuclear cells, regulate the expression of adhesion molecules in phagocytes and inhibit the production of IL-12 in lymphocytes, increase the production of IgA and IgG and decrease the total concentration of IgE. These have been used for decades as an adjuvant in immunotherapy because of their immune modulating effect.(90, 91).

Good Clinical Practice Yes 100%

Chapter 9. SCIT: AIT safety, adverse events and their management

Table 9.1

SUMMARY Chapter 9: Adverse Events		
GUIMIT experts recommend/suggest, taking into account evidence in MRG*		Agreement
9.1a In relation to AIT (SCIT and/or SLIT), is premedication with a second generation H1 antihistamine and/or leukotriene receptor antagonist necessary to prevent or reduce mild local or systemic adverse effects?	We suggest: Yes	100%
9.7 Is the use of a leukotriene receptor antagonist considered effective to prevent or reduce adverse reactions on AIT?	We suggest Yes	100%
9.1b In relation to immunotherapy (SCIT and/or SLIT): Does premedication reduce or prevent anaphylaxis?	We recommend: No	100%
9.2 In patients receiving Hymenoptera venom immunotherapy (VIT) and who have systemic adverse reaction to AIT, is it recommendable to... : a. premedicate with 2nd generation H1-antihistamines? b. Premedicate with omalizumab to prevent adverse reactions to AIT administration?	a. We recommend Yes b. We suggest Yes (according to total IgE)	a. 100% b. 100%
9.6 Could a patient, who shows adverse reactions with systemic symptoms, be treated with H1 antihistamines or systemic corticosteroids before or instead of epinephrine? a. When only one organ-system is affected (e.g. hives or rinorrea only) b. When 2 or more organ-systems are affected (e.g. rinorrea and hives)	a. We suggest Yes - Respiratory condition: Beta agonists - Skin or nasal condition: Antihistamine b. We recommend No (diagnosis is anaphylaxis!)	100%
9.4 Is epinephrine the first-choice medication for initial management of anaphylaxis?	We recommend Yes. Dosage: 0.01mL/kg, maximum 0.5mL I.M.	100%
9.5 After a serious adverse event (anaphylaxis), Should systematic corticosteroids be prescribed?	We suggest Yes, if there was hypotension (Reduces the risk of biphasic anaphylaxis)	100%
9.8 After an adverse reaction to immunotherapy: should the dose and/or concentration be adjusted in case of...		100%
A. a local reaction (LR)?	We suggest No	100%
B. an extensive LR (>2.5cm) or repetitive LRs?	We suggest Yes	100%
C. a systemic reaction?	We recommend Yes	Adjusted #
Joint clinical experience of GUIMIT experts (Delphi simplified): evidence 1c**		
If a patient presents anaphylaxis after a SCIT shot with cough, rhinorrhea and mild hives, without hypotension and is managed with epinephrine and sent home, would you prescribe a 2nd generation H1-antihistamine for 7 days?	Yes (30% recommends yes, 52% suggests yes)	
If a patient has post-SCIT anaphylaxis with hypotension and is managed with epinephrine, when sent home: would you indicate a 2nd generation H1-antihistamine for up to	Yes (46% recommends yes, 44% suggests yes)	

7 days and oral CS [prednisone/ prednisolone (1mg/kg)] for up to 5 days?		
**** Good practice points**		
9.3 Signs of a severe systemic reaction include: a. Key symptoms b. Early symptoms	We suggest yes. (see list) Hypotension is a symptom of severity	100%

*MRG – Main Reference Guidelines. The level of evidence and recommendation was sought in each of the main reference guidelines (source tables 1); evidence and recommendations were merged to issue a recommendation for a certain action (source tables 2). Links to these tables are found in Annex 1
** Source: Anonymous answer from the 57 GUIMIT experts. With a broad consensus, it is possible to assume a level of evidence 1c, according to CEBM.
# After voting, the nuclear group of coordinators discussed this point and raised the proposed suggestion to the level of recommendation, emphasizing patient's safety.

9.1 Introduction

Local adverse reactions (LRs) are common in AIT. In SCIT, more than half of the patients have a wheal at the site of administration(s) at some point (see Chapter 4AB), while in SLIT in the European modality in which there is - almost - no updosing phase, up to 70% could have some local symptom in the oral cavity in the first few weeks, see chapter 5. Systemic reactions (SR) and eventually even anaphylaxis or very rarely anaphylactic shock might also occur, though the latter one has never been reported in SLIT. Chapters 4AB and 5 reviewed risk factors for SR and in Chapter 7 GUIMIT experts suggest the indispensable and optimal requirements for materials that have to be present at the site where AIT is administered, in order to give a quick and timely handling in case of a SR. This chapter will review the usefulness of premedication, symptoms and classification of the severity of a SR and its management, as well as the actions to be taken after a SR.

9.2 Premedication to reduce the frequency of mild events (but not anaphylaxis)

Based on the MRGs' information, the physician can pre-medicate with a second generation, non-sedative H1-antihistamine or with an antileukotriene (92) to decrease the intensity and frequency of LRs. The H1-antihistamine, taken one or two hours before applying the AIT, could also be useful to decrease the frequency of SRs or to avoid them after all. However, pre-medicating does not prevent anaphylaxis. Both, with SCIT and with SLIT, pre-medication has a good safety profile and does not affect the efficiency of AIT.(93, 94)

Antileukotriene
We suggest Yes 100%
Evidence: 2a
Recommendation: B

In conclusion, in selected cases, the GUIMIT experts suggest pre-medication with an H1-antihistamine one or two hours before SCIT administration, to reduce LRs and mild SRs. Especially with a grouped schedule (cluster, rush and ultra-rush schedules), the safety increases (see 4.4) and during the updosing phase pre-medication could be useful to allow increasing the dosage without having to detain due to adverse reactions.

We suggest Yes 100%
Evidence: 2+
Recommendation: A

In patients managed with VIT who present SRs, in addition to applying H1-antihistamines or antileukotrienes, pretreatment with the anti-IgE monoclonal antibody, starting several weeks before restarting VIT might be an option, to decrease the risk of another SR. Considering the effectiveness, but also the cost, the GUIMIT experts suggest starting the administration of omalizumab five weeks before restarting VIT (administer -5sem, -3sem, -1sem), calculating the dose depending on the patient's weight and total serum IgE and to continue omalizumab for four or six month simultaneously with VIT, along with non-sedating second generation H1 antihistamine.

Omalizumab: We suggest Yes 100%
Evidence: 3
Recommendation: C

Good practice point
100%

9.3 Symptoms suggestive of a systemic adverse reaction and alarm symptoms

Although most international immunotherapy guidelines do not include guidelines on clinical data that may precede a serious SR, they are mentioned in the German Immunotherapy Guide in addition to the World Allergy Organization (WAO) anaphylaxis guideline. The general rule is that the shorter the time between the administration of the AIT and the onset of the first symptom, the more severe the possible SR might be. It is extremely rare for anaphylaxis to start more than 30 minutes post-administration.

9.3.1 Early signs and symptoms of anaphylaxis

Some symptoms and early signs of anaphylaxis that are mentioned in the literature are burning sensation or itching in palms and soles, fear and anxiety (sense of 'pending doom'), perianal and peri-genital itching, urgency to urinate or to have a bowel movement, uterus cramping or metallic taste; Children can show behavior changes or weakness, sneezing attacks or generalized itching prior to the development of the cardiovascular and respiratory symptoms, typical of anaphylaxis.

Table 9.2: Clinical criteria for diagnosing anaphylaxis

Clinical scenario	**Skin**	**Respiratory/GI**	**Cardiovascular**
Scenario 1: Acute onset of a reaction (minutes to several hours)	involvement of skin and/or mucosal tissue (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THESE →	Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)	Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
Scenario 2: Two or more of skin/RespDigest/CV that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):	Involvement of skin and/or mucosal tissue (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)	Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) And/or Persistent GI symptoms (eg, crampy abdominal pain, vomiting)	Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence
Scenario 3: Reduced BP after the exposure to a <u>known</u> allergen for that patient (minutes to several hours)	Any symptom or none	Any symptom or none	a. *Infants and children*: low systolic BP (age specific) or > 30% decrease in systolic BP* b. *Adults*: systolic BP of <90 mm Hg or > 30% decrease from that person's baseline

BP = blood pressure; CV = cardiovascular; GI = gastrointestinal, PEF = peak expiratory flow;
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg 1 [2 3 age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years
Adapted from: Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014; 69(8): 1026-45.

9.3.2 Classic symptoms and signs of anaphylaxis

Table 9.2 enlists the classic symptoms and signs of anaphylaxis, considering different clinic scenarios.(95) Table 9.3 shows the proposal of how to classify the severity of anaphylaxis,(96) although the international discussion on creating a better system is still ongoing.(97) Once a patient shows a drop in blood pressure (hypotension), the diagnosis is anaphylactic shock. Fortunately, once anaphylaxis is detected and timely managed, the risk it evolves into an anaphylactic shock decreases; however shock cannot always be prevented.

Good practice point
100%

Table 9.3

Degree	Skin	Digestive	Respiratory	Cardiovascular
I	Pruritus, redness, hives angioedema	-	-	-
II	Pruritus, redness, hives angioedema	Nausea, cramps	Rinorrea, hoarseness, dyspnoea	Tachycardia (elevation >20/min relative to baseline), hypotension (drop >20 mm/Hg from baseline), arrhythmia
III	Pruritus, redness, hives angioedema	Vomiting, defecation	Laryngeal oedema, bronspasm, cyanosis	Shock
IV	Pruritus, redness, hives angioedema	Vomiting, defecation	Respiratory arrest	Circulatory arrest

Adapted from Ring et al. Lancet,1977.

9.4. Classification of systemic adverse reactions to AIT (SCIT, SLIT and VIT)

A group of experts, in an effort coordinated with WAO, classified systemic reactions secondary to SCIT and it was subsequently agreed that the classification was also valid for post-SLIT SR, see Figure 9.1, see next page.

9.5. Treatment of systemic reactions and anaphylaxis

If the patient shows an adverse reaction after the administration of AIT that involves one organ or system, the definition is a SR; that could be mild or severe, depending on intensity of the symptoms. The treatment of a SR that is not anaphylaxis could be with a second generation H1-antihistamine. If the lower airways are the involved organ, the first medication should be a fast-acting, inhaled bronchodilator. If the reaction progresses and it extends to other organ(s), anaphylaxis treatment should be started.

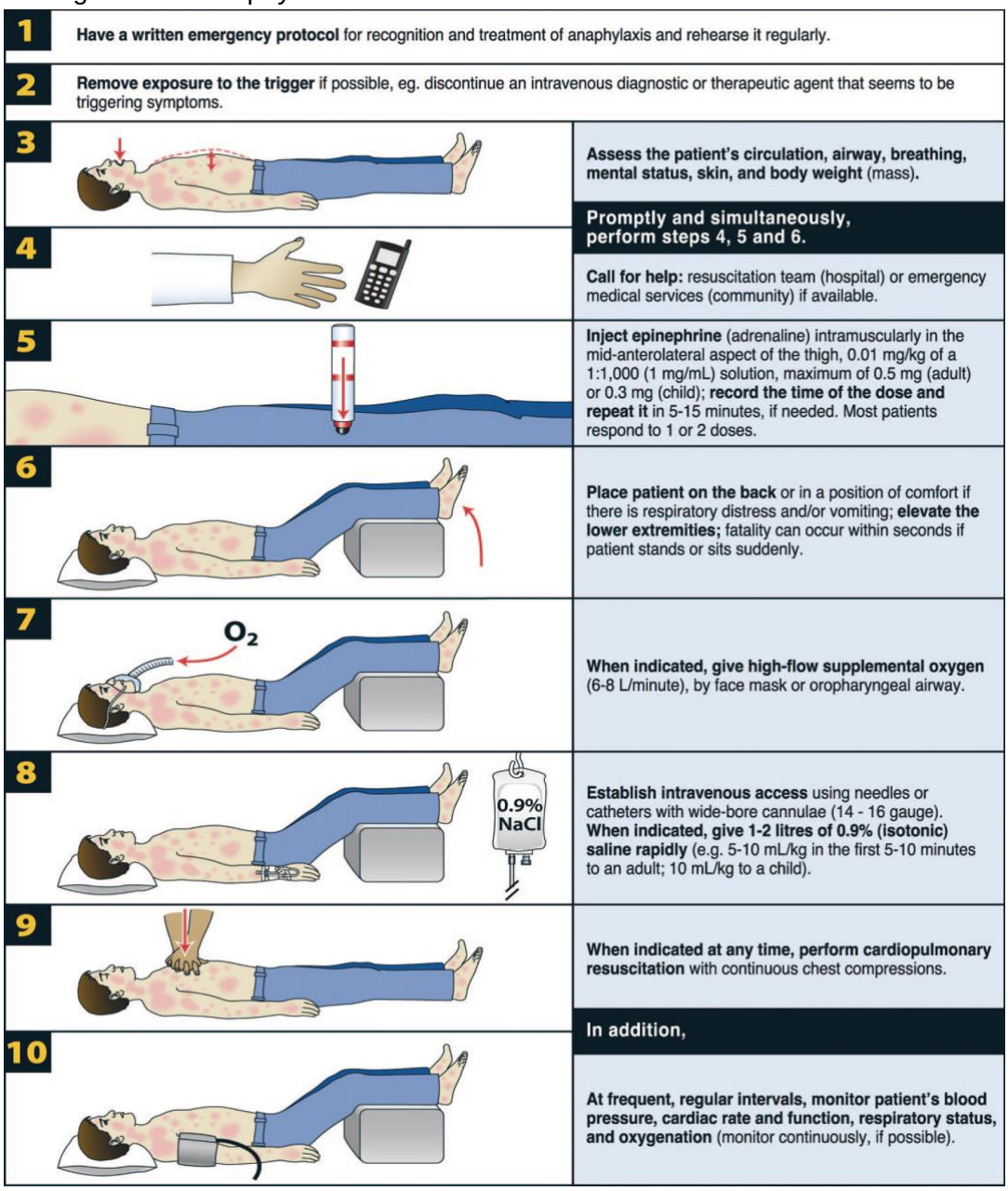
Good practice point
100%

However, if the patient has symptoms in two or more organs systems, by definition it is anaphylaxis, and its treatment will be as described in the figure 9.2. Epinephrine is the only first-choice drug treatment for the treatment of anaphylaxis. Intramuscular administration is recommended to speed up your systemic absorption, because during anaphylaxis there is a decreased perfusion of subcutaneous tissue, in addition to local paleness due to intense vasoconstriction. Epinephrine is given at a dose of 0.01mL/kg/dose, maximum dose

Adrenaline IM, 100%
Recommend Yes
Evidence: 2a
Recommendation: A

0.50mL. It can be repeated every 5-10 minutes if necessary. The only exception could be patients under treatment with beta-blockers who develop anaphylaxis. In this case it is also recommended to administer glucagon, 20-30mcg/kg/dose, up to 1 mg to improve the response to epinephrine that could be partially blocked.

Figure 9.2 Poster developed by experts from the World Allergy Organization for the management of anaphylaxis



Reproduced with permission from(98)

Figure 9.1 WAO Grading system of systemic reactions with allergen immunotherapy

World Allergy Organization SC Immunotherapy Systemic Reaction Grading System				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptoms of one organ system[a] *present* **Cutaneous** Urticaria , flushing generalized sensation, of heat or warmth [b] **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper Respiratory** Rhinitis symptoms (e.g. sneezing, rhinorrea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to come from the upper airway, not the lung, larynx, or trachea **or** Conjunctival Conjunctival erythema, pruritis or tearing **Other** Nausea,metallic taste	Symptoms of *more than one organ* system present **or** **Lower respiratory** Asthma symptoms: cough, wheezing, shortness of breath (e.g. less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** Gastrointestinal Abdominal cramps, vomiting. or diarrhea **or** **Other** Uterine cramps	**Lower respiratory** Asthma symptoms (e.g. 40% PEF or FEV1 drop. NOT responding to an inhaled bronchodilator). **or** **Upper respiratory** Laryngeal, uvula or tongue edema with or without stridor	**Lower or Upper Respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death
Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4. **Note:** children with anaphylaxis seldom convey a sense of impending doom and their behavior changes; e.g., becoming very quiet, or irritable and cranky may be a sign of anaphylaxis.				
Scoring includes a suffix that denotes if and when epinephrine is administered in relationship to onset of symptoms a= ≤ 5minutes, b= 6-10 minutes, c= 11-20 minutes and d= >20 minutes, z= no epinephrine				
The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should also include first symptom and time of onset of symptom (s) after the subcutaneous allergen immunotherapy injection and suffix reflecting if and when epinephrine was administered e.g., Grade 2a; rhinitis: 10 minutes				
First symptom and time of onset after the subcutaneous immunotherapy injection[c] First symptom _____ Time of onset of first symptom _____ Grade _____				
Comments:[4]				

a) Each Grade is based on organ system involved and severity. Organ systems are defined as: cutaneous, conjunctival, upper respiratory, lower respiratory, gastrointestinal, cardiovascular and other. A reaction from a single organ system such as cutaneous, conjunctival, upper respiratory , but not asthma, gastrointestinal or cardiovascular is classified as a Grade 1 . Symptoms from more than one organ system or asthma, gastrointestinal, cardiovascular are classified as Grades 2 or 3. Respiratory failure, hypotension with or without loss of consciousness define Grade 4 and death Grade 5.The Grade is determined by the physician's clinical judgment.

b) This constellation of symptoms may progress rapidly to anaphylaxis

c) Symptoms occurring within the first minutes after the injection should be considered as a sign of severe anaphylaxis. Mild symptoms may progress rapidly to severe anaphylaxis and death
d) If signs or symptoms are not included in the table a present or the differentiation between a SR and vasovagal (vasodepressor) reaction, which may occur with any medical intervention is difficult, please include comment, as appropriate.

Adapted from Cox L, Larenas-Linnemann D, Lockey D, et al. JACI 2010. (99)

9.6. Post-treatment of a systemic reaction or anaphylaxis

None of the main reference guidelines addresses this aspect. After a SR the patient should be kept under observation for at least 30 minutes after the resolution of the event. After anaphylaxis the patient should be observed and monitored for at least an hour. On discharge, GUIMIT suggests continue medication with a non-sedating second generation H1 antihistamine, accompanied by the temporally adjustment of asthma maintenance treatment, if necessary.

Good practice point 100%; GUIMIT survey: suggests

After an event with anaphylaxis and hypotension (anaphylactic shock) 1 mg/kg of systematic corticosteroids are recommended, with a maximum of 50mg of prednisone or equivalent for five days, along with a second generation H1 antihistamine, to reduce the risk of biphasic anaphylaxis. The physician may consider to admit the patient for a 12-24-hour observation period, in case of a biphasic reaction.

Good practice point 100%; GUIMIT survey: recommends

9.7. Adjustment of AIT dosage and schedule after an adverse reaction

Based on the above GUIMIT suggests to make a decision to adjust the AIT dose, depending on the severity of the adverse reaction. Most of the adverse reactions are local, mild and don't need dose-adjustment, as single local reactions don't predispose to SR. But, after large local reactions (>3 cm) and especially in the case of repetitive large reactions there has been an increase in the risk of SR(100). Here GUIMIT suggests adjusting AIT's schedule and reduce the dose to the last well-tolerated dose. After a SRs the main reference guidelines and GUIMIT suggest adjusting the AIT dose; depending on the severity of the SR such adjustment will be to the previous dose or a tenth part of the last tolerated dose. After an anaphylactic shock or multiple SRs, GUIMIT suggests considering the benefits of continuing AIT against its risks, as a patient that has presented a SR has a higher risk of presenting it again. It should be taken into account that the practice of AIT dose-adjusting is based on allergists' experiences, as there are no evidence-based recommendations.

Isolated large local We suggest No
Evidence: Ⅱ
Recommendation: C

Repetitive LL, or SR: We Suggest Yes
Evidence: 3
Recommendation: N.e.

Chapter 10: Future: New Indications and Immunotherapy Modalities under investigation

Table 10. 1

Table 10.1 Summary of novel and future (still in research) indications and modalities for allergen immunotherapy		
GUIMIT experts recommend or suggest according to evidence in the main reference guidelines *		Agreement
10.1.1 In **adolescents and adults** with monosensitized AR: has the administration of AIT by the intralymphatic route shown safety and efficacy?	Not enough scientific evidence	87%
10.1.2. In **children** with monosensitized AR: has the administration of AIT by the intralymphatic route shown safety and efficacy?	Not enough scientific evidence	96%
10.2. In **children, adolescents or adults** with mono/ polisensitized asthma: has the administrationof AIT by intralymphatic route shown safety and efficacy?	Not enough scientific evidence	100%
10.3.1 In **the adolescent/adult** patient with mono/polysensitized RA, has the administration of AIT by intranasal route shown safety and efficacy?	We suggest NO	100%
10.3.2 In **children** with monosensitized AR has the administration of AIT by intranasal route shown safety and efficacy?	We suggest NO	100%
10.4.1 In **children, adolescents** or **adults** with monosensitized AR has the administrationof AIT by epicutaneous route shown safety and efficacy?	Not enough scientific evidence	100%
10.4.2 In **children**, **adolescents** or **adults** with AR (polysensitized to grass pollen) has the administration of AIT by epicutaneous route shown safety and efficacy?	We suggest yes	100%
10.5 In **children**, **adolescents** or **adults** with mono/polysensitized asthma has the administrationof AIT by epicutaneous route shown safety and efficacy?	Not enough scientific evidence	100%
10.6.1 Is the administration of AIT with recombinant allergens in **adolescents/adults** with respiratory allergies safe and effective?	We suggest yes	100%
10.6.2 Is the administration of AIT with recombinant allergens in **children** with respiratory allergies safe and effective?	Not enough scientific evidence	100%
10.7.1 In patients **older than 6 years** with Hymenoptera Venom Allergy who poorly tolerated VIT: does the concomitant use of Omalizumab improve tolerance and reduce adverse effects?	We suggest YES	100%

10.7.2 In patients **older than 6 years** with Respiratory Allergy who poorly tolerated AIT: does the concomitant use of Omalizumab improve tolerance and reduce adverse effects?	We suggest YES	100%
Consensus based on clinical experience of GUIMIT experts (Delphi simplified) ‡: evidence 1c		
In Mexican patients with allergy who poorly tolerate SCIT and without the possibility of SLIT would you consider ILIT: - for allergic rhinoconjunctivitis (ARC)? - for allergic asthma?	ARC: Maybe (7%recommended, 33% suggest, 33% neutral) Asthma: Yes (7% recommended, 41%suggest , 31% neutral)	
Point of good practice		
Promote the realization of clinical research protocols in Mexican patients with ILIT, EPIT and recombinant allergens SCIT	We recommend: Yes	100%

* Level of evidence and recommendation was sought in each main reference guideline (source tables 1); evidence and recommendation merged to issue a recommendation for a certain action (source tables 2). The links to these tables are in annex 1.

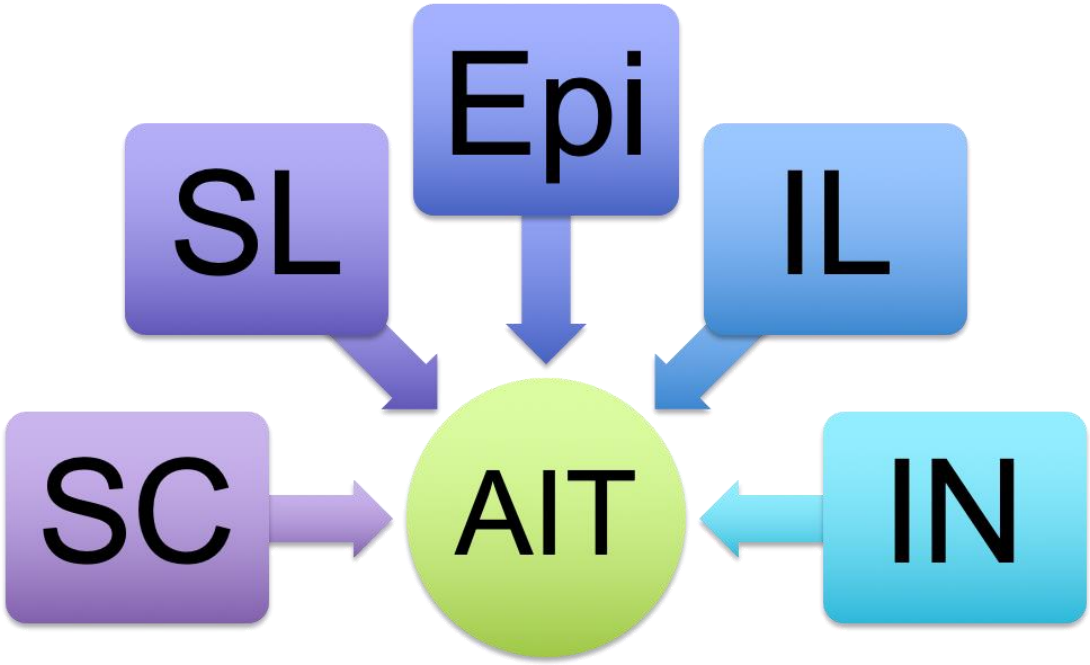
** Anonymous reply from the 57 GUIMIT experts. With a broad consensus, a level of evidence 1c is obtained, according to CEBM.

AR = allergic rhinitis, AIT = Allergen immunotherapy, VIT = hymenoptera venom immunotherapy, SCIT = subcutaneous immunotherapy, SLIT = sublingual immunotherapy, EPIT = epicutaneous immunotherapy, ILIT = intra-lymphatic immunotherapy, INIT = intranasal immunotherapy.

10.1 Introduction

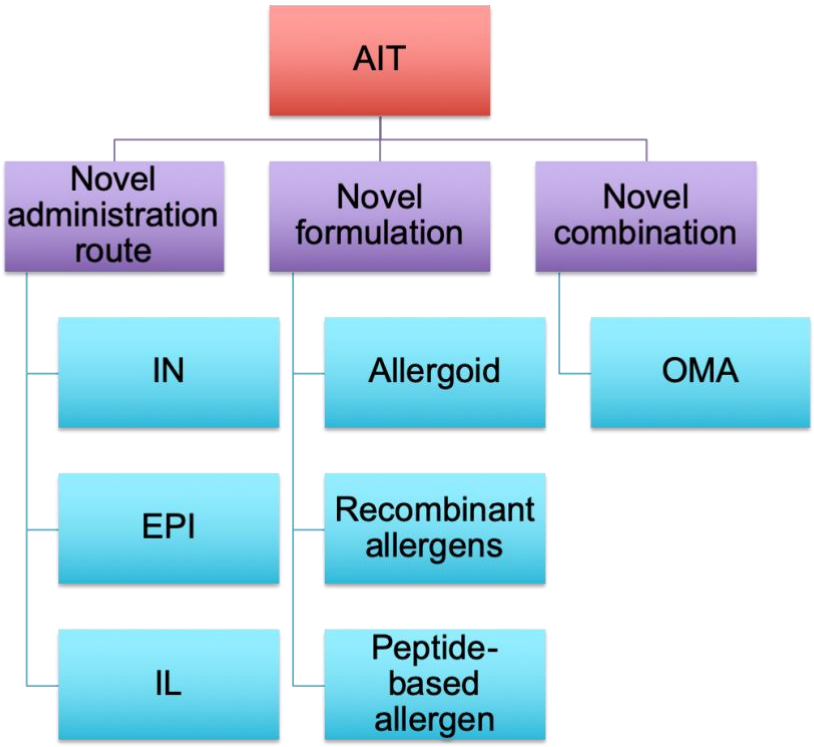
The administration of AIT (either subcutaneous or sublingual) has demonstrated efficacy and safety. It has been established that the allergen-specific inflammatory cascade is being reversed from the first year of administration onward and throughout the rest of treatment (minimum for three years). But, most importantly the long-term clinical benefit is maintained once completed (see chapters 4 and 5). International efforts have proposed new routes of administration (figure 10.1), with the main goal of reducing treatment length and having an alternative for administration when adverse effects occur. Within this section we present the current evidence on intra-lymphatic (ILIT), epicutaneous (EPIT) and intranasal (INIT) immunotherapy. The efficacy and safety of recombinant allergens and synthetic peptides have also been proven. The use of biological agents concomitantly administered with AIT can improve its safety (figure 10.2). So far we do not have commercially available allergenic extracts nor the devices used in clinical trials where new routes have being described. GUIMIT seeks to promote clinical research within the Mexican population.

Figure 10.1



AIT: Allergen Immunotherapy, SC: subcutaneous, SL: sublingual, Epi: epicutaneous, IL: intralymphatic, IN: intranasal

Figure 10.2



AIT: Allergen Immunotherapy, Epi: epicutaneous, IL: intralymphatic, OMA: omalizumab

10.2 Allergic rhinitis and intra-lymphatic immunotherapy

Intra-lymphatic immunotherapy (ILIT) has shown clinical benefit for monosensitized adolescents and adults with AR; studies with a solid design have shown clinical benefit in patients: decrease of symptoms and medication use, improvement in the quality of life, in addition to being very safe. The advantages also include a very low number of shots (only three with four-week intervals), shorter duration (eight weeks in total) and a very considerable reduction in the amount of allergen given in each dose (1/1000 of the SCIT dose). The procedure is performed by direct needle puncture in an inguinal lymph node and guided by ultrasound (figure 10.3); no sedation is required nor analgesia since it has been referred to as "less painful than a venipuncture".

GUIMIT does not issue a recommendation or suggestion since Mexico does not have extracts used in other countries and no Mexican studies have been carried. So GUIMIT promotes clinical research. There is not enough scientific evidence to support the use of ILIT among the pediatric population with mono or polysensitized allergic rhinitis, or in polysensitized patients. GUIMIT does not issue a recommendation or suggestion.

10.3 Asthma and intra-lymphatic immunotherapy

There have been no clinical studies on the use of allergenic extracts for ILIT within the pediatric population, adolescents or adults with the diagnosis of allergic asthma.

GUIMIT does not issue a recommendation or suggestion.

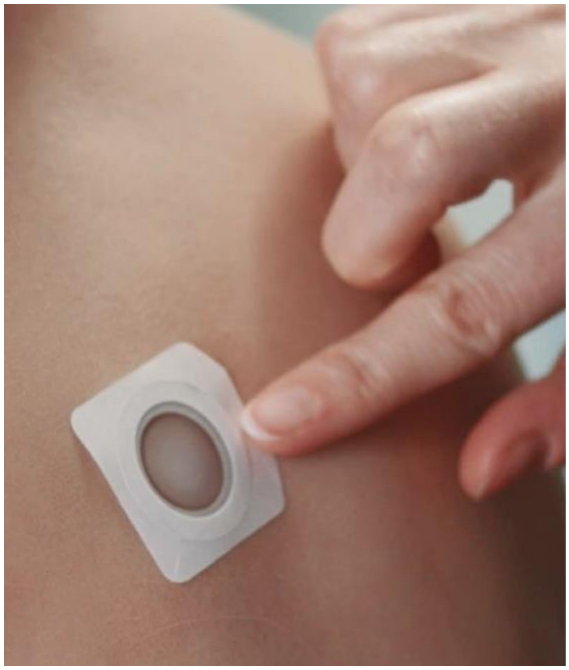
10.4 Allergic rhinitis and intranasal immunotherapy

At the end of the 20th century, Intranasal immunotherapy (INIT) administration was proposed as an alternative to patients with poor tolerance to SCIT. Clinical trials demonstrated the adequate efficacy and safety profile (in terms of severe allergic reactions) of ITIN comparable to SCIT. However, patients were less adherent to treatment due to the local adverse effects associated with this novel route of administration. In Mexico there are neither available extracts nor the devices for INIT administration. GUIMIT suggests not using ITIN in patients with poor SCIT tolerance, in whom it is better to consider SLIT.

10.5 Allergic rhinitis and epicutaneous immunotherapy

In patients with polysensitized AR (pediatric, adolescent or adult), the administration of epicutaneous immunotherapy (EPIT) has shown clinical benefit(2): decreased symptoms and medication use, improvement in quality of life and safety. Skin patches containing the allergens are being used, which keep allergen in direct contact with the epidermis of the forearms between 8 and 48 hours. The administration is daily (for foods) or weekly (figure 10.4). GUIMIT suggests using EPIT in patients with AR sensitized to grass pollen (low quality of evidence). In Mexico we do not have extracts nor the device for its administration. GUIMIT promotes clinical research protocols with EPIT in the Mexican population. There is no scientific evidence to support the use of allergenic extracts for EPIT among children, adolescents or adults with diagnosis of AR polysensitized to non-homologous extracts, or within asthmatic patients.

In this regard there have been no clinical trials.



Epicutaneous administration of Peanut Immunotherapy Viaskin Peanut© (2018, DBV Technologies) EPIT is under clinical investigation and hasn't been approved for commercial uses. Photography with permission by DBV Technologies

10.6 AIT with recombinant allergens

Advances in recombinant DNA technology have allowed the development of recombinant allergens, synthesized only with allergenic molecules. These are comparable to their natural counterparts in terms of immunogenicity, although thier allergenicity is reduced since their structure is very small. In recent years the efficacy and safety of recombinant allergens in SCIT have been demonstrated. GUIMIT suggests using SCIT with recombinant allergens in adolescents or adults with respiratory allergies, although extracts are not currently marketed in Mexico. There is no scientific evidence to support the use of SCIT with recombinant allergens in children, even though it promises to be a variant with a better safety profile. No clinical trials have yet been performed in this age-group. Table 10.2 shows a summary of the advantages and disadvantages of AIT administration routes, those currently in use and those under investigation.

Table 10.2
10.2 Current routes and research prospects of AIT administration with allergens and their pros and cons

Administration Route	Clinical Use	Allergen (example given)	Advantages	Disadvantages
SCIT	Respiratory Allergy Hymenoptera Venom Allergy	House dust mite, coackroach, mold, animal dander, tree,	Monthly administration Efficacy Long-term effect	Local and systemic reactions Duration of administration > 3 years

		grass and weed pollen		$
SL	Respiratory Allergy Latex Allergy	House dust mite, coackroach, mold, animal dander, tree, grass and weed pollen	Safety Efficacy Long-term effect	Daily administration Duration of administration > 3 years $$$$$
EPIT	Respiratory allergy Food allergy	Grass pollen Food	Patch administration: Inhalant: weekly Food: daily	Local side effect Duration of administration years
ILIT	Respiratory allergy	Grass and Birch pollen cat	Duration of administration 8 weeks Cost-effective	Application by trained doctor Equipment (USG)
INIT	Respiratory allergy	Grass and Weed pollen Mites	Very safe	Very bothersome local side effects Bad attachment
OIT	Food allergy	Food: milk, egg, peanut	Safety Rises symptom threshold, very cheap	Effect during AIT

AIT: Allergen Immunotherapy, SC: subcutaneous, SL: sublingual, Epi: epicutaneous, IL: intralymphatic, IN: intranasal
(2)

10.7 Administration of Omalizumab concomitantly to AIT

The use of Omalizumab concommitantly with the administration of SCIT (especially during the dose increase phase, using either a cluster or conventional build-up phase) has shown safety, efficacy and improved tolerance to SCIT.
GUIMIT suggests using omalizumab in patients > 6 years with venom allergy and poor tolerance to VIT (presence of systemic reaction) or with respiratory allergies and poor tolerance to the administration of SCIT..

10.8 Latex immunotherapy

Latex immunotherapy was considered within the scope of GUIMIT, however, none of the three main reference guidelines issues a recommendation on its use. Although there are inconsistencies in the epidemiological data reported on latex allergy, in general it mainly affects the at risk population: patients with congenital malformation, in particular myelomeningocele (> 25%)(101), health care workers(102)and rubber workers. GUIMIT recommends the use of latex-free material in patients with risk factors with a positive allergic sensitization profile.

As for latex AIT, studies that report efficacy date from more than a decade ago (4, 5) or are of low quality (5). The same applied here what applied for inhalant allergen AIT: the higher the dosage the higher the efficacy, but also the increased risk of anaphylaxis. One of the few reports of anaphylaxis with SLIT was with a latex extract (6). In addition, at this time we do not have a standardized latex extract in Mexico. Therefore, GUIMIT suggests only using AIT with latex extract in the context of clinical research, preferably SLIT.

10.9 Conclusion

Currently, the study on allergic diseases, from the molecular mechanisms to the clinic, and the incessant development of information technology and communication allow innovations with real everyday impact. GUIMIT considers a point of good practice to keep our concepts up to date, promote continuing education and create academic/scientific networks to enhance exchange of knowledge and cooperation.

Implementation of GUIMIT 2019: Facilitators, Obstacles and Dissemination

In order for the concepts, expressed in GUIMIT 2019, to improve the practice of AIT/VIT in our country several steps could be indicated. First allergists and allergy fellow have to become aware of its existence, second the knowledge of its content has to be promoted so that finally the third step can be reached: its implementation. Learning from the experience with the previous Mexican AIT guideline 2011, it became clear that the dissemination of the guideline can be facilitated at different levels:

1) by publishing it in the specialty-specific journal with the most widespread (electronic) distribution in Latin America, the *Revista Alergia Mexico.*
2) by creating expectation of its launch: with the survey sent out to all allergists about controversial points in AIT/VIT, see figure A2
3) by present it in national forums of the specialty, especially the National congresses
4) promoting it with the Program Directors, asking them to contribute to the content already from the very first steps of the development process of the guideline.
5) promoting it among allergy fellows, proposing to CONICA some questions about GUIMIT to be included in the final exam of the specialty.

All these points are being taken care of.

Among the obstacles in the first place is the well-known resistance to change, inherent to the human being. Also, the allergen extract doses proposed in GUIMIT contain a higher amount of allergen than that occupied in some places at the moment. Increasing the concentration of maintenance treatment will increase the cost and might also temporary increase the frequency of adverse reactions. Both can cause rejection. That is why we chose to present all the options of allergenic extracts available in Mexico, standardized and non-standardized ones and those of both international and national origin, understanding that the second options are those with the lowest costs, although they will not always have the same level of quality as those of high cost.

Although the cost of AIT could be raised by using allergen extracts of higher quality and/or of higher concentration, it has been clearly documented that proper management of SCIT and SLIT ultimately reduces the long-term cost of allergic diseases (103, 104)and may even reduce the frequency of severe asthma exacerbations.(35)

GUIMIT contains several tools that could support its implementation. Chapters 4-6 support the explanation of dosage in tables and figures. It contains Summary Tables at the beginning of the Chapters, to facilitate the presentation of the most important concepts, and we shared the slides used for the presentation in forums with all GDG members.

In Mexico we still lack the tools to monitor GUIMIT's implementation by auditing the Allergy centers at the moment. However, we hope that observing the desired effect in our patients using state-of-the-art immunotherapy, SC, SL or VIT, is rewarding and might stimulate us to continue.

Financing and conflicts of interest

GUIMIT was developed as an academic initiative of national experts in AIT, stimulated by both National Colleges of the specialty. However, the Colleges had no direct interference in the content nor contributed financially. They did assign delegates to the GDG. Financial support was received to cover the costs of the face-to-face meetings, the publication and print-outs from (in order of financial contribution): Diemsa-ALK, Inmunotek, Alerquim, Sanfer, Mylan, Senosiain, LAM-laboratorios, Abalat, Pisa de México and Glenmark-Mexico. All members of the guideline's development group declared their conflicts of interest.

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Addendum 1

The GUIMIT Source Data consists of Source Data 1 and Source Data 2 for each chapter. Source Data 1 contains the key clinical questions with the answers, their level of evidence and recommendation, found in the reference guidelines of each chapter. Source Data 2 consists of the key clinical questions and the merged evidence and merged recommendations that result in the proposed answer for Mexico. The white column in the middle includes the suggested response for GUIMIT, which is issued taking into account the evidence and the level of recommendation of the reference guidelines, together with the cost, safety, and possible preferences of patients for a certain action based on experience of the GUIMIT workgroup and in the context of the local reality.

The reader can find these source files by filling in the DOI numbers issued below on the following webpages: https://www.doi.org or in the upper part of https://www.researchgate.net .

Chapter 1.1

Source Data 1: DOI: 10.13140/RG.2.2.27044.30088 (English)
Source Data 2: DOI: 10.13140/RG.2.2.13734.57925

Chapter 1.2

Source Data 1: DOI: 10.13140/RG.2.2.15798.14407
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Chapter 2

Source Data 1 y 2: DOI: 10.13140/RG.2.2.29865.44648

Chapter 3

Source Data 1: does not apply.

Chapter 4.2

Source Data 1: DOI: 10.13140/RG.2.2.30819.17449 (English)
Source Data 2: DOI: 10.13140/RG.2.2.14041.95840 (English)

Chapter 4.3

Source Data 1: DOI: 10.13140/RG.2.2.32916.32640 (English)
Source Data 2: DOI: 10.13140/RG.2.2.29560.88323 (English)

Chapter 5

Source Data 1: DOI: 10.13140/RG.2.2.36481.48480 (English)
Source Data 2: DOI: 10.13140/RG.2.2.13295.48806

Chapter 6

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Chapter 7

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Chapter 8

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Chapter 9

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Chapter 10

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