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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, 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 (link to GUIMIT 2019-online). 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 poly-sensitization 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.

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.*

Secondly, more than 80% of Mexican patients are poly-sensitized,[43] and when a careful clinical 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

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.*

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 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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