

Extrapolating Evidence-Based Medicine of AIT Into Clinical Practice in the United States



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EXECUTIVE SUMMARY

This review sought to critically assess evidence-based medicine (EBM) for debated concepts in US allergy immunotherapy (AIT) practice for respiratory allergies in the context and quality of today's regulatory standards. In addition, EBM for patient-centered AIT issues and the approach to implementation of AIT EBM in future clinical practice were addressed. The EBM for each concept was briefly summarized, and when possible, a practical, concise recommendation was given.

EBM in debated concepts for AIT: Individuals of all ages can have allergic rhinoconjunctivitis (ARC) and may have multiple allergen sensitivities or comorbid atopic conditions (eg, asthma). Therefore, there has been much research into the efficacy and safety of AIT for various patient subgroups. Based on the available evidence, single-allergen AIT can effectively treat sensitivity toward that specific allergen, even in polyallergic patients; however, data are still lacking on the efficacy of multiallergen subcutaneous immunotherapy (SCIT) to treat more than 1 clinically relevant sensitivity and effective dosing for multiallergen SCIT. AIT is recommended as a safe and effective therapy across age groups, although in older patients more data are needed to confirm the efficacy of AIT. Comorbidities that could put older patients at a higher risk of an anaphylactic event following AIT administration should be considered. AIT should not be prescribed in patients with severe or uncontrolled asthma, and patients should be screened before injections for loss of asthma control. Initiation of AIT should not occur during pregnancy, but if a woman on AIT becomes pregnant and is receiving a therapeutic dose, she may remain on treatment.

Proper diagnosis of the appropriate allergen sensitivities is a critical component of AIT practice. Skin prick test or allergen-specific serum IgE should be used for the assessment of allergens for AIT. Skin prick test can be affected by technique, age, medications, skin color, and the concentration of the allergen extracts used; therefore, negative and positive controls should always be used. The use of nasal and conjunctival allergen challenges is not recommended for routine diagnosis, but in specialized centers, these challenges may be conducted in patients with both negative skin prick test result and allergen-specific serum IgE who are highly suspected of having ARC. Telemedicine cannot replace in-person care during diagnosis, although it can be complementary to in-person care by providing convenient and high-quality health care access.

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There is a dose effect with AIT, and for SCIT, the dose that is well tolerated and falls within the probable effective dose range needs to be determined for each individual. Most of the allergen liquid extracts used for SCIT in the United States were “grandfathered in” without evaluation under today’s standards for regulatory approval. There are currently 18 allergen liquid extracts in the United States that have been standardized for potency. In the United States, use of allergen liquid extracts for sublingual immunotherapy (SLIT)-drop administration is not recommended. Effective SLIT-tablet dosing has been established in clinical trials and should be prescribed in accordance with prescribing labels. To date, there have been no biomarkers identified that correlate with the clinical efficacy of AIT, and the decision to stop or maintain treatment should be based on clinical response. If a patient is responding to treatment, at least 3 years of treatment is recommended to achieve a sustained effect.

EBM for patient-centered AIT issues: As with many treatments, patient adherence to AIT remains a challenge. Shared decision making with patients should be an integral part of AIT practice to optimize adherence and outcomes. The use of digital tools and health care apps is recommended to help remind patients of their SCIT appointments or to take their daily SLIT-tablet dose. Patients should be informed that in addition to improving ARC symptoms, AIT can have the added benefit of reducing ARC-related costs and health care utilization.

Evidence-based guidelines or practice parameters addressing both SCIT and SLIT in the treatment of ARC and asthma are essential documents to inform decision making for patients and health care providers. EBM guidelines and recommendations should be followed by prescribers of AIT and modified for regional factors as necessary.

Future directions for implementing EBM for AIT for tomorrow’s allergy specialists in the United States: Allergy Fellows help shape the future of patient care. To encourage implementation of EBM for AIT, Allergy Fellows need education regarding the available EBM. Training programs for allergy/immunology specialists should increase their focus on AIT, including education on evidence-based dosing and hands-on training for the preparation and mixing of SCIT extracts.

Allergy/immunology specialists in the United States prescribing allergy immunotherapy (AIT) have placed a heavy value on practical experience and anecdotal evidence rather than research-based evidence. With the extensive research on AIT conducted in the last few decades, the time has come to better implement evidence-based medicine (EBM) for AIT. The goal of this review was to critically assess EBM for debated concepts in US AIT

practice for respiratory allergies in the context and quality of today’s regulatory standards. Debated topics reviewed were the efficacy and safety of AIT in various subgroups (eg, polyallergic patients, older patients, patients with asthma, and pregnant women), diagnosis topics (eg, skin prick test vs allergen-specific serum IgE, factors affecting skin prick tests, use of nasal or conjunctival allergen challenges, and telemedicine for diagnosis),

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Abbreviations used

ABAI- American Board of Allergy and Immunology
 ACAAI- American College of Allergy, Asthma & Immunology
 AE- adverse event
 AIT- allergy immunotherapy
 Apps- applications
 ARC- allergic rhinoconjunctivitis
 EBM- evidence-based medicine
 FDA- Food and Drug Administration
 HDM- house dust mite
 ID- intradermal
 NAC- nasal allergen challenge
 SCIT- subcutaneous immunotherapy
 SDM- shared decision making
 sIgE- specific IgE
 SLIT- sublingual immunotherapy
 SPT- skin prick test

and dosing topics (eg, optimal dosing for subcutaneous immunotherapy and sublingual immunotherapy tablets, US liquid allergen extract history, duration of treatment, and biomarkers of efficacy). In addition, EBM for patient-centered AIT issues (eg, adherence, use of practice guidelines, and pharmacoeconomics) and the approach to implementation of AIT EBM in future clinical practice were addressed. The EBM for each concept was briefly summarized, and when possible, a practical, concise recommendation was given. © 2022 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2023;11:1100-15)

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INTRODUCTION

Allergy immunotherapy (AIT) for the treatment of allergic rhinoconjunctivitis (ARC) has been used in practice for more than 100 years (Figure 1). Because of this long history, allergy/immunology specialists in the United States prescribing AIT have placed a heavy value on practical experience and anecdotal evidence rather than research-based evidence. With the extensive research on AIT conducted in the last few decades, the time has come to better implement evidence-based medicine (EBM) for AIT. A survey conducted among allergists during a 2021 advisory board of EBM in AIT indicated that allergy/immunology specialists in the United States are ready to revisit current practice and shift education and training toward EBM for AIT (Moisés Calderon, MD, personal communication, 2021). The results of the survey spurred the development of this review, with an objective of providing EBM and recommendations for AIT in the treatment of ARC from a US perspective for implementation into clinical practice. The goal of this review was to critically assess EBM for debated concepts in US AIT practice for respiratory allergies in the context and quality of today's regulatory standards. In addition, we address key issues in EBM for patient-

centered AIT issues and the approach to implementation of AIT EBM in future clinical practice.

EBM IN DEBATED CONCEPTS FOR AIT**Can polyallergic patients be effectively treated with AIT? (Rémi Gagnon)**

Polyallergic patients are those who have been shown by positive skin prick test (SPT) results and/or positive serum-specific IgE (sIgE) to be sensitized to multiple allergen extracts and with clinically relevant symptoms that correspond to sensitization.¹ Studies have shown that for a specific allergen extract, polysensitized patients may receive similar benefit as mono-sensitized patients from AIT to a single-allergen extract.²⁻⁷ AIT practice for polyallergic patients differs considerably between the United States and Europe. In the United States, it is common practice to include all allergen extracts in a subcutaneous immunotherapy (SCIT) treatment for which the patient has clinical sensitivity,⁸ whereas European practice is to primarily treat with only 1 or 2 of the most clinically important allergen extracts.^{1,9,10} Four older randomized, double-blind, placebo-controlled studies indicate the effectiveness of multiallergen extracts for asthma^{11,12} or for reducing the symptoms of a single clinically relevant sensitivity.¹²⁻¹⁴ The ability of a multiallergen SCIT extract to reduce symptoms to more than 1 clinically relevant sensitivity has not been adequately assessed in placebo-controlled trials. The most recent US SCIT study with multi-allergen extracts, conducted in 1997, did not meet its primary end point.¹⁵

In contrast to SCIT, sublingual immunotherapy (SLIT) treatment is often with monoallergen SLIT-tablets. Simultaneous treatment with 2 SLIT-tablets appears to be safe after 2 weeks of taking the tablets separately (morning and evening).¹⁶ The clinical efficacy of combined SLIT-tablets with more than 1 allergen is yet to be determined.

Recommendation. Single-allergen AIT can effectively and safely treat sensitivity toward that specific allergen, even in polyallergic patients. Dosing of multiallergen SCIT is empirical because dose-finding trials are inadequate. Data on the efficacy of multiallergen AIT for treating more than 1 clinically relevant sensitivity are also lacking.

What factors affect interpretation of SPT results? (Hunter Hoover, Greg Plunkett, and Lawrence DuBuske)

Several skin testing methods are used for diagnosis in the United States. The performance of SPT and intradermal (ID) tests is reviewed in the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology (ACAAI) practice parameters for allergy diagnostic testing, with SPT being the preferred method over a single-dose ID.¹⁷ Positive ID test results after a negative SPT result have failed to correlate with natural exposure to allergens, sIgE, or basophil histamine release. Some clinicians formulate SCIT using a series of ID titrations that can normalize the strength of variable-potency extracts.^{18,19}

There are multiple factors that must be considered when diagnosing allergy by SPT. For example, the extract potency and the device used for SPT can cause trauma and deliver various amounts of liquid, which affects wheal size.²⁰ Interpretation of

positivity to the individual extracts can vary. Most clinical trials define a positive as a wheal 3 to 5 mm greater than that achieved with the negative control. Alternatively, some clinical practices define a positive as a wheal equal to or greater than that achieved with the positive histamine control. Therefore, depending on the device, weaker allergens might appear negative using a 6 mg/mL histamine control but positive for a 1 mg/mL histamine control.^{21,22}

Age (ie, infants or the elderly) or medications such as antihistamines can reduce skin reactions. The site of testing can affect wheal size, with the back being more reactive than the forearm.^{8,17,23} In addition, skin color can affect some skin test results.¹⁷ The histamine positive control identifies the importance of these factors. A negative 50% glycerin control is used to identify patients experiencing dermatographia.

Allergens used in the United States for diagnostics are formulated the same as the bulk 50% glycerin SCIT extracts. For nonstandardized extracts, 1:10 and 1:20 weight/volume is the predominant strength. The ability of these extracts to elicit positive SPT wheals varies because of the wide range of potency of extracts, inherent biological properties, and lot-to-lot variability.²³⁻²⁵ Extracts in the United States are not dialyzed and can therefore have interfering substances that can cause false-positive reactions, such as histamine in venoms or irritating substances in molds.^{26,27} Few studies have attempted to optimize the concentration of SPT extracts.²⁵ European diagnostic extracts are formulated specifically for SPT to minimize false positives and negatives by dialysis and adjusting concentrations. Comparisons have been made between European Union and US extracts by major allergen levels.^{8,28,29} These European Union extracts are manufactured to give a wheal equivalent to that achieved with a 6-mg/mL histamine extract using a lancet. As the concentration increases, more positive results that correlate with provocation testing are obtained. At a high concentration, false-positive results occur. US extracts with higher concentrations might give false positives; however, it has been shown that asymptomatic patients with positive birch test results can develop birch allergy later in life.³⁰ Some standardized extracts are formulated on the basis of ID titration results and can be either more dilute than the nonstandardized species (eg, some house dust mite [HDM] or grass extracts) or more concentrated (eg, cat extracts). Therefore, determining the optimum concentrations for SPT depends on the goals of the clinician.

Recommendation. Allergen extracts used in the United States are not fully optimized to diagnose allergy to the highest degree of sensitivity and specificity. Rather, they are extracted at the most practical highest concentration possible, which may affect SPT results. Negative and positive controls should always be used to mitigate confounding reactivity factors. We recommend international standardization of SPT methods.

Is serum sIgE or SPT better for determining allergen sensitivity? (Lawrence DuBuske)

Allergen-specific serum IgE (sIgE) assessments reflect antibodies that have been made recently (half-life is ~48 hours) that rise with seasonal and casual exposure to allergens.³¹ Elevated levels of allergen-specific sIgE are evidence of ongoing T_H2-driven immune responses triggered by a specific allergen, regardless of the presence of symptoms. Allergen-specific sIgE results are quantitative, providing a potential advantage over SPT

results, which are only qualitative unless measured in millimeter and compared with a negative control.³² SPT identifies the presence of allergen-specific IgE bound to mast cells and is often more sensitive than sIgE for identifying previous production of allergen-specific IgE.³³ The increased diagnostic sensitivity of SPT must be balanced against the risk of lower specificity of clinically meaningful allergy. Positive SPT results can therefore occur without current clinical allergy. This can adversely impact selection of patients for AIT. In a trial of the 5-grass SLIT-tablet, in subjects with positive grass SPT results but negative grass allergen-specific sIgE, there was no response to grass SLIT-tablet therapy.³⁴ Thus, to detect an immune modulation of T_H2 responses toward a given allergen, it is necessary to show that there is current production of allergen-specific sIgE toward that allergen and it may result in clinical allergy. Just like SPT extracts, allergen-specific sIgE assessments vary from analyte to analyte across different manufacturers' systems, largely because of differences in potency and the allergens used for testing.³⁵ Paper disc-based allergens have been supplanted by cellulose foam; moving from 2 to 3 dimensions as a means of exposing allergens enhances sensitivity for interaction with allergen-specific sIgE. Further enhancements have included liquid-phase interactions using paramagnetic particles, and improvement in tracers, which have transitioned from enzyme-based light tracers, to fluorescent tracers, to chemiluminescent tracers in various systems, resulting in enhanced sensitivity to detect allergen-specific IgE. Although allergen-specific sIgE testing may be more expensive on an analyte-by-analyte basis than SPT, insurance contractual relationships may mitigate the difference in costs.

Multiplex arrays, such as the Immuno Solid Phase Allergen Chip, have been used in Europe to detect allergen-specific sIgE to more than 100 allergens using only a very small amount of serum.³⁶ These multiplex arrays have the ability to detect specific sIgE directed against selected components of allergens, profilins, lipocalins, and other panallergens.³⁵ This may allow better detection of the exact cause of sensitization in situations in which cross-reactivity may give an impression of a sensitization, but in actuality is due to a panallergen-specific IgE.³⁷ Such situations can lead to unnecessary allergens being included in AIT.

Recommendation. A clinical history of allergy must be confirmed by allergen-specific sIgE or SPT in the assessment of appropriate allergen(s) for inclusion in AIT.

How has the definition of quality for allergen extracts evolved over time? (Greg Plunkett)

The first commercial production of allergen extracts in the United States began in the 1920s.³⁸⁻⁴⁵ Regulatory authority for allergen extracts came under the US Food and Drug Administration (FDA) in 1972. Manufacturers then obtained FDA facility licenses and biological licenses for all the extracts they were producing. At that time there was no process for standardization among the extracts. Because there were more than 1500 liquid extracts produced by 21 companies, in 1974 the FDA appointed a panel of leading allergists to review the existing literature for evidence of efficacy and safety and proper branding of these extracts (Figure 1). On completion in 1981, the panel reported on 965 extracts for diagnosis, finding 26% safe and effective, and of the 603 for therapy, finding only 1% safe and effective. Of the remainder, 48% of those for diagnosis and 65% of those for therapy were thought to have a favorable risk/benefit and could

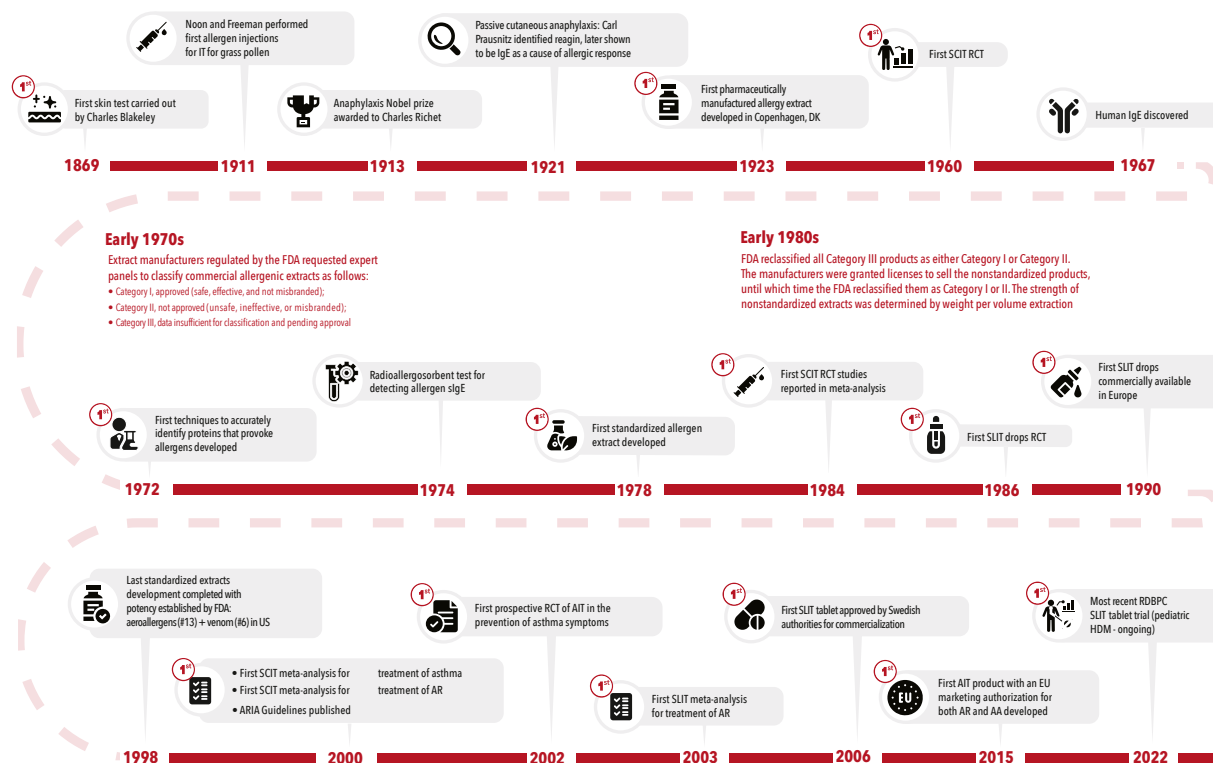


FIGURE 1. Timeline of AIT history. AA, allergic asthma; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; EU, European Union; IT, immunotherapy; RCT, randomized controlled trial; RDBPC, randomized, double-blind, placebo-controlled.

remain on the market until further evidence could justify approval. The remainder of the extracts were removed from the market. Two additional rounds of panel reviews were conducted, the second being from 2003 to 2011 when the FDA did a comprehensive internal review of the more than 1200 allergen extracts present in the existing manufacturers' licenses. Fifteen products were removed, most notably HDM extracts because of variability and nondefined source material. The panel found 480 extracts in which diagnosis and treatment was addressed in the literature, 207 extracts for which only diagnosis was addressed, 565 extracts with minimal or no supporting literature, and 17 with potential safety concerns. The final report was circulated for public comment⁴³; however, no follow-up has been published and these extracts have not undergone formal regulatory review of submitted efficacy and safety data. US allergen manufacturers continue to produce several hundred extracts for AIT from pollens, foods, fungi, animal epithelia, insects, and environmental sources.^{23,46} Efficacy and safety of individual compounding of allergen liquid extracts have not been reviewed and are not regulated by the FDA.

In separate actions, between 1981 and 1998, the FDA created 19 standardized liquid extracts defined by measures of potency that vary according to extract, such as micrograms for venoms and short ragweed, FDA units for cat, bioequivalent allergy units for cat and grass, and allergy unit for HDM (Figure 1). The FDA reviews and releases for sale each lot of the standardized extracts. The standardized cat pelt extract is no longer available.

Liquid extracts are produced in FDA-licensed facilities using a "Coca's solution."⁴⁷ Fifty percent glycerin was found to improve the stability of the allergen extracts²³; therefore, "Glycerin Coca's" extracts are used extensively for AIT and exclusively for skin prick testing. After preparation of the extract and sterile filtration, the extract is tested for sterility and animal safety, and usually a total protein test is performed (protein nitrogen unit). Documentation is verified according to FDA compliance guidelines of current Good Manufacturing Practices.^{38,39,41,42,45,48} Nonstandard extracts are defined by weight/volume or protein nitrogen unit unitage.

Beginning in the early 2000s, newly discovered allergens and AIT formulations were required to undergo the stringent FDA approval process that includes data from phase 1 to 3 studies. There have been some guidance documents for studies and licensure,⁴⁹ as well as requirements that were developed for approval of the grass, HDM, and ragweed SLIT-tablets. These approvals demonstrate the quality control, labeling, and clinical safety and efficacy studies needed for new allergen biologics. No other new extracts for AIT have entered the market other than the SLIT-tablets since these latest requirements have been put into place.

Recommendation. Oversight and regulation by the FDA ensure allergen extracts are manufactured under strict rules of cGMP and Good Laboratory Practice. Among the hundreds of liquid extracts on the market, 19 have been standardized for

TABLE I. Allergen content and probable effective dose ranges of standardized liquid aeroallergen extracts available in the United States

Allergen	Major allergen	Major allergen content, range ^{52,53,*}	Expressed concentration	Practice Parameter probable effective dose range ⁸	Amount of concentrate to add to 5-mL vial for 0.5 mL maintenance dose (concentrate strength)
Orchard <i>Dactylis glomerata</i>	Dac g 5	294-2414 µg/mL	100,000 BAU/mL	1000-4000 BAU	0.1-0.4 mL (100,000 BAU/mL)
Meadow Fescue <i>Festuca pratensis</i>	Fes p 5	75-204 µg/mL	100,000 BAU/mL	1000-4000 BAU	0.1-0.4 mL (100,000 BAU/mL)
Rye, Perennial <i>Lolium perenne</i>	Lol p 5	157-526 µg/mL	100,000 BAU/mL	1000-4000 BAU	0.1-0.4 mL (100,000 BAU/mL)
June (Kentucky Blue) <i>Poa pratensis</i>	Poa p 5	190-330 µg/mL	100,000 BAU/mL	1000-4000 BAU	0.1-0.4 mL (100,000 BAU/mL)
Timothy <i>Phleum pratense</i>	Phl p 5	260-1336 µg/mL	100,000 BAU/mL	1000-4000 BAU	0.1-0.4 mL (100,000 BAU/mL)
Bermuda <i>Cynodon dactylon</i>	Cyn d 1	20-449 µg/mL	10,000 BAU/mL	300-1500 BAU	0.3-1.5 mL (10,000 BAU/mL)
Redtop <i>Agrostis alba</i>	Agr a 5	NA	100,000 BAU/mL	1000-4000 BAU	0.1-0.4 mL (100,000 BAU/mL)
Sweet Vernal <i>Anthoxanthum odoratum</i>	Ant o 5	NA	100,000 BAU/mL	1000-4000 BAU	0.1-0.4 mL (100,000 BAU/mL)
Short ragweed	Amb a 1	335-763 µg/mL	Weight/volume	1000-4000 BAU	0.24-0.48 mL (250 AgE U/mL)
Cat hair <i>Felis domesticus</i>	Fel d 1	24-79 µg/mL	10,000 BAU/mL	1000-4000 BAU	1-4 mL (10,000 BAU/mL)
HDM <i>Dermatophagoides pteronyssinus</i>	Der p 1 Der p 2	38-98 µg/mL 28-104 µg/mL	10,000; 30,000 AU/mL	500-2000 AU	0.5-2.0 mL (10,000 AU/mL)
HDM <i>Dermatophagoides farinae</i>	Der f 1 Der f 2	21-140 µg/mL 51-140 µg/mL	10,000; 30,000 AU/mL	500-2000 AU	0.5-2.0 mL (10,000 AU/mL)

AgE, Antigen E; AU, allergy unit; BAU, bioequivalent allergy unit; NA, not available.

*Values represent allergen content in US FDA reference extracts and allergen extracts manufactured in the United States.

potency by an FDA standard and 18 are currently available. Other liquid extracts were “grandfathered in” for approved use of allergy treatment knowing that they could not meet today’s regulatory approval standard. International harmonization and standard methodologies could enhance the progress of such products going forward. SLIT-tablets are a treatment option that have gained full regulatory approval with completed phase 1 to 3 clinical development programs.

What is the importance of dosing of AIT with aeroallergens? (Hendrik Nolte)

Aeroallergen AIT efficacy and safety is dose- and time-dependent.^{50,51} Too low a dose of AIT is well tolerated but ineffective, and too high a dose is effective but is associated with unacceptable levels of adverse events (AEs).⁸ SCIT treatment is tailored on the basis of individual patient tolerance, typically falling within a range of maintenance target doses (Table I).^{8,52,53} SLIT-tablets (timothy grass, 5 grass mix, HDM, ragweed, Japanese cedar pollen, birch-tree pollen) are approved in various countries on the basis of results from multiple dose-ranging trials. The allergen content and approved daily doses of SLIT-tablets available in the United States are presented in Table II. In an online survey of ACAAI members conducted in 2018, which unfortunately only had a 10.8% response, 31% of the responders reported that they had prescribed off-label SLIT-drops.⁵⁴ In another survey, 31% of US otolaryngologists reported using SLIT-drops.⁵⁵ SLIT-drop dosing with US extracts is empirical

because dose-finding studies have only been conducted for HDM and ragweed extracts.⁵⁶⁻⁵⁸ In the 2018 survey of US allergists, the cumulative monthly SLIT-drop doses used by 77% of the respondents were less than 20 times their customary SCIT dose.⁵⁴ Because dose-response studies with SLIT-tablets have shown effective cumulative monthly doses to be at least 22.5 times the maintenance SCIT dose, this suggests that many of these allergists are prescribing less-than-optimal SLIT-drop doses.

The principle of a dose response for AIT has been established on the basis of results from 13 single-allergen SCIT studies evaluating grass, tree, ragweed, HDM, cat, and dog extracts.⁵⁰ Ten of these studies observed dose-related efficacy.⁵⁰ Several dosing trials have demonstrated a less effective or ineffective dose.⁵³ Based on dose-response studies, the American Academy of Allergy, Asthma & Immunology/ACAAI practice parameter provides probable effective SCIT dose ranges.⁸ However, the studies used to establish the probable effective doses are heterogeneous with respect to extract characterization and standardization, study design, and efficacy outcomes. As such, a European task force could not establish a universal effective target dose for SCIT.⁵⁰

The selection of the SLIT-tablet doses for adults and children is based on the safety and efficacy results from phase 1 dose-escalation trials and pivotal phase 2 and 3 trials in separate adult and pediatric trials using grass, ragweed, birch, cedar, and HDM SLIT-tablets.^{34,51,59-85} Clinical trials for all US-approved

TABLE II. Allergen content and approved daily doses of SLIT-tablets available in the United States

SLIT-tablet	Major allergen	Major allergen content*	Daily dose
HDM	1:1:1:1 Der p 1, Der p 2, Der f 1, Der f 2	30 µg	12 SQ-HDM
Ragweed	Amb a 1	12 µg	12 Amb a 1 U
Timothy grass	Phl p 5	15 µg	2800 BAU
5-grass	Phl p 5	25 µg	300 IR ^{†,‡}

BAU, Bioequivalent allergy unit; IR, index of reactivity.

*The accuracy of the measurement of major allergen content is method-dependent and may vary between assays.

†Daily dose after 2 d of up dosing with 100 IR dose in children ages 10-17 y.

‡300 IR is equivalent to approximately 9000 BAU.

SLIT-tablets have shown a less effective or ineffective dose in addition to the highest effective doses.⁵³ SLIT-tablets have been shown to have more consistent major allergen content than SCIT extract.⁸⁶ Although SCIT requires up dosing to reach a safe and effective maintenance dose, SLIT-tablet treatment may be safely initiated at the maintenance dose.^{8,87}

Treatment effects for SLIT-tablets may be seen as early as after 4 to 8 weeks of treatment in challenge studies and after 8 to 14 weeks in field-based trials.^{64,79,88,89} The treatment effect reaches a plateau after 16 to 26 weeks of treatment; longer treatment periods do not increase overall magnitude of efficacy.^{51,63,90} SCIT and grass SLIT-tablet year-round dosing for at least 3 years leads to sustained and disease-modifying effects for up to 2 years posttreatment.⁹⁰⁻⁹³ A statistically significant treatment effect at 1 year posttreatment has been shown with preseasonal and coseasonal administration of a 5-grass SLIT-tablet, but the results did not meet the FDA criterion of a sustained effect.⁹⁴ Sustained efficacy with less than 3 years of treatment has not been fully evaluated, but 2 years appears insufficient for a sustained effect.⁹⁵

Children and adults are treated with the same AIT dose because dosing is not weight-based. There have been no dose-finding SCIT trials with US extracts in children. The safety and efficacy of grass, ragweed, HDM, and cedar SLIT-tablets using adult doses have been confirmed in phase 3 pediatric trials.^{60,61,67,75,78,81}

Recommendation. Dosing of SCIT should be determined for each individual by up dosing to reach a well-tolerated maintenance dose that falls within the probable effective dose. SLIT-tablet dosing should be in accordance with prescribing labels. Dosing of extracts for SLIT-drops is not approved or validated in the United States and is not recommended. Three years of AIT treatment is recommended to achieve a sustained effect.

Can telemedicine be adequate for allergic diagnosis? (Justin Greiwe)

Before the severe acute respiratory syndrome coronavirus 2 novel coronavirus (coronavirus disease 2019) pandemic, the use of telemedicine in day-to-day allergy practices was extremely limited.^{96,97} Since then, telemedicine services have drastically increased, leading to extensive policy changes at both the state and national levels.⁹⁸ Synchronous “real-time” patient visits comprise most virtual encounters,⁹⁹ whereas asynchronous “store-and-forward” applications such as electronic consultations (eConsults) are gaining popularity given their ability to improve

access to specialty care.¹⁰⁰⁻¹⁰⁵ There is emerging evidence that the use of telemedicine can improve overall health outcomes, with care comparable to that of in-person visits.¹⁰⁶ This is especially true for chronic diseases, including asthma.¹⁰⁷⁻¹¹⁰ In addition to improved care, both patients and physicians have indicated a high level of satisfaction with their virtual visits and expressed positive attitudes toward the adoption of telemedicine.¹¹¹⁻¹¹⁵ The diagnosis of ARC through history, allergen-specific sIgE testing, and initiation of treatment using over-the-counter/prescription medications is similar between telemedicine and office-based practice, although nasal examination using an otoscope is not feasible virtually. If AIT is being considered, in-office spirometry and lung auscultation should be completed because poorly controlled asthma is widely considered the most important risk factor for fatal reactions on AIT.²¹ The safety of monitoring the first administration of SLIT-tablets via telemedicine still needs to be evaluated. Real-time video consultations have the added benefit of providing valuable information about the patient’s home environment, which could influence treatment recommendations.¹¹⁶ Although telehealth may increase access by making care more convenient, skeptics of this technology point to data suggesting that direct-to-consumer telehealth may increase utilization and health care spending.¹¹⁷ There is also data that patients who relied on live video visits for enhanced access were less connected to their primary care provider, leading to fragmented care and the overprescribing of antibiotics.¹¹⁸⁻¹²⁰ It is important to note that barriers to telemedicine access still exist, especially in rural, minority, and technologically underserved communities.¹²¹⁻¹²³

Recommendation. Since the start of the coronavirus disease 2019 pandemic, telemedicine has quickly become an integral part of an increasingly technologically focused health care system. Although telemedicine cannot replace in-person care, we recommend the use of telemedicine as a complement to in-person care to provide patients with high-quality, reliable, and convenient access to allergists. Telemedicine services can also be considered as a platform for patient education, care coordination, and medication monitoring.

Can nasal or conjunctival provocation tests be used for allergic diagnosis? (Jonathan Corren)

Nasal and conjunctival allergen challenges have been shown to be useful for studying the pathogenesis of ARC,¹²⁴ and serve as important outcome measures for assessing the efficacy of ARC treatments.⁹⁵ However, the use of provocation testing in clinical practice is not well-defined and varies worldwide. Nasal allergen challenge (NAC) has been officially recommended in at least 1 country¹²⁵ and in some areas is used ad hoc¹²⁶ as an adjunctive test in patients with perennial ARC to confirm the relationship between an allergen and symptoms before initiating AIT. However, there have been no controlled trials demonstrating that selection of patients for AIT based on NAC results improves the efficacy of AIT. NAC has also been used to diagnose local ARC in patients who have characteristic symptoms of perennial or seasonal ARC but who have negative allergy SPT result and serum tests for specific IgE.¹²⁷ Patients with local ARC frequently have similar mucosal histologic and immunologic findings to those of patients with ARC and positive systemic markers of allergy.¹²⁶ Patients with local ARC have been shown to respond to AIT directed at allergens detected by NAC.¹²⁶

TABLE III. Summary of sustained treatment or disease-modifying effects with SLIT-tablets recognized by regulatory authorities*

SLIT-tablet	Recognized sustained effect	Duration of sustained effect after stopping treatment	Recognized disease-modifying effect
Timothy grass	Yes†	2 grass pollen seasons	Yes†
5-grass	Yes‡	1 grass pollen season	No
Ragweed	No	—	No
Cedar	No	—	No
Tree	No	—	No
HDM			
300 IR	Yes§	1 y	No
12 SQ-HDM	No	—	No

IR, Index of reactivity.

A disease-modifying effect is defined as a sustained significant and clinically relevant efficacy in posttreatment years.¹³²

*Recognized effect by regulatory authorities in at least 1 country. Sustained and/or disease-modifying effects are not recognized in all countries.

†After 3 y of continuous daily treatment.

‡After 3 y of preseasonal and coseasonal treatment.

§After 1 y of continuous daily treatment.

Recommendation. NAC and conjunctival allergen challenges remain important tests for clinical and translational research in ARC. Although NAC holds promise as an adjunctive test in patients with putative ARC and may assist in confirming ARC in selected cases before starting AIT, we do not recommend its routine use in clinical practice. However, specialized centers experienced with NAC may consider performing this test in patients highly suspected of having ARC with negative skin and serum IgE test results.

What is the long-term efficacy of AIT? (Michael Blaiss)

AIT can lead to persistent improvement in ARC symptom relief for years after treatment discontinuation, thus demonstrating disease-modifying effects.^{90-92,128-130} At least 3 years of treatment appears necessary for a sustained effect after AIT discontinuation.¹³¹ The US prescribing information for the timothy grass SLIT-tablet specifically states a sustained effect for 1 grass pollen season after 3 years of continuous treatment (Table III). No other SLIT-tablet available in North America is recognized by the FDA as having a sustained effect, although sustained or disease-modifying effects of SLIT-tablets have been recognized by regulatory authorities in other countries (Table III).¹³² Long-term effects of AIT in both seasonal and perennial ARC include reductions in nasal symptoms and rescue medication use, and overall improvement in quality of life.¹³³ These changes have been documented in all age groups, including the elderly.¹³⁴ In the management of asthma, a review of 88 studies demonstrated that SCIT has a beneficial effect on asthma control when added to regular pharmacologic treatment, as well as improvement in airway hyperreactivity.¹³⁵ In addition, there are studies showing a steroid-sparing effect with SCIT¹³⁶ and more convincing data with the HDM SLIT-tablet.^{137,138} A few studies have demonstrated that long-term pollen SCIT and SLIT-tablets and long-term HDM SLIT-drops may prevent the development of asthma in children with ARC.^{90,92,139} There are limited data that AIT can reduce the likelihood of new allergen sensitizations in monosensitized patients.^{140,141}

Recommendation. We recommend at least 3 years of AIT treatment to achieve sustained clinical improvement of ARC symptoms, reduced ARC rescue medication, and enhancement of health-related quality of life. In patients with allergic asthma,

AIT should be considered as an adjunct treatment to pharmacotherapy. More studies are needed before firm recommendations can be made concerning the initiation of AIT for the prevention of the development of allergic asthma or new sensitizations.

What are the biomarkers for AIT efficacy? (Jonathan Corren)

Various biomarkers including skin tests, antibody measurements, functional assays, and cell phenotyping have been evaluated for their potential to assist in the selection and monitoring of patients undergoing AIT. Specific IgE is routinely measured by clinicians for the diagnosis of allergy before starting AIT. However, baseline levels of specific IgE and specific IgE/total IgE ratio have not been shown to be consistently predictive of clinical responsiveness to AIT.^{142,143} Allergy skin test responses and serum antibody levels (eg, specific IgE, specific IgG₄, and specific IgE/IgG₄ ratio) assessed during AIT as markers of efficacy have demonstrated that although these test results may be altered, the changes do not correlate with clinical improvement.^{144,145}

Basophil activation assays, commonly assessed by upregulation of surface markers CD63 and CD203C, have not been shown to correlate with improvements in rhinitis.¹⁴⁶ However, a more recently developed functional assessment of allergen-IgE complexes, which alter B-cell antigen presentation and T_H2 activation, can be measured using an IgE-facilitated allergen binding assay; assay results during treatment have been shown to correlate significantly with changes in clinical symptoms.¹³⁰ Currently, testing for IgE-facilitated allergen binding assay is used only in research settings and is not available commercially; therefore, its use in clinical settings has not been assessed.

Measurement of blood cell phenotypes, including IL-10—producing innate lymphoid cells, regulatory dendritic cells, T_H cells, T-follicular helper cells, and regulatory T and regulatory B cells, have demonstrated significant changes in these cell populations during AIT, which correlate with clinical response.¹⁴⁷ However, the complexity and cost of these assays relegate their use to research studies only.

Recommendation. Although allergy testing and/or measurement of specific IgE are critical in establishing allergen sensitivities before starting AIT, none of these tests or other serum antibody levels have been shown to correlate with clinical

changes during AIT. Other tests, including assessments of basophil activation, assessment of IgE-facilitated allergen binding assay, or cellular phenotypes, are not clinically available and are largely limited to research settings. The decision whether to continue or stop AIT after an adequate trial should be based on clinical response, not biomarkers.

At what age limit is AIT no longer appropriate? (Lawrence DuBuske)

Older ARC treatment guidelines indicated that AIT was not recommended for elderly patients because of the potentially enhanced risk of severe AEs associated with comorbidities.^{148,149} Studies conducted for FDA consideration for both SCIT and SLIT-tablets excluded subjects older than 65 years, or even 50 years.^{73,77,150} In particular, safety concerns included the ability of older patients to survive anaphylaxis due to possible underlying cardiovascular disease and the likelihood that elderly patients were more likely to take medications contraindicated for AIT, including beta-blockers.^{151,152} More recent US practice parameters for AIT and for the management of ARC indicate that there is no absolute upper age limit for the use of AIT,^{8,153} although the 2020 US ARC management practice parameters noted that the evidence for efficacy or safety of SCIT in older patients was insufficient.¹⁵⁴ Although older age is no longer considered a contraindication for AIT, experts maintain that a risk versus harm assessment needs to be considered before initiating AIT in older patients because comorbidities that could impact the safety of AIT may be more common in this population.^{155,156} The 2019 ARIA Care pathways for AIT further acknowledges that a better understanding of the role of AIT in older patients is needed because immunologic and allergic characteristics differ between older allergic patients and young and middle-aged adults.¹⁵⁶

A few randomized controlled trials evaluating the safety and efficacy of SCIT or SLIT-drops have been conducted specifically in adults older than 60 or 65 years.¹⁵⁷⁻¹⁶⁰ In all of these trials, AIT treatment significantly improved symptoms and reduced rescue medication use versus placebo or from baseline and was well tolerated.

Recommendation. Views on the use of AIT in older patients have evolved in the last 20 years, with current consensus indicating that there is no upper age limit for initiating AIT. However, caution should be used to evaluate the risk/harm ratio in patients who have comorbid conditions that might put them at a higher risk for an anaphylactic event following AIT administration. For these patients, SLIT is a better option due to the improved safety margin. More data are needed to confirm the efficacy of AIT in older patients.

Does efficacy or safety of AIT differ between children, adolescents, and adults? (Susan Wasserman)

Clinical experience does not indicate a differential treatment effect (including safety and efficacy) of AIT by age. Subpopulation analyses from large phase 3 SLIT-tablet trials conducted in children and adults support the clinical experience of a balanced treatment effect across age groups.^{67,69} Meta-analyses of AIT also suggest similar treatment effects in children and adults.^{161,162} ARC treatment guidelines and product labels do not recommend treating children (>5 years) and adults differently with

AIT. Regulatory agencies do not currently accept clinical efficacy data conducted in adults to be extrapolated to children.

Studies comparing the safety profile of SLIT-tablets in adults, adolescents, and children have found no marked differences in the incidence or severity of AEs. The most common AEs are mild-to-moderate local site reactions (oral pruritus, throat irritation, ear pruritus, mouth swelling).^{60,69,70} The randomized, double-blind, placebo-controlled trial of ragweed SLIT-tablet in children found that although the AE profile was similar, discontinuations due to AEs were lower in children aged 5 to 11 years than in adolescents aged 12 to 17 years.⁷⁵

Recommendation. AIT is recommended as a safe and effective therapy across all age groups. Patients and caregivers should be counseled that AEs are generally local in nature. Some evidence suggests that young children may tolerate treatment more readily than adolescents or adults, with fewer discontinuations due to AE. This observation needs to be further confirmed in adequately powered clinical trials.

What is the safety of AIT in patients with asthma? (David Bernstein and Leonard Bacharier)

In North America, the incidence for fatal anaphylaxis between 2008 and 2018 was estimated at 1 in 7.2 million SCIT injections and for near-fatal anaphylaxis 1 in 160,000 injection visits.¹⁶³ This applies to patients receiving aqueous aeroallergen extracts. Uncontrolled and severe asthma was the most consistent feature associated with 62% of fatal events.¹⁶⁴ Based on a survey of North American allergists, it was found that 50% of cases of nonfatal anaphylaxis to SCIT occur in patients with severe asthma (as defined by the European Respiratory Society/American Thoracic Society).^{163,165} Clinical practices that choose not to initiate SCIT in patients with uncontrolled asthma are less likely to experience SCIT-related anaphylaxis.¹⁶³

Most patients (60%-85%) receiving SLIT-drops or SLIT-tablets experience adverse reactions. Most of these reactions are local side effects such as mild itching and swelling of the lips and floor of the mouth. Anaphylaxis with SLIT is rare, although 11 cases of nonfatal anaphylaxis related to SLIT have been reported as of 2012.¹⁶⁶ In a large placebo-controlled trial of an HDM SLIT-tablet in patients with uncontrolled asthma, no systemic reactions were reported.¹³⁸ It remains uncertain whether SLIT administered for asthma outside of the clinical trial environment and in a real-world setting is associated with a comparable favorable safety profile as that seen in carefully selected, monitored, and motivated patients participating in clinical trials.

Recommendation. AIT should not be prescribed in patients with severe or uncontrolled asthma. Pre-SCIT injection screening of all patients with asthma for loss of asthma control is recommended and has been widely adapted, although this strategy is yet to be validated.⁸ It is recommended that the first dose of a SLIT-tablet be taken in a doctor's office followed by a 30+-minute observation period, in accordance with product labeling. Any significant AE that occurs in the real-world clinical setting should be reported.¹⁶⁷

Does pregnancy have an impact on determining AIT eligibility? (Jennifer Namazy)

Allergic rhinitis affects up to one-third of women of child-bearing age^{168,169} and may worsen, improve, or remain unchanged during pregnancy. Unlike asthma, uncontrolled ARC is

not associated with adverse maternal or fetal outcomes.¹⁷⁰ However, uncontrolled ARC can be associated with increased anxiety symptoms,¹⁷¹ poor sleep, and worsening of asthma symptoms.^{172,173} Despite being a common treatment modality for more than 100 years, AIT has not been prospectively studied in pregnancy. This may be due to ethical reasons and the risk of AIT's adverse reactions. Two studies found no increased risk of complications such as prematurity, preeclampsia, or congenital malformations.^{174,175} In 1 of the studies, of the 3 patients who developed a systemic allergic reaction in response to SCIT, none were found to have perinatal complications.¹⁷⁵ Information regarding the safety of SLIT during pregnancy is also lacking. A prospective study in women on SLIT-drops during pregnancy reported no increase in perinatal death, prematurity, preeclampsia, or congenital malformations compared with controls.¹⁷⁶ One retrospective study evaluating safety of SCIT during pregnancy had a very small proportion who started during pregnancy.¹⁷⁵ Although the authors did not report maternal or fetal complications in those women starting SCIT during pregnancy, further studies are needed.

Recommendation. Allergy organizations in the United States and Europe currently discourage the initiation of AIT during pregnancy until more data are available.^{8,177} If a patient is on AIT before becoming pregnant, continuing treatment through pregnancy appears to be safe. If a woman becomes pregnant during the build-up phase of SCIT and the dose is therapeutic, it is recommended that she remain at that dose through the course of pregnancy. If the SCIT dose is not therapeutic, then a shared decision-making (SDM) conversation needs to take place with the patient to discuss continuing based on current symptoms or stopping therapy and restarting therapy postpregnancy.

EBM FOR PATIENT-CENTERED AIT ISSUES

What is the role of SDM and patient preference in AIT? (Priya Bansal and Tonya Winders)

SDM is an integral part of the allergist and patient interaction for determining need and feasibility of AIT for both children and adults.¹⁷⁸ SDM ensures all treatment options have been fully presented without provider bias, allowing for the patient to align their values and preferences when choosing the best option. During an SDM discussion, the allergist weighs the diagnosis, current treatment protocols, and AIT options, which includes a discussion of the benefits, risks, and costs of SLIT-tablets and SCIT. The patient discusses their needs, lifestyle concerns, such as their ability to commit to weekly office visits for SCIT, or their ability to be compliant with a daily SLIT-tablet, previous medical experiences and treatments, and concerns regarding their current medication protocol. SDM increases adherence, outcomes, and satisfaction.¹⁷⁸

Patient preference should be a key component of AIT SDM discussions. A 2016 study conducted in Germany found that the 3 most important factors in patients considering AIT included the number and duration of physician visits, the frequency of life-threatening anaphylactic shocks, and local side effects.¹⁷⁹ Preferences were for fewer visits with shorter duration, lower risk of anaphylactic shocks, and rash/swelling on upper arm preferred over itching/swelling under tongue.

Ideally, tools and patient decision aids should be incorporated into the SDM discussion and are currently available with guides

such as those designed by the ACAAI and the Allergy & Asthma Network.¹⁸⁰ Barriers to SDM include difficulty accessing decision aids quickly in the clinic and the time needed for this information exchange. However, these can be worked on via a team approach with the staff to assist with time management and increase efficiency. These tools and aids can also be used to further solidify trust within the doctor-patient relationship and lead to enhanced compliance and improved outcomes.

Recommendation. SDM should be an integral part of discussing AIT with patients to optimize adherence and outcomes. The allergist must understand the concerns and barriers of the patient to provide proper care and treatment. SDM is a long-term partnership between the allergist and the patient that solidifies their relationship and improves outcomes.

How can modern technology be used to improve adherence? (Priya Bansal)

The coronavirus disease 2019 pandemic led to the rapid adoption of telemedicine and other digital health tools in the allergy clinic to improve remote health care monitoring for the patient.¹⁸¹ Part of these technological innovations was with health care applications (apps).¹⁸² The My Pollen Forecast-Allergies app provides a 2-day pollen forecast and tracks the patient's symptoms over time. The patient creates a digital diary they use to determine their triggers and assess their improvement over time. The patient can then share this diary with their allergist to modify their medication regimen and provide documentation for their AIT outcomes. To improve compliance with either daily SLIT-tablet dosing or SCIT appointments, apps such as Txt Reminders send a reminder text message and/or phone call to the patient at a frequency they choose. If appointments for SCIT are scheduled in a clinic, another method of sending and confirming patient reminders is through the allergy office electronic health record portal reminder system. Another tool, the My OIT app, tracks the daily oral immunotherapy dose and symptoms, sets reminders, and helps with dosing conversions. It also assists patients in reaching out to their allergist. This aid can also easily be used for SLIT tablets. Follow-up visits are also important for maintaining adherence. A frequency of every 3 months for follow-up visits has been shown to keep patients at an adequate adherence level to SLIT-tablets for at least 2 years.¹⁸³

Recommendation. Technology in health care is swiftly transforming its landscape. Digital apps and tools should be discussed with patients to further SDM. The use of such tools is recommended to help remind patients of their SCIT appointments or to take their daily SLIT-tablet dose.

What is the long-term pharmacoeconomic benefit of AIT? (Marcus Shaker)

In addition to the clinical benefits of AIT, it can provide significant health-economic benefits from a societal perspective. The pharmacoeconomic benefits of AIT relate to several aspects of the therapy. AIT is unique from pharmacotherapy in that it can provide a long-lasting disease-modifying benefit even after therapy is completed.^{91,184} This aspect of AIT results in significant reductions in the use of symptom-relieving medications,^{91,184} which is important not only for payers but also for patients who increasingly bear the brunt of costly deductibles and co-pays associated with pharmacy benefit programs. In addition, while offsetting some costs of pharmacotherapy over longer-term

time horizons, AIT also improves quality of life and subsequent health state utility. For example, in a pharmacoeconomic study of grass SLIT-tablet, patients experienced an additional 72 days of good health over a 9-year time horizon.¹⁸⁵ Lastly, an important consideration is that the disease-modifying effect of AIT translates to averted costs and impairment from comorbid conditions such as allergic asthma.^{186,187}

A 2021 review of the pharmacoeconomic benefit evaluating studies from 1996 to 2020 found significant cost-savings associated with AIT,¹⁸⁸ with cost-effectiveness demonstrated after as little as just a few months. For example, in a US study of children with ARC receiving 18 months of AIT, median per-patient total health care costs were significantly lower than those of matched controls not receiving AIT (\$3247 vs \$4872; $P < .001$).¹⁸⁹ In a separate report, children in the United States receiving AIT for 6 months had significantly less pharmacy, outpatient, and inpatient resource utilization compared with before starting AIT.¹⁹⁰ Benefits have also been demonstrated in international economies. In an Italian study evaluating Parietaria pollen SCIT over 3 years, a net saving of \$830 per year in ARC-related costs was reported.¹⁹¹ In another 9-year Markov model, both SCIT and SLIT to grass pollen was cost-effective, with SCIT showing slightly greater cost-effectiveness (incremental cost-effectiveness ratio: €11,418 [SCIT] and €15,212 [SLIT]).¹⁹²

Recommendation. The health benefits from AIT can reduce ARC-related costs and health care utilization. AIT can be considered as a cost-effective treatment option for ARC.

How should guidelines and clinical practice parameters be used to impact today's practice? (David Bernstein, Leonard Bacharier, and Susan Wasserman)

Evidence-based guidelines or practice parameters addressing both SCIT and SLIT in the treatment of ARC and asthma have been developed by expert committees in the United States, Europe, and other countries.^{8,9,154,156,193-198} Recommendations evolve as new data become available. These documents are practical and comprehensive in addressing most aspects of AIT treatment including disease indications, efficacy, methods of administration, managing risk of anaphylaxis, special populations, different allergen formulations, and so forth. Specifically in the management of asthma, guidelines can help physicians understand the importance of ARC in asthma and help them determine when to recommend AIT.^{195,196,198}

Evidence-based AIT guidelines have been disseminated at professional meetings and incorporated into allergy training program curricula, although it is unknown whether these are widely used in clinical practice. Integrated care pathways can encourage the translation of these guidelines to national or local practice, improve education, and reduce prescribing errors.¹⁹⁹

Recommendations. Updated guidelines and practice parameters are essential documents that provide a foundation for evidence-informed decision making for patients, families, clinicians, and other health care providers. We recommend that prescribers of AIT follow EBM guidelines and recommendations, with the acknowledgment that regional differences in population characteristics, local cost and approval status of specific treatments, community members' values and preferences, and other

regionally variable contextual factors need to be taken into consideration.

FUTURE DIRECTIONS FOR IMPLEMENTING EBM FOR AIT FOR TOMORROW'S ALLERGY SPECIALISTS IN THE UNITED STATES (WANDA PHIPATANAKUL, NICHOLAS KOLINSKY, SHAHNEZ FATTEH, AND JUSTIN GREIWE)

Allergy Fellows help shape the future of patient care and have multiple opportunities to advance EBM. However, to implement EBM for AIT, Allergy Fellows need education regarding the available EBM. Educational speaker programs and national/regional professional society meetings are opportunities for Allergy Fellows to learn about advancements in EBM. Allergy Fellows can bring this knowledge back to their training programs, creating awareness of new evidence-based practice guidelines. Chief Allergy Fellows, especially, are in a position to advance EBM through cultivating an evidence-based educational curriculum and leading by example, through conscientious use of the best EBM in their practice. Allergy Fellows need to learn from and emulate their mentors and allergy/immunology leaders who use the best EBM in their practice.

A greater emphasis needs to be placed on lifelong learning given how quickly our specialty is changing, and ongoing support of basic science research should be a top priority if we want to continue to advance our field.²⁰⁰ Participation from Allergy Fellows in research and clinical trials should be encouraged as an educational tool. Allergy Fellows play an integral role by initiating research projects, recruiting patients, and expediting the research and clinical trial process. The resulting pivotal research findings and clinical trial outcomes may influence future practice guidelines.

The current educational curriculum for many Allergy Fellows may benefit from more of a focus on AIT. Allergy Fellows need to be educated about different types of AIT, how to select which form of AIT is appropriate for each individual patient, efficacy and clinical trial data, and SCIT dosing and preparation. To accomplish this goal, free, easy-to-access educational programs and lectures on AIT need to be available for Allergy Fellows. Research and clinical trial updates, from established thought leaders on the subject of EBM in AIT, would be valuable to training programs. These resources could be accessed through multiple professional society web-based platforms.

Although background knowledge and advancement of the EBM supporting AIT practice is important, the main unmet need in AIT education is the lack of hands-on training during accreditation. Providing Allergy Fellows the opportunity to write and prepare mixed SCIT extracts could be an invaluable experience to help strengthen the fundamentals of AIT as well as expose fellows to U.S. Pharmacopeia Chapter 797 guidelines for best practice when compounding sterile preparations. These hands-on workshops could be free and accessible courses for Allergy Fellows, supported by various sources including professional allergy and immunology societies and pharmaceutical companies. A standardized video series on extract preparation would be invaluable. Algorithms related to AIT such as stratification of patient selectivity, allergen extract mixing protocols (including cross-reactivity of pollens), optimizing extract doses, duration of treatment, and assessment of patient response are all essential for AIT implementation. Incorporation of E-tools and

telemedicine can be used in training of extract mixing, and apps to monitor aerobiology and patient symptoms may allow for greater participation in treatment.

Other educational areas that could be addressed in more detail include the following:

- Competency in managing risk of SCIT
- Enhanced experience and training with accelerated build-up, cluster regimens
- Anaphylaxis treatment preparedness, when to prescribe epinephrine
- Understanding the disease-modifying effects of AIT from a biological and molecular standpoint
- Proper billing and coding, chart documentation, and review of payer reimbursement
- Increasing access to AIT in underserved populations

Of utmost importance in implementing EBM in AIT is the emerging curriculum of the American Board of Allergy and Immunology (ABAI), which focuses on basic scientific principles that can be applied to clinical practice. In 2019, the ABAI developed a committee charged with modifying the blueprint for the Certification Examination to fit in line with the needs of the practicing allergy/immunology specialists. The goal was to reduce basic science content to no more than 25% of the exam and link test items with clinical context and rely less on rote memory. The blueprint was approved in 2021 for implementation in the 2022 Certification Examination. ARC, asthma, and AIT are key topic areas in this blueprint, given its importance in the specialty. Furthermore, a category of Emerging Health Priorities was added to the Certification and Maintenance of Certification/Continuing Assessment Program to ensure that there is timely inclusion of new areas/topics that are critically important to practicing allergists, such as novel FDA-approved immune therapeutics and pandemic-related topics.

In addition, the ABAI underwent implicit bias training at the fall 2021 in-person meeting to increase awareness and sensitivity in reducing bias in their questions in sensitive areas related to race, sex, ethnicity, socioeconomic status, and other variables to ensure they are on par with efforts to improve Diversity, Equity, and Inclusion in their certification activities.

Recommendation

We recommend that training programs increase their focus on AIT and its evidence-based dosing for SCIT and SLIT-tablets. In addition, we recommend that training programs provide real-world, hands-on experience for their Allergy Fellows in the mixing and preparing of SCIT extracts. The curriculum of the ABAI should continue to emphasize the importance of AIT.

CONCLUSIONS

Many developments have progressed the field of AIT since it was first practiced more than 100 years ago. Subsequently, for most aspects of AIT practice the time has come to move beyond empirical-based AIT to EBM for AIT. There are still some hotly debated issues that lack data of sufficient quality to provide firm EBM recommendations. We look forward to results from future research addressing these data gaps and encourage allergy/immunology training programs to emphasize the importance of EBM in tomorrow's allergy/immunology specialists.

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