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Clinical Practice Guideline: Immunotherapy for Inhalant Allergy

Richard K. Gurgel, MD, MSCI[1], Fuad M. Baroody, MD[2], Cecelia C. Damask, DO[3], James "Whit" Mims, MD[4], Stacey L. Ishman, MD, MPH[5], Dole P. Baker, Jr., MD[6], Kevin J. Contrera, MD, MPH[7], Fariha S. Farid, DO[8], John A. Fornadley, MD[9], Donna D. Gardner, DrPH, RRT, RRT-NPS[10], LaKeisha R. Henry, MD[11], Jean Kim, MD, PhD[12], Joshua M. Levy, MD, MPH[13], Christine M. Reger, DNP, CRNP[14], Howard J. Ritz, DMSc, PA-C[15], Robert J. Stachler, MD[16], Tulio A. Valdez, MD, MSc[17], Joe Reyes, MS[18], and Nui Dhepyasuwan, MEd[18]

Abstract

Objective. Allergen immunotherapy (AIT) is the therapeutic exposure to an allergen or allergens selected by clinical assessment and allergy testing to decrease allergic symptoms and induce immunologic tolerance. Inhalant AIT is administered to millions of patients for allergic rhinitis (AR) and allergic asthma (AA) and is most commonly delivered as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). Despite its widespread use, there is variability in the initiation and delivery of safe and effective immunotherapy, and there are opportunities for evidence-based recommendations for improved patient care.

Purpose. The purpose of this clinical practice guideline (CPG) is to identify quality improvement opportunities and provide clinicians trustworthy, evidence-based recommendations regarding the management of inhaled allergies with immunotherapy. Specific goals of the guideline are to optimize patient care, promote safe and effective therapy, reduce unjustified variations in care, and reduce the risk of harm. The target patients for the guideline are any individuals aged 5 years and older with AR, with or without AA, who are either candidates for immunotherapy or treated with immunotherapy for their inhalant allergies. The target audience is all clinicians involved in the administration of immunotherapy. This guideline is intended to focus on evidence-based quality improvement opportunities judged most important by the guideline development group (GDG). It is not intended to be a comprehensive, general guide regarding the management of inhaled allergies with immunotherapy. The statements in this guideline are not intended to limit or restrict care provided by clinicians based on their experience and assessment of individual patients.

Action Statements. The GDG made a *strong recommendation* that (Key Action Statement [KAS] 10) the clinician performing allergy skin testing or administering AIT must be able to diagnose and manage anaphylaxis. The GDG made *recommendations* for the following KASs: (KAS 1) Clinicians should offer or refer to a clinician who can offer immunotherapy for patients with AR with or without AA if their patients' symptoms are

[1]University of Utah, Salt Lake City, Utah, USA
[2]The University of Chicago Medicine, Chicago, Illinois, USA
[3]Lake Mary ENT and Allergy, Lake Mary, Florida, USA
[4]Wake Forest Baptist Health, Winston Salem, North Carolina, USA
[5]University of Wisconsin-Madison, Madison, Wisconsin, USA
[6]Anderson ENT & Facial Plastics, Anderson, South Carolina, USA
[7]University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[8]Polyclinic, Seattle, Washington, USA
[9]Associated Otolaryngologists of PA, Inc, Hershey, Pennsylvania, USA
[10]Allergy & Asthma Network, Fairfax, Virginia, USA
[11]Ear Nose & Throat Consultants, Henderson, Nevada, USA
[12]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[13]National Institute on Deafness and Other Communication Disorders, Bethesda, Maryland, USA
[14]University of Pennsylvania, Otolaryngology–Head and Neck Surgery, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[15]Albany Med Health System, Glens Fall, New York, USA
[16]Stachler ENT, PC, West Bloomfield, Michigan, USA
[17]Stanford University, Palo Alto, California, USA
[18]American Academy of Otolaryngology–Head and Neck Surgery Foundation, Alexandria, Virginia, USA

Corresponding Author:
Richard K. Gurgel, MD, MSCI, University of Utah, 50 North Medical Drive, Salt Lake City, UT 84132-0001, USA.
Email: richard.gurgel@hsc.utah.edu

inadequately controlled with medical therapy, allergen avoidance, or both, or have a preference for immunomodulation. (KAS 2A) Clinicians should not initiate AIT for patients who are pregnant, have uncontrolled asthma, or are unable to tolerate injectable epinephrine. (KAS 3) Clinicians should evaluate the patient or refer the patient to a clinician who can evaluate for signs and symptoms of asthma before initiating AIT and for signs and symptoms of uncontrolled asthma before administering subsequent AIT. (KAS 4) Clinicians should educate patients who are immunotherapy candidates regarding the differences between SCIT and SLIT (aqueous and tablet) including risks, benefits, convenience, and costs. (KAS 5) Clinicians should educate patients about the potential benefits of AIT in (1) preventing new allergen sensitizations, (2) reducing the risk of developing AA, and (3) altering the natural history of the disease with continued benefit after discontinuation of therapy. (KAS 6) Clinicians who administer SLIT to patients with seasonal AR should offer pre- and co-seasonal immunotherapy. (KAS 7) Clinicians prescribing AIT should limit treatment to only those clinically relevant allergens that correlate with the patient's history and are confirmed by testing. (KAS 9) Clinicians administering AIT should continue escalation or maintenance dosing when patients have local reactions (LRs) to AIT. (KAS 11) Clinicians should avoid repeat allergy testing as an assessment of the efficacy of ongoing AIT unless there is a change in environmental exposures or a loss of control of symptoms. (KAS 12) For patients who are experiencing symptomatic control from AIT, clinicians should treat for a minimum duration of 3 years, with ongoing treatment duration based on patient response to treatment. The GDG offered the following KASs as *options*: (KAS 2B) Clinicians may choose not to initiate AIT for patients who use concomitant beta-blockers, have a history of anaphylaxis, have systemic immunosuppression, or have eosinophilic esophagitis (SLIT only). (KAS 8) Clinicians may treat polysensitized patients with a limited number of allergens.

Keywords

allergen immunotherapy, allergic asthma, allergic rhinitis, anaphylaxis, inhalant allergy, subcutaneous immunotherapy, sublingual immunotherapy

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Inhalant allergen immunotherapy (AIT) is administered to millions of patients for allergic rhinitis (AR) and allergic asthma (AA). Despite its widespread use, there are multiple clinical dilemmas that exist, including patient selection, modes of immunotherapy delivery, and ongoing needs to evaluate and ensure the safety and efficacy of this valuable intervention.

AR and AA are caused by an immunoglobulin E (IgE)-mediated inflammatory response to proteins (or glycoproteins) carried by inhaled organic particles such as pollen, animal dander, mold spores, and/or mite/insect debris.[1] Inhalant allergies can be treated by immunotherapy, pharmaceuticals, or by reducing environmental exposure to the allergen.[2]

AIT is the therapeutic exposure to an allergen or allergens selected by clinical assessment and allergy testing. AIT decreases allergic symptoms and induces immunologic tolerance in a clinically significant portion of allergic persons.[3] AIT for inhalant allergens is most commonly delivered as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). Immunotherapy is unique among allergy therapies in the ability to maintain a reduction in allergy symptoms after treatment is discontinued.[4] In this manuscript, the induction of immune tolerance by AIT is referred to as "immunomodulation" (Refer to **Table 1**). AIT also has the risk of inducing allergic reactions including anaphylaxis.[5]

Variability in the initiation and delivery of safe and effective immunotherapy provides opportunities for evidence-based recommendations for improved patient care. The multiple clinical decisions and evolving literature generate a need for current expert opinion and evidence-based recommendations in the form of a clinical practice guideline (CPG).

Definitions

There are multiple terms utilized in the immunotherapy literature that are specific to allergy sensitization, pathophysiology, or immunotherapy. As some variation among authors and historical usage exists, the primary concepts are defined in **Table 1**. This document was edited for consistent use of these definitions.

Guideline Scope and Purpose

A clinical practice guideline (CPG) is defined, as outlined by the Institute of Medicine, as "statements that include recommendations intended to optimize patient care that are informed by systematic review of the evidence and an assessment of the benefits and harms of alternative care options." The purpose of this CPG is to provide clinicians trustworthy, evidence-based recommendations regarding the management of inhaled allergies with immunotherapy.[6]

This Immunotherapy for Inhalant Allergy CPG identifies quality improvement opportunities for clinicians who administer AIT. The goal is to optimize patient care, promote safe and effective therapy, reduce unjustified variations in care, and reduce the risk of harm.

This guideline is intended for any clinician involved in the administration of immunotherapy for allergic patients aged 5 years and older in any care setting. This applies to all Key Action Statements (KASs) unless otherwise specified. The target audience, referred to as clinicians in this CPG, includes physicians (specialists and primary care providers), advanced practice providers, and allied health professionals. The guideline does not focus on evaluation or medical management of allergic rhinitis (AR), allergic conjunctivitis (AC), or allergic asthma (AA) nor environmental controls, but assumes instead that prior to consideration of initiation of

Table 1. Abbreviations and Definitions of Common Terms

Term	Definition
Allergen epitope	An amino acid sequence that binds to specific IgE of an allergic person causing an immunologic response with correlating clinical symptoms. Shared allergen epitopes are presumed to be the basis for allergic cross-reactivity.
Allergen	A protein or glyco-protein containing 1 or more allergen epitopes that can bind to IgE causing an immunologic reaction. These are named by the species of origin and order of discovery. (eg, Der p 1 is the first allergen identified for *Dermatophagoides pteronyssinus*)
Inhalant allergens	For allergens to cause symptoms, there must be a route of exposure such as inhalation, ingestion, injection, or skin contact. Inhalant allergens primarily cause symptoms via inhalation and contact with respiratory mucosa.
Allergen particles	Allergens are carried by particles that can be inhaled and are buoyant in air primarily due to size. They are usually referred to by order, family, genus, or species of origin (or vernacular equivalents). Examples of allergen particles include pollen and animal dander.
Allergen sensitization	Allergen sensitization refers to a positive allergy skin test or a test confirming binding to allergen-specific IgE. Testing can be positive with or without the presence of clinical allergy symptoms.
Inhalant allergy	A condition in which IgE-mediated symptoms are induced when naturally occurring amounts of allergen particles contact the respiratory mucosa. There can be co-exposures such as to the ocular conjunctiva, nasal mucosa, and bronchial epithelium.
Inhalant AIT	The treatment of inhalant allergy through repeated administration of allergens at regular intervals to reduce allergic symptoms.
SCIT	AIT administered by injecting allergen into the subcutaneous tissue.
SLIT	AIT administered by placing allergen topically underneath the tongue. This can be in the form of aqueous (SLIT-aqueous) or tablet (SLIT-tablet) allergen.
Immunomodulation	Altering the immune response resulting in continued benefit after discontinuation of AIT.
Tolerogenic	Capable of producing immunological tolerance.
Pre-seasonal SLIT	Administered weeks to months prior to the onset of the relevant allergen season.
Co-seasonal SLIT	Administered during the relevant allergen season.
Polyallergic	Both history and testing confirm that a patient has allergies to multiple allergens.
Polysensitized	Multiple allergens positive on allergy testing.

Abbreviations: AIT, allergen immunotherapy; IgE, immunoglobulin E; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

immunotherapy, all underlying conditions, and other potential contributing factors, have already been addressed and properly managed.

The population of patients targeted in this guideline are those with AR, with or without AA, who are either candidates for immunotherapy or treated with immunotherapy for their inhalant allergies. This population is at higher risk for other allergic co-morbidities such as AC, but co-morbidities were not used to exclude patients. Due to the practicalities of allergy testing, clinical assessment, and available data, the guideline targets patients 5 years of age or older.

The quality improvement opportunities were selected by the authors collectively, with public comment for input, and are not a comprehensive guide for patient management. The guideline recommendations are not intended to restrict care for any particular patient. The guideline is not intended to limit or replace individualized patient care or clinical judgment. The guideline recommendations are focused on quality improvement opportunities based on a carefully developed and transparent process that incorporates harm-benefit balance and strength of evidence. Expert consensus of the authors is used to resolve gaps in the evidence.[7] Identified evidence gaps are used to select research needs and develop quality improvement strategies.

Health Care Burden

Epidemiology

There is an epidemiological correlation between AR and asthma.[8] In the literature, the prevalence of AR has been reported to range between 5% and 50%, varying widely by geography and methodology used for diagnosing AR.[9-14] European cohort studies, using both clinical symptoms and allergy testing for diagnosis, estimate the prevalence to be around 15%.[15-17] Sensitization, mainly to foods, can begin as early as 6 months of age with sensitization to inhalant allergens at an older age.[18] In the International Study of Asthma and Allergies in Childhood, a worldwide epidemiological research program established in 1991 to investigate asthma, rhinitis, and eczema in children, the prevalence for current allergic rhinoconjunctivitis in the 6- to 7-year age group was 8.5% and in the 13- to 14-year age group was 14.6%.[11,12]

More than 50 million Americans suffer from allergies each year.[19] Approximately 25 million people in the United States have asthma.[20] The prevalence of concomitant AR in patients with asthma varies in population studies with rates reported between 20.3% and 93.5%.[21-27]

Allergies and Quality of Life (QOL)

High-quality evidence evaluating the impact of AR on QOL demonstrates that AR patients suffer from decreased general and disease-specific QOL due to impacts on physical and mental health. Persistent AR has a more profound impact on QOL than seasonal AR.[28-33] The effect on QOL in patients suffering from AR is on par with other chronic diseases including epilepsy, liver disease, and migraines.[34] Successful treatment of AR leads to improved overall and disease-specific QOL.[35]

AR and Asthma Socioeconomics

AR poses a significant socioeconomic burden as a result of its chronicity and prevalence with its true burden involving direct, indirect, and societal costs.[36,37] Direct costs relate to the financial expenditures on health care; and indirect costs relate to loss of productivity related to disease including absenteeism, and presenteeism, and additional costs include those due to reduced QOL.[34,38-40]

In the United States, allergies are the sixth leading cause of chronic illness with an annual cost in excess of $18 billion.[41,42] Meltzer and Buckstein estimated that the total direct medical cost of AR is approximately $3.4 billion, with almost half of this cost attributable to medications.[43] Through loss of work and decreased school attendance, AR is responsible for $2 to $4 billion annually in lost productivity.[2] The annual economic cost of asthma from 2008 to 2013 was more than $81.9 billion which included medical costs, loss of work, and loss of school days.[44]

Workforce

Despite the breadth of AR and asthma in the United States, a relatively small population of clinicians offer immunotherapy, including different specialties such as allergy/immunology (A/I), otolaryngology, pulmonology, pediatrics, internal medicine, and family practice. The Association of American Medical Colleges in its most current workforce report (2021) revealed a total of 5009 active A/I physicians in direct patient care, translating to approximately 1.0 A/I physician per 65,197 population.[45] In 2009, 294 A/I fellows completed their fellowship training and 1406 otolaryngology residents completed their training.[46]

Burden of Immunotherapy

A published calculation determined that immunotherapy for AR with or without asthma is cost effective.[47] However, AIT does have risks including the potential for systemic reactions (SRs) such as urticaria, gastrointestinal upset, wheezing, and anaphylaxis. The rate of SRs from SCIT reported in a national surveillance study from 2008 to 2013 remained stable,[48] compared to previous surveillance studies,[49] at 1.9% of patients, with 0.08% and 0.02% experiencing Grades 3 and 4 SRs, respectively (**Table 2**). In another surveillance study, 7 fatalities were reported with SCIT between 2008 and 2017 in the United States.[50] SRs occurred in 1.4% of patients receiving SLIT-Aq, including 0.03% with Grade 3 SRs.[29] There were no SLIT-related fatalities reported.

Adherence to immunotherapy is important as a minimum of 3 years of treatment is needed to obtain long-term clinical benefit (Refer to KAS 12). Unfortunately, nonadherence to immunotherapy can be high. A wide range of adherence rates, from 7% to 97% have been reported in a review by Senna et al.[52] Possible reasons for an incomplete treatment course include inconveniences and cost due to regular office visits resulting in time away from work/school. Early discontinuation of therapy could diminish the known benefit of AIT.[53] Although reported estimates of attrition/noncompliance rates with SCIT can be high, it is not known how much money is spent on SCIT that is discontinued prematurely and thus does not achieve the intended benefit of a course of treatment. In a recent systematic review of real-world persistence and adherence in SCIT by Lin et al,[54] persistence and adherence rates are poor (<80%); however, they range widely, explained in part by interstudy differences in measuring and reporting adherence-related findings. Although SLIT offers patients more convenient dosing than SCIT, it still relies on daily dosing for many years to optimize effectiveness. In a study by Hura et al examining compliance in SLIT patients, they found that 61.6% discontinued their treatment prematurely.[55]

Methods

This guideline was developed using an explicit and transparent *a priori* protocol for creating actionable statements based on supporting evidence and the associated balance of harm as outlined in the third edition of the *Clinical Practice Guideline Development Manual: A Quality-Driven Approach for Translating Evidence into Action*.[7]

Stakeholder Involvement

The guideline development group (GDG) consisted of 17 panel members representing experts in otolaryngology and allergy or members who have expertize in CPG development. Panel members came from a variety of practice settings, training backgrounds, and stages of training. The GDG also included a consumer/patient representative. The GDG held 3 conference calls and 2 virtual meetings during which they defined the scope and objectives of the guideline, reviewed comments from the expert panel review for each KAS, identified other quality improvement opportunities, reviewed the literature search

Table 2. World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present[a] **Cutaneous** Generalized pruritus, urticaria, flushing, or sensation of heat or warmth[b] **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis—(eg, sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to originate in the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Erythema, pruritus, or tearing **Other** Nausea, metallic taste, or headache	***Symptom(s)/sign(s) of more than 1 organ system present***[a] **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea **or** **Other** Uterine cramps	**Lower respiratory** Asthma (eg, 40% PEF or FEV1 drop NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula, or tongue edema with or without stridor	**Lower or upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death

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Abbreviations: FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow.

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

[b]This constellation of symptoms may rapidly progress to a more severe reaction.

results, and drafted/revised the document in multiple rounds of review.

Literature Search and Selection

An information specialist conducted 2 literature searches from October through December 2022 using a validated filter strategy to identify CPGs, systematic reviews, meta-analyses (MAs), and randomized-controlled trials (RCTs).

The following databases were searched for relevant studies: AHRQ EPC Reports, Biosis, Citation Index, CINAHL, ClinicalTrials.gov, CMA Infobase, Cochrane CENTRAL, Cochrane Database of SRs, CRD Web (DARE, NHS EED, HTA), ECRI Trust, Embase, Google Scholar, Guidelines International Network, HSTAT, New Zealand Guidelines Group, NICE Guidance & Advice, Proquest Central, PubMed, Scopus, SIGN, TRIPdatabase.com, and WHO ICTRP. The databases were searched using both controlled vocabulary words and synonymous free-text words for the topic of interest (Immunotherapy for Inhalant Allergy). The search strategies were adjusted for the syntax appropriate for each database/platform. The search was not limited to clinical study design and was limited to the English language. The full strategy is found in **Appendixes A** and **B**. These search terms were used to capture all evidence on the population, incorporating all relevant treatments and outcomes.

The initial English-language searches identified 148 CPGs, 240 systematic reviews/MAs, and 998 RCTs published from January 2012 through December 2022. CPGs were included if they met quality criteria of (a) an explicit scope and purpose, (b) multidisciplinary

stakeholder involvement, (c) systematic literature review, (d) explicit system for ranking evidence, and (e) explicit system for linking evidence to recommendations. Systematic reviews were included if they met quality criteria of (a) clear objective and methodology, (b) explicit search strategy, and (c) valid data extraction methods. RCTs were included if they met quality criteria of (a) trials involved study randomization, (b) trials were double-anonymized, and (c) trials denoted a clear description of withdrawals and dropouts of study participants. After removing duplicates, irrelevant references, and non-English-language articles, the 4 reviewers retained 59 CPGs, 148 systematic reviews/MAs, and 450 RCTs that met inclusion criteria. Additional evidence was identified, as needed, including a targeted search in March 2023 to support the needs of the GDG to supplement and fill knowledge gaps. Therefore, in total, the evidence supporting this guideline includes 23 CPGs, 46 systematic reviews/MAs, 62 RCTs, and 81 observational and other studies.

Classification of Evidence-Based Statements

Guidelines are intended to produce optimal health outcomes for patients, to minimize harm and to reduce inappropriate variations in clinical care. The evidence-based approach to guideline development requires the evidence supporting a policy be identified, appraised, and summarized and that an explicit link between evidence and statements be defined. Evidence-based statements reflect both the *grade (level) of aggregate evidence* and the *balance of benefit and harm* that is anticipated when the statement is followed. The Oxford Center for Evidence-Based Medicine grades of evidence was used. **Table 3** defines the grades of aggregate evidence[56] and **Table 4** defines the strength of action (obligation) based on the interaction of grade and benefit-harm balance.[57]

Development of Key Action Statements

KASs were developed following the 2 literature searches and the assessment of the evidence. The GDG proposed topics within the scope of the guideline supported by the evidence and where there is perceived gap in care. A preliminary list of quality improvement topics was released for public comment. The resulting topics gathered from the public comment were ranked based on importance among the GDG members. In total, 50 topics were determined and ranked by the GDG prior to the first meeting. An explicit and transparent *a priori* protocol for creating actionable statements based on supporting evidence and the associated balance of benefit and harm was used, with assistance from electronic decision support software (BRIDGE-Wiz, Yale Center for Medical Informatics), which was used to facilitate creating actionable recommendations and evidence profiles.[58]

After the KASs were derived, the GDG debated the strength of the recommendation and the strength of evidence. The evidence-based approach to guideline development requires the evidence supporting a policy be identified, appraised, and summarized; and that, an explicit link between evidence and statements be defined. Evidence-based statements reflect both the *quality of evidence* and the *balance of benefit and harm* that is anticipated when the statement is followed. Therefore, the strength of recommendation was determined with an adapted version of the American Academy of Pediatrics classification scheme in **Table 4**.[1,57]

American Academy of Otolaryngology–Head and Neck Foundation (AAO-HNSF) staff used the Guideline Implementability Appraisal to appraise adherence to methodologic standards, to improve the clarity of recommendations, and to predict potential obstacles to implementation.[59] The GDG received summary appraisals and modified an advanced draft of the guideline based on the appraisal. The final draft of the CPG was revised based on comments received during multidisciplinary peer review, open public comment, and journal editorial peer review. A scheduled review process will occur at 5 years from publication, or sooner if new compelling evidence warrants earlier consideration.

Guidelines are not intended to supersede professional judgment but rather may be viewed as a relative constraint on individual clinician discretion in a particular clinical circumstance. Less frequent variation in practice is expected for a "strong recommendation" than might be expected with a "recommendation." "Options" offer the most opportunity for practice variability. Clinicians should always act and decide in a way that they believe will best serve their patient's interests and needs, regardless of guideline recommendations. They must also operate within their scope of practice and according to their training. Guidelines represent the best judgment of a team of experienced clinicians and methodologists addressing the scientific evidence for a particular topic.[57] Making recommendations about health practices involves value judgments on the desirability of various outcomes associated with management options. Values applied by the GDG sought to minimize harm and diminish unnecessary and inappropriate therapy. A major goal of the panel was to be transparent and explicit about how values were applied and to document the process.

Financial Disclosure and Conflicts of Interest

The cost of developing this guideline was covered in full by the AAO-HNSF. Potential conflicts of interest for all panel members in the past 2 years were compiled and distributed before the first conference call. After review and discussion of these disclosures,[60] the GDG concluded that individuals with potential conflicts could remain on the panel if they: (1) reminded the panel of potential conflicts before any related discussion, (2) recused themselves from a related discussion if asked by the panel, and (3) agreed not to discuss any aspect of the guideline with industry before publication. Finally, panelists were reminded that conflicts of interest extend beyond financial relationships and may

Table 3. Grades of Aggregate Evidence

Grade	OCEBM level	Treatment	Harm	Diagnosis	Prognosis
A	1	Systematic review[a] of randomized trials	Systematic review[a] of randomized trials, nested case-control studies, or observational studies with dramatic effect[a]	Systematic review[a] of cross-sectional studies with consistently applied reference standard and blinding	Systematic review[a] of inception cohort studies[b]
B	2	Randomized trials, or observational studies with dramatic effects or highly consistent evidence	Randomized trials, or observational studies with dramatic effects or highly consistent evidence	Cross-sectional studies with consistently applied reference standard and blinding	Inception cohort studies[b]
C	3-4	Non-randomized or historically controlled studies, including case-control and observational studies	Nonrandomized controlled cohort or follow-up study (post-marketing surveillance) with sufficient numbers to rule out common harm; case-series, case-control, or historically controlled studies	Nonconsecutive studies, case-control studies, or studies with poor, non-independent, or inconsistently applied reference standards	Cohort study, control arm of a randomized trial, case series, or case-control studies; poor quality prognostic cohort study
D	5	Case reports, mechanism-based reasoning, or reasoning from first principles			
X	n/a	Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit over harm			

Adapted with permission from the Oxford Levels of Evidence 2 developed by the OCEBM Levels of Evidence Working Group.[56]
Abbreviation: OCEBM, Oxford Centre for Evidence-Based Medicine.
[a]A systematic review may be downgraded to level B because of study limitations, heterogeneity, or imprecision.
[b]A group of individuals identified for subsequent study at an early, uniform point in the course of the specified health condition, or before the condition develops.

Table 4. Strength of Action Terms in Guideline Statements and Implied Levels of Obligation

Strength	Definition	Implied obligation
Strong recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or, in the case of a strong negative recommendation, that the harms clearly exceed the benefits) and that the quality of the supporting evidence is high (Grade A or B). In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.[57]	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation means the benefits exceed the harms (or, in the case of a negative recommendation, that the harms exceed the benefits), but the quality of evidence is not as high (Grade B or C). In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.[57]	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option[a]	An option means that either the quality of evidence is suspect (Grade D) or that well-done studies (Grade A, B, or C) show little clear advantage to one approach vs another.[57]	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.

Refer to **Table 3** for definitions of evidence grades.
[a]Option resembles the "Weak Recommendation" utilized in the GRADE classification system: Grading of Recommendations Assessment, Development and Evaluation.

include personal experiences, how a participant earns a living, and the participant's previously established "stake" in an issue.[61] Conflicts were again delineated at the start of the meeting and at the start of each teleconference meeting, with the same caveats followed. All conflicts are disclosed at the end of this document.

Guideline Key Action Statements (KASs)

Each evidence-based statement is organized in a similar fashion: a KAS is in bold, followed by the strength of the recommendation in italics. Each KAS is followed by an "action statement profile" that explicitly states the quality improvement opportunity, aggregate evidence quality, level of confidence in evidence (high, medium, low), benefits, harms, risks, costs, and a benefits-harm assessment. Additionally, there are statements of any value judgments, the role of patient preferences, clarification of any intentional vagueness by the panel, exceptions to the statement, any differences of opinion, and a repeat statement of the strength of the recommendation. Several paragraphs subsequently discuss the evidence supporting the statement. An overview of each evidence-based statement in this guideline can be found in **Table 5**.

For the purposes of this guideline, *shared decision-making* refers to the exchange of information regarding treatment risks and benefits, as well as the expression of patient preferences and values, which result in mutual responsibility between the patient and clinician in decisions regarding treatment and care.[62]

Statement 1: Candidacy for AIT

Clinicians should offer or refer to a clinician who can offer AIT for patients with AR with or without AA if their patients' symptoms are inadequately controlled with medical therapy, allergen avoidance, or both, or have a preference for immunomodulation.

Evidence Strength: Recommendation based on CPGs, systematic reviews, and RCTs with a preponderance of benefit over harm.

Action Statement Profile: 1

- Quality improvement opportunity: Underutilization of immunotherapy; improve access to appropriate therapy; potential for the prevention of development of asthma and new allergic sensitizations; increase awareness of the potential for inhibition of allergic response
  (National Quality Strategy Domain: Coordination of Care, Prevention and Treatment of Leading Causes of Morbidity and Mortality)
- Aggregate evidence quality: Grade A, based on CPGs, systematic reviews, and RCTs
- Level of confidence in the evidence: High
- Benefits: Improving symptom control; improving QOL; potential secondary prevention of new sensitizations and the development of asthma for patients with AR; decreased absenteeism; decreased medication use; alternatives for people who cannot take certain

Table 5. Summary of Guideline Key Action Statements

Statement	Action	Strength
KAS 1: Candidacy for Allergen Immunotherapy	Clinicians should offer or refer to a clinician who can offer immunotherapy for patients with allergic rhinitis with or without allergic asthma if their patients' symptoms are inadequately controlled with medical therapy, allergen avoidance, or both, or have a preference for immunomodulation.	Recommendation
KAS 2A: Who Should NOT Get Allergen Immunotherapy	Clinicians should not initiate allergen immunotherapy for patients who are pregnant, have uncontrolled asthma, or are unable to tolerate injectable epinephrine.	Recommendation
KAS 2B: Who May NOT Get Allergen Immunotherapy	Clinicians may choose not to initiate allergen immunotherapy for patients who use concomitant beta-blockers, have a history of anaphylaxis, have systemic immunosuppression, or have eosinophilic esophagitis (SLIT only).	Option
KAS 3: Asthma Assessment	Clinicians should evaluate the patient or refer the patient to a clinician who can evaluate for signs and symptoms of asthma before initiating allergen immunotherapy and for signs and symptoms of uncontrolled asthma before administering subsequent allergen immunotherapy.	Recommendation
KAS 4: Education Regarding SLIT Versus SCIT	Clinicians should educate patients who are immunotherapy candidates regarding the differences between SCIT and SLIT (aqueous and tablet) including risks, benefits, convenience, and costs.	Recommendation
KAS 5: Education Regarding Preventive Qualities of Allergen Immunotherapy	Clinicians should educate patients about the potential benefits of allergen immunotherapy in (1) preventing new allergen sensitizations, (2) reducing the risk of developing allergic asthma, and (3) altering the natural history of the disease with continued benefit after discontinuation of therapy.	Recommendation
KAS 6: Pre-/Co-Seasonal Therapy	Clinicians who administer SLIT to patients with seasonal allergic rhinitis should offer pre- and co-seasonal immunotherapy	Recommendation
KAS 7: Selecting Clinically Relevant Allergens	Clinicians prescribing allergen immunotherapy should limit treatment to only those clinically relevant allergens that correlate with the patient's history and are confirmed by testing.	Recommendation
KAS 8: Treating Polysensitized Patients With Limited Allergens	Clinicians may treat polysensitized patients with a limited number of allergens.	Option
KAS 9: Local Reactions and Allergen Immunotherapy Escalation	Clinicians administering allergen immunotherapy should continue escalation or maintenance dosing when patients have local reactions to allergen immunotherapy.	Recommendation
KAS 10: Anaphylaxis Identification and Management	The clinician performing allergy skin testing or administering allergen immunotherapy must be able to diagnose and manage anaphylaxis.	Strong recommendation
KAS 11: Retesting During Allergen Immunotherapy	Clinicians should avoid repeat allergy testing as an assessment of the efficacy of ongoing allergen immunotherapy unless there is a change in environmental exposures or a loss of control of symptoms.	Recommendation
KAS 12: Duration for Allergen Immunotherapy	For patients who are experiencing symptomatic control with allergen immunotherapy, clinicians should treat for a minimum duration of 3 years, with ongoing treatment duration based on patient response to treatment.	Recommendation

Abbreviations: KAS, Key Action Statement; SLIT, sublingual immunotherapy.

medications (eg, occupational concerns like Federal Aviation Administration guidelines, access)

- Risks, harms, costs: Anaphylaxis; side effects; local and regional allergic reactions (eg, arm swelling); may require additional medications; may not be effective or partially effective; associated time especially with SCIT (weekly); lost time from school/work; may not be covered by insurance; co-payments

- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: There is underutilization of effective immunotherapy. Patient preference and QOL are not always taken into consideration
- Intentional vagueness: Inadequately controlled with medical therapy was used not to create a specific legal standard of care; pharmacologic therapy does not include SLIT; inadequate control includes patient's reluctance to continue medical therapy and/or desire for more longstanding control of their symptoms or immunomodulation
- Role of patient preferences: Low in regard to clinicians offering the therapeutic option of AIT and high in regard to shared decision-making and including patient's preference of management options
- Exceptions: Patients who are not candidates for immunotherapy who are referenced in KAS 2
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this KAS is to ensure that candidates are offered immunotherapy appropriately thus minimizing underutilization of this treatment modality. Per the CPG: AR, patients who have been diagnosed with AR through history and physical examination, have inadequate control of symptoms (sneezing, nasal, and/or throat itching, rhinorrhea, nasal congestion) with pharmacologic therapy and/or environmental controls, and have positive skin testing or specific serum IgE testing, should be offered, or referred to a clinician who can offer, sublingual or SCIT.[2] AIT can also be offered to patients in whom medical therapy is contraindicated. The Focused Updates to the Asthma Management Guidelines recommend SCIT as an adjunctive treatment for individuals who have demonstrated allergic sensitization and evidence of worsening asthma symptoms after exposure to the relevant antigen(s) either intermittently (eg, allergy to pets), on a seasonal basis (eg, allergy to grass or ragweed), or a chronic basis (eg, allergy to dust mites).[63] Patients with AR and/or AA whose symptoms are not controlled with appropriate pharmacologic therapy and/or environmental control have improved symptom control, QOL, potential secondary prevention of new sensitization, and the development of asthma after instituting AIT.

High-quality evidence (61 RCTs and multiple systematic reviews) exists to support the effectiveness of AIT in achieving symptom control in the treatment of AR. This effectiveness is generally measured by improvement in allergy symptoms and reduction in allergy medication usage.[64-66] Systematic reviews also demonstrate improved symptom control and improved QOL in patients with ARC and/or AA.[2,63,67-74]

Medication reduction in response to treatment with AIT is demonstrated in AR and AA. The reduction in use of inhaled corticosteroid (ICS) medications has been demonstrated in mild to moderate asthma patients while maintaining control of asthma.[75]

The prevention of asthma and secondary sensitizations has also been demonstrated though sometimes controversial; this will be further discussed in KAS 5 and so will the continued benefit for symptoms of AR years after cessation of AIT (Refer to KAS 12). There is strong evidence demonstrating the cost savings of AIT over symptomatic medication use in adults and children.[76,77] Shared decision-making is encouraged to allow patients to self-advocate and request the option of AIT. The impact of need for long-term daily pharmacologic therapy and patient desire to have definitive treatment rather than a lifelong commitment to pharmacological management should be considered by the referring and/or treating clinician. Clinicians should document these discussions in the medical record.

In summary, clinicians should discuss AIT options with their patients with AR and/or AA whose symptoms are inadequately controlled with medical therapy, allergen avoidance, or both, or who have preference for immunomodulation (Refer to **Table 1** for definition). AIT has been shown to improve symptoms and QOL while reducing rescue medication intake in these patients. AIT also has the potential to reduce new allergic sensitizations, and the development of asthma. AIT is the only treatment option that has been shown to result in continued control of the symptoms of AR after cessation of therapy.

Statement 2A: Who Should Not Get AIT

Clinicians should not initiate AIT for patients who are pregnant, have uncontrolled asthma, or are unable to tolerate injectable epinephrine.

Evidence Strength: Recommendation based on observational studies, practice parameters, and CPGs with a preponderance of benefit over harm.

Action Statement Profile: 2A

- Quality improvement opportunity: Familiarity with the contraindications will lead to safer prescribing and improved patient safety
  (National Quality Strategy Domain: Patient Safety, Prevention and Treatment of Leading Causes of Morbidity and Mortality)
- Aggregate evidence quality: Grade C, based on observational studies and inclusion in Practice Parameters/CPG based on expert consensus for asthma; Grade C for pregnancy and epinephrine
- Level of confidence in the evidence: Medium for asthma
- Benefits: Avoid morbidity and mortality; improve patient safety
- Risks, harms, costs: Suboptimal treatment of disease; costs can lead to higher health care utilization with uncontrolled asthma and allergic disease
- Benefits-harm assessment: Preponderance of benefit over harm

- Value judgments: Clinicians should not offer immunotherapy to patients with absolute contraindications
- Intentional vagueness: None
- Role of patient preferences: None in terms of initiating AIT during pregnancy; low on continuing ongoing AIT after onset of pregnancy and in cases of uncontrolled asthma and poor tolerance to epinephrine
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this KAS is to avoid harm when initiating immunotherapy in patients at increased risk. AIT is a commonly used treatment for allergic diseases and contraindications are uncommon but should be reviewed in all patients prior to initiation of AIT. For both SLIT and SCIT, the adverse event of greatest severity is anaphylaxis. Therefore, many of the absolute and relative contraindications to AIT are directly related to this risk.

Immunotherapy During Pregnancy

While there is limited data on the safety of AIT in pregnant women, the available evidence and most recommendations suggest that it can be continued safely in women who have already been receiving the treatment before pregnancy and are on maintenance immunotherapy dosing.[3,10,78] No significant difference was found in the incidence of prematurity, hypertension/proteinuria, congenital malformations, or perinatal deaths between women continued on maintenance AIT (SCIT and SLIT) during pregnancy and controls.[79-81] However, there is very little data on initiating immunotherapy during pregnancy. In the above 3 trials, only small numbers of women (7,[81] 24,[80] and 31[79]) were initiated on AIT during pregnancy and did not have maternal or fetal complications. Therefore, based on low level of evidence with small numbers of investigated patients that is not sufficient to assure safety considering the significant potential risks, women should avoid starting immunotherapy for the first time during pregnancy. If pregnant, they should not be escalated to a higher dose if already receiving immunotherapy.[79,82] Pregnant patients should always discuss the potential risks and benefits of continuing AIT treatment with their health care provider.[49]

Patients With Uncontrolled Asthma

Patients with uncontrolled or severe asthma (Refer to KAS 3) should not receive AIT due to the increased risk of severe asthma exacerbations and SRs which can be fatal.[49,63,83] This is because asthma patients have hyperresponsive airways, and exposure to allergens during immunotherapy can trigger severe bronchospasm and potentially life-threatening asthma attacks and respiratory failure.[49,83]

The AIT: A Practice Parameter Third Update from the Joint Task force representing the American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy Asthma and Immunology (ACAAI) recommends that immunotherapy be postponed until the patient's asthma is well controlled.[3] This means that the patient should have good control of their asthma symptoms, and their lung function should be stable before initiating immunotherapy.[84] Studies have found that poorly controlled asthma is a major risk factor for fatal allergic reactions from SCIT.[49,84,85] In addition, patients with poorly controlled asthma are already at a higher risk of exacerbations, which further increases the risk of severe allergic reactions during immunotherapy.[49] In the AAAAI/ACAAI SCIT surveillance study (2013-2017), out of a total of 7 fatalities during this time period, 4 occurred in patients with asthma, including severe asthma in at least 2 cases.[86] Not only should clinicians withhold initiation of AIT in patients with uncontrolled asthma, they should also assess individuals with asthma on AIT for worsening asthma symptoms that suggest recent loss of asthma control before administering each SCIT injection. Clinicians should consider withholding SCIT injections temporarily in patients whose asthma symptoms have worsened until their asthma control is restored.[63] Severe or uncontrolled asthma is also listed as a contraindication for the administration of SLIT tablets by the US Food and Drug Administration (FDA).[87]

Unable to Tolerate Injectable Epinephrine

Another important factor to take into account before recommending immunotherapy is the patient's ability to use epinephrine. Although there are no absolute contraindications for the use of epinephrine, there are instances that warrant using it with caution such as hypersensitivity to sympathomimetic drugs and closed-angle glaucoma. There are other medical conditions such as hypertension, angina, and tachycardia for which the use of epinephrine can lead to exacerbations and where patients can be more sensitive to the effects of epinephrine.[88] These patients should not receive immunotherapy without consulting with their clinician who manages these co-morbid conditions since epinephrine is the first-line treatment for severe allergic reactions, including anaphylaxis.[49,85,89]

Statement 2B: Who May Not Get AIT

Clinicians may choose not to initiate AIT for patients who use concomitant beta-blockers, have a history of anaphylaxis, have systemic immunosuppression, or have eosinophilic esophagitis (EoE) (SLIT only).

Evidence Strength: Option based on case reports with a preponderance of benefit over harm.

Action Statement Profile: 2B

- Quality improvement opportunity: Familiarity with the contraindications will lead to safer prescribing and improved patient safety
  (National Quality Strategy Domain: Patient Safety)
- Aggregate evidence quality: Grade D, based on case reports for beta-blockers, history of anaphylaxis; control studies and case reports for systemic immunosuppression (for patients with cancer and human immunodeficiency virus [HIV]) and history of anaphylaxis, and case reports for patients with EoE
- Level of confidence in the evidence: Medium
- Benefits: Avoid morbidity and mortality
- Risks, harms, costs: Suboptimal treatment of disease; costs can lead to higher health care utilization with uncontrolled asthma and allergic disease
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Optimizing the risk-benefit ratio among patients for whom the evidence is lacking (eg, patients with autoimmune diseases)
- Intentional vagueness: None
- Role of patient preferences: Moderate with shared decision-making between patient, AIT-administering practitioner, and other subspecialists (eg, cardiologists as relating to beta-blocker use) about whether or not to initiate immunotherapy in the presence of the specified conditions
- Exceptions: None
- Policy level: Option
- Differences of opinion: None

Supporting Text

The purpose of this KAS is to reduce harm when initiating AIT. Known relative risks include, but may not be limited to, beta-blocker use, history of anaphylaxis, systemic immunosuppression, and EoE (SLIT only). Changes in risk profile and health need to be monitored not only when AIT is initiated, but also throughout the course of AIT.

Clinicians May Choose Not to Initiate Immunotherapy for Patients Who Use Concomitant Beta-Blockers

This discussion applies to beta-blockers used during AIT, regardless of the indication for beta-blocker use. Some beta-blockers, particularly nonselective beta-blockers like propranolol, interfere with the effects of epinephrine, which is used to treat anaphylaxis. This can make it more difficult to manage an allergic reaction during immunotherapy. Epinephrine is a nonselective agonist of all adrenergic receptors. Epinephrine treats upper airway mucosal edema, angioedema, hypotension, urticaria, and shock by increasing peripheral vascular resistance via alpha-1 receptors and increases cardiac output via beta-1 receptors; it also reverses bronchoconstriction thus treating lower respiratory symptoms and leads to vasodilation through its effect on beta-2 adrenergic receptors.[89] Concomitant beta-blocker use is not an absolute contraindication to immunotherapy, but their use can increase the risk of uncontrolled hypertension if anaphylaxis occurs and may require adjustments to the dosage and administration of immunotherapy.[49,83,90] If a patient on a beta-blocker receives a systemic dose of epinephrine, the beta-blocker prevents the vasodilation, leaving unopposed alpha vasoconstriction. This can result in elevation of the systolic blood pressure.[91]

For this reason, it is important for the clinician and the care team who are administering AIT to take an in-depth history which includes detailed medication history and review of the medical record, including current beta-blocker use, and to monitor the patient carefully during AIT. Consultation with the clinician prescribing a beta-blocker may be warranted if AIT is being considered. Therefore, the use of concomitant nonselective beta-blockers like propranolol is a relative contraindication to AIT[86,92] with shared decision-making (regarding the potential risk of a more severe reaction) playing an important role when considering AIT with concomitant beta-blocker use.[93]

Clinicians May Choose Not to Initiate Immunotherapy for Patients Who Have a History of Anaphylaxis

Patients with a history of anaphylaxis may also not be suitable candidates for immunotherapy. Anaphylaxis is a severe and potentially life-threatening allergic reaction that can occur suddenly and rapidly progress to a life-threatening situation. Immunotherapy can increase the risk of anaphylaxis in these patients, which may be more severe and difficult to manage. Therefore, a history of anaphylaxis is a relative contraindication to AIT with shared decision-making (regarding the potential risk of a more severe reaction) playing an important role when considering AIT in a patient who has had a history of anaphylaxis.[83,86,90,93]

Clinicians May Choose Not to Initiate Immunotherapy for Patients Who Have a History of Systemic Immunosuppression

Systemic immunosuppression, such as from chemotherapy or immunosuppressive medications, is considered relative a contraindication to immunotherapy. These patients have a weakened immune system, which may lead to an inadequate immune response to allergens and which could potentially limit the efficacy of AIT.[86,90] Immunosuppressed patients have largely been excluded from clinical immunotherapy trials and data is lacking on their response to AIT. Therefore, systemic immunosuppression is a relative contraindication to AIT.

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with HIV infection; therefore, HIV infection has been considered a relative contraindication for AIT. However, in the

past decade or so, highly active antiretroviral therapy (HAART) has improved the immune function and life expectancy in HIV-infected patients. In a small study, Iemoli et al[94] evaluated the safety and effectiveness of 1 year of therapy with SLIT-Tablet (SLIT-T) in a group of grass pollen-allergic HAART-treated HIV-positive patients (n = 13). Compared to controls, the SLIT-T-treated patients had significant improvement in symptoms, medication scores, and QOL. HIV viral load and peripheral CD4 T lymphocyte counts were also monitored and did not show significant change after treatment compared to baseline. There are 3 additional case reports in the literature that describe immunotherapy in patients with HIV, and all show clinical improvement in allergic symptoms. In one, a patient received immunotherapy for several years without a change in CD4 or HIV viral load,[95] and in the other,[96] the patient showed a transient rise in viral load and CD4 counts while on SCIT which returned to a stable baseline with ongoing HAART therapy. In 2021, Latysheva et al[97] treated 2 HIV-positive patients with birch tablet immunotherapy with no obvious side effects, but CD4 counts and viral loads were not monitored. The decision to pursue AIT in HIV-positive patients should be made after the risks and evidence are discussed with them.

Clinicians May Choose Not to Initiate SLIT for Patients With EoE

There are 3 case reports in the literature from Europe and Japan about the onset of EoE after initiation of SLIT. In 2 cases, this was after therapy with the tablet form[98,99] and the third case was with SLIT-Aq.[100] The prescribing information of the FDA-approved SLIT tablets currently available in the US lists a history of EoE as a contraindication to use. The rationale is that exposure of the esophageal mucosa to allergens in predisposed individuals could precipitate esophageal eosinophilic infiltration. This is supported by evidence in the literature which shows a seasonal prevalence of EoE[101] and a high prevalence of eosinophil infiltration of the esophagus in allergic patients in season.[102] Therefore, clinicians should not offer SLIT for patients with EoE but could still offer treatment with SCIT.

Statement 3: Asthma Assessment

Clinicians should evaluate the patient or refer the patient to a clinician who can evaluate for signs and symptoms of asthma before initiating AIT and for signs and symptoms of uncontrolled asthma before administering subsequent AIT.

Evidence Strength: Recommendation based on RCTs, CPGs, and systematic review of observational studies with a preponderance of benefit over harm.

Action Statement Profile: 3

- Quality improvement opportunity: Avoid the potential for severe systemic adverse events and the higher risk of fatality if AIT is administered (or continued) in the presence of uncontrolled asthma; decrease variability in practice if there are clinicians who do not routinely assess for uncontrolled asthma before administering AIT
  (National Quality Strategy Domains: Patient Safety, Coordination of Care, Prevention and Treatment of Leading Causes of Morbidity and Mortality)
- Aggregate evidence quality: Grade B, based on systematic review of RCTs, observational studies, and CPGs
- Level of confidence in the evidence: High
- Benefits: Improve outcomes through identifying patients potentially at risk; prevention of morbidity and mortality; facilitate further care
- Risks, harms, costs: No risks or harms; potential increase of cost and time, emotional stress, and use of resources in determining asthma diagnosis
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Not all clinicians assess asthma prior to initiation of or during AIT
- Intentional vagueness: Not defining "assessment" in the statement but supporting text does include information about patient-reported, subjective assessment and means for objective assessment
- Role of patient preferences: None
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to recommend that clinicians evaluate patients for asthma status prior to initiating AIT and assess asthma control when administering AIT to patients with co-existing asthma. Data support a positive impact of AIT on asthma outcomes and QOL in patients with mild to moderate disease.[103-109] Although there are studies demonstrating safety and tolerance of AIT in children and adults with asthma,[110,111] caution is recommended in AR/ARC patients receiving AIT who have co-morbid asthma. Asthma, especially severe asthma, is a major risk factor for severe and fatal SRs. Strategies to reduce risks with individuals with comorbid asthma may lower these risks.[63,83,112]

Severe asthma has been defined by the Global Initiative for Asthma (GINA) 2023 as asthma that is uncontrolled despite adherence with optimized high-dose ICS-long-acting beta agonist therapy and treatment of contributory factors or that worsens when high-dose treatment is decreased.[113] While there is no universal definition of uncontrolled asthma, the general consensus is that uncontrolled asthma includes poor symptom control and/or frequent exacerbations requiring oral corticosteroids or hospitalization.[63,114-117] Uncontrolled asthma has been associated with SRs to SCIT, increasing morbidity and mortality; therefore, assessment of asthma

control should be performed prior to initiation of immunotherapy as well as ongoing prior to each injection during build-up and maintenance phases of AIT.[83,112]

Screening and assessment of asthma should include subjective data through symptom screening which may include subjective and/or objective assessments. Subjective evaluation should utilize a validated symptom questionnaire such as the asthma control test (ACT),[118,119] Asthma Control Questionnaire,[120] or the Asthma Impairment and Risk Questionnaire.[121] Objective measures may include measurement of forced expiratory volume in 1 second (FEV1), peak expiratory flow, or full spirometry testing.[63,112,122] If asthma is suspected and currently undiagnosed, AR/ARC patients should be evaluated for the possible presence of comorbid asthma or referred to a clinician who can evaluate for possible asthma and help the patient reach optimal control of suspected undiagnosed asthma before initiating AIT. Likewise, if poor control of known asthma is suspected, clinicians should manage asthma, or refer to a clinician who can manage, and optimize asthma control, before continuing AIT.

In an ACAAI and AAAAI survey of clinicians providing immunotherapy, it was noted that not prescribing SCIT in individuals with uncontrolled asthma was associated with fewer Grade 3 SRs (Refer to **Table 2**).[83,112] The 2020 Focused Updates to the Asthma Management Guidelines[63] advise that clinicians should not administer SCIT in individuals with severe asthma, should not initiate or administer SCIT in patients with asthma symptoms, and should ascertain that asthma is optimally controlled before initiating SCIT to minimize the risk of harmful SRs.

Before each SCIT injection, clinicians should assess for worsening and uncontrolled asthma and withhold SCIT temporarily until asthma control is restored. Similarly, the recommendations for SLIT include administering the first dose under medical supervision after assessing for asthma control and then having the patient self-administer the remaining doses at home after receiving education on the use of autoinjectable epinephrine.[63] Strategies to mitigate risks to patients with co-existing asthma receiving AIT include not initiating AIT in patients with uncontrolled asthma until their control has stabilized and assessing mild to moderate asthmatics on SCIT prior to each injection for asthma control as well as monitoring patients after administration of AIT.[83]

Statement 4: Education Regarding SLIT Versus SCIT

Clinicians should educate patients who are immunotherapy candidates regarding the differences between SCIT and SLIT (aqueous and tablet) including risks, benefits, convenience, and costs.

Evidence Strength: Recommendation based on expert opinion regarding patient education, with a preponderance of benefit over harm.

Action Statement Profile: 4

- Quality improvement opportunity: Improve patient decision-making, standardize patient care, patient safety, and person-and family-centered care
  (National Quality Strategy: Patient Safety, Person- and Family-Centered Care)
- Aggregate evidence quality: Grade D for education regarding AIT, based on expert opinion; Grade B for the comparison of SLIT versus SCIT efficacy, based on small prospective, randomized, placebo-controlled studies and case-control studies
- Level of confidence in the evidence: High for education overall
- Benefits: Improved patient decision-making; facilitates shared decision-making
- Risks, harms, costs: Time
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Not all options are being presented to patients, there is concern about financial bias in the education provided
- Intentional vagueness: The type of education is not specified and is best tailored to the educational needs of each patient
- Role of patient preferences: None—everyone should be educated
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion:Differences of opinion: None

Supporting Text

The purpose of this statement is to promote clinician-guided education regarding SLIT (aqueous and tablet) versus SCIT in order to empower AIT candidates for the treatment of AR with an understanding of the differences in associated risks and benefits, including efficacy, convenience, and associated cost. The heterogeneity of AIT options and variations in regional practice may lead to patient confusion and inadequate outcomes. Treatment adherence is a limiting factor for all forms of AIT and may be addressed by engaging in informed decision-making and other approaches to increase trust in physicians, patient compliance, and ultimately positive treatment outcomes.[123]

Patient education is an essential step in determining the appropriate route of AIT for a given individual. While education is best held between the treating physician and patient at the time of clinical evaluation, other providers, including advanced practice providers, pharmacists, allergy nurses, and staff may also contribute.[124] Barriers to education include the associated time and volume of information to be presented. Whenever possible, a handout or other teaching aid (**Figure 1**) is recommended to facilitate patient review and understanding.[125,126]

Educating patients on the efficacy comparing SLIT and SCIT is complicated by relying on trials focused on a

CLINICAL PRACTICE GUIDELINES

PATIENT INFORMATION

TREATMENT OPTIONS FOR ALLERGEN IMMUNOTHERAPY (SCIT VS. SLIT)

Allergen immunotherapy (AIT) is a type of treatment used to reduce allergy symptoms and improve quality of life. AIT has been shown to be safe and effective for treating allergic rhinitis (hay fever). For allergens that are inhaled, AIT is usually administered using one of two methods:

- Subcutaneous immunotherapy (SCIT), which involves placing allergens under the skin with a needle
- Sublingual immunotherapy (SLIT), which involves using drops or tablets placed under the tongue

Both SCIT (shots) and SLIT (tablets and drops) are considered safe and effective. However, there are differences in associated risks and benefits, including efficacy, convenience, and cost. Patients should discuss the available options with their healthcare provider. For a more detailed comparison, please refer to the comparison table below.

COMPARISON OF SCIT AND SLIT FOR ALLERGIC RHINITIS

	SCIT (SHOTS)	SLIT (TABLETS)	SLIT (DROPS)
Safety	Higher risk of local and systemic (whole body) reactions relative to SLIT	Mild local and rare systemic reactions	Mild local and rare systemic reactions
Regulatory	Approved by the US Food and Drug Administration (FDA)	Approved by the US FDA	Not approved by the US FDA and is considered "off-label"
Administration	Given in a doctor's office during regular clinic visits	Given in a doctor's office during first dose, at home after the first dose	Given in a doctor's office during first dose, at home after the first dose
Number of Allergens Delivered	Can be tailored to match all positive allergy tests	Limited to certain allergens like grass, house dust mites (HDM), or ragweed	Can include 1 to 10 allergens, but there's some debate and evidence is limited
Efficacy	Works better compared to SLIT	Not as effective as SCIT	Not as effective as SCIT
Cost	Insurance covered	Insurance covered	Usually out of pocket

Gurgel RK, Baroody, FM, Damask, CC, et al. Clinical Practice Guideline: Immunotherapy for Inhalant Allergy. *Otolaryngology–Head and Neck Surgery*. 2024;170(S1):S1-S42.

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Figure 1. Patient information sheet for treatment options for allergen immunotherapy (subcutaneous immunotherapy [SCIT] vs. sublingual immunotherapy [SLIT]).

single allergic source (eg, grass, ragweed, or cat) to inform treating patients exhibiting multiple allergies (by history and testing). Moreover, the effective allergen dose for SCIT and SLIT is better defined for some allergens than others and better known for SLIT-T than SLIT-Aq. Also, the number of allergens delivered by SLIT-T and SLIT-Aq are substantially fewer than can be delivered by SCIT (Refer to KAS 8).

Fourteen trials comparing SCIT and SLIT were identified (**Table 6**). Generally, sample sizes were small

Table 6. SLIT Versus SCIT Trials

References	Size	Comparison	Finding
Hamada et al[127]	N = 88	NR HDM SLIT-T vs Rush SCIT	SCIT earlier efficacy (5.5 vs 18 months) SCIT more SR (18.2% vs 0) Discontinuation lower in SCIT (0/44 vs 9/44)
Mungan et al[128]	N = 36	R HDM SLIT-Aq vs SCIT vs Placebo	Rhintis Score Changes similar SCIT and SLIT and better than placebo
Knichi et al[129]	N = 71	DBRPC Birch pollen, SLIT-Aq vs SCIT	"SLIT diminished the median disease severity to one-half and SCIT to one-third of placebo treatment. No statistical significant difference between the two groups was observed"
Pokladnikova et al[130]	N = 64	R, Open Label, Grass pollen, SLIT-Aq vs SCIT vs control	"Median visual analog score for the SLIT vs SCIT group: 38 mm vs 49 mm, P.07; RQLQ for the SLIT vs SCIT group: 41% vs 48%, P.75"
Mauro et al[131]	N = 34	R Birch; SLIT-Aq vs SCIT	There was no significant difference in mean symptom-medication score between SCIT and SLIT. Systemic reactions occurred in 16% of SCIT treated but in none of SLIT treated.
Scadding et al[132]	N = 106	DBRPC, Grass, SLIT-T vs SCIT vs Placebo	2 years of SLIT did not improve primary outcome, nasal challenge, at 3 years. "Not powered to compare SLIT vs SCIT"
Ventura et al[133]	N = 40	RPC, Juniper, SLIT-Aq vs SCIT vs SLIT placebo vs SCIT placebo	ECP from nasal lavage reduced in both SCIT $P < .001$ and SLIT $P < .001$
Aasbjberg et al[134]	N = 40	R, Grass, SLIT-T vs SCIT vs Neither	Changes in immunologic markers vs controls for SCIT and SLIT. "Significant differences between SCIT and SLIT tablet were observed early, but the differences diminished with the length of treatment, especially for FAP inhibition."
Quirino et al[135]	N = 20	RPCB, Grass, SLIT/placebo SCIT vs SCIT/placebo SLIT	No significant differences in medication or symptoms scores between SCIT and SLIT. Immunologic tests improved in SCIT but not SLIT.
Yukselen et al[136]	N = 30	DBRPC, HDM, SLIT-Aq vs SCIT vs Placebo	"No statistical difference between SCIT and SLIT was observed in terms of the reduction in symptoms of rhinitis ($P = .28$), or in medication scores associated with rhinitis ($P = .18$) and asthma ($P = .31$). Only asthma symptoms decreased significantly in the SCIT group ($P = .01$) when compared with the SLIT group." SCIT significant vs placebo; SLIT not.
Keles et al[137]	N = 51	R, HDM, SCIT vs SCIT esc/SLIT maintenance vs SLIT vs Pharmacotherapy	"In the SCIT and SCIT plus SLIT groups, the number of asthma attacks and inhaled corticosteroid dosage decreased compared with baseline values at the months 4, 12, and 18 but only at month 12 in the SLIT group. The improvement in visual analog scores for rhinitis was significant only in the SCIT plus SLIT group."
Tahamiler et al[138]	N = 193	Randomized, HDM, SCIT vs SLIT- SLIT-Aq	SCIT statistically superior to SLIT at 3 years and at 3 years after discontinuation for total symptoms.
Piazza and Bizzaro[139]	N = 57	Open, HDM, SCIT vs SLIT-Aq vs Nasal vs Control	"Subcutaneous, but not sublingual and nasal, immunotherapy induced a significant clinical benefit ($P < .001$)"
Eifan et al[140]	N = 48	RC, Open, HDM, SCIT vs SLIT-Aq vs Control	SCIT and SLIT showed significant symptoms improvement to control and baseline. No significant difference between SCIT and SLIT.

(11/14 trials N < 100) with heterogeneity in the study designs. Three trials were double-blind, randomized, placebo-controlled trials (DBRPCTs), 9 were not blinded but randomized, and 2 were nonrandomized. Four trials had no placebo or control, 5 had a placebo arm, and 5 had a nonplacebo control arm. Statistically similar efficacy between SLIT and SCIT was found for clinical endpoints in 11/14 trials. Three house dust mite (HDM) trials comparing SLIT-Aq versus SCIT concluded SCIT to be more effective. Overall, small trials comparing SLIT and SCIT generally show efficacy for both against baseline, controls, or placebo while favoring SCIT. The trials are often underpowered to compare 2 effective therapies to each other, and there is a scarcity of DBRPCTs.

Both SCIT and SLIT are cost-effective and safe interventions for the treatment of AR (**Table 7**). When comparing the 2, general trends emerge. While both interventions have an established safety profile, sublingual routes (aqueous and tablets) have a relatively lower prevalence of SRs.[141] This allows many providers to offer SLIT as a home-based intervention with daily administration without direct physician oversight. Additionally, there are Canadian and European data stating that SLIT (tablets or drops) is more cost-effective than SCIT.[142-144] Many variables may impact the cost of SCIT and SLIT. When indirect costs, such as patient time and travel, are considered, the cost may be comparable.[68,145-151]

Patient counseling can be supplemented by written handouts, consent forms, online resources, and information provided through the electronic medical record (ie, after visit summaries). Education may be imparted by physicians, advanced practice providers, and allergy nurses among others. Parents and caregivers should be included in the education. A sample patient handout comparing SLIT and SCIT is provided in **Figure 1**.

In conclusion, there is evidence for SCIT, SLIT-Aq, and SLIT-T providing safe and effective immunotherapy options. Clinicians should educate immunotherapy candidates about their options and employ shared decision-making.

Statement 5: Education Regarding Preventive Qualities of AIT

Clinicians should educate patients about the potential benefits of AIT in (1) preventing new allergen sensitizations, (2) reducing the risk of developing AA, and (3) altering the natural history of the disease with continued benefit after discontinuation of therapy.

Evidence Strength: Recommendation based on MAs reviewing the benefits of AIT in preventing new allergen sensitization and preventing AA with a preponderance of benefit over harm.

Action Statement Profile: 5

- Quality improvement opportunity: Increasing awareness of secondary benefits of AIT; prevention and treatment of morbidity and mortality; promoting most effective treatment practices; person and family-centered care, health, and well-being of communities to enable healthy living (National Quality Strategy Domain: Person- and Family-Centered Care)
- Aggregate evidence quality: Grade B, based on MAs and systematic reviews of observational studies and RCTs; Grade D for the educational component of the statement
- Level of confidence in the evidence: Medium
- Benefits: Informing the patients, allowing for shared decision-making, may influence the decision to receive AIT
- Risks, harms, costs: Time, cost of educational materials
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: These concepts are not consistently included in patient education
- Intentional vagueness: Education: not outlining techniques or curriculum; use of the word "potential" because the literature regarding the exact degree of benefit is not consistent
- Role of patient preferences: None

Table 7. Comparison of SCIT and SLIT Modalities of Allergen Immunotherapy (AIT) for Allergic Rhinitis (AR)

	SCIT	SLIT (tablets)	SLIT (aqueous)
Safety	Increased risk of local and systemic reactions relative to SLIT	Mild local and rare systemic reactions	Mild local and rare systemic reactions
Regulatory	US FDA approved	US FDA approved	Not US FDA-approved (off-label)
Administration	Regular clinic visits	Home after first dose	Home after first dose
Number of allergens delivered	Can mirror all selected allergens	Limited to Grass, HDM, or Ragweed	1-10 (debated with limited evidence)
Efficacy	Improved vs SLIT	Decreased vs SCIT	Decreased vs SCIT
Cost	Insurance covered	Insurance covered	Usually out of pocket

This table is meant to be a quick reference summary. Variations exist.
Abbreviations: AIT, allergen immunotherapy; FDA, Food and Drug Administration; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this KAS is to emphasize the importance of patient education about the qualities of immunotherapy in preventing new sensitizations, development of asthma, and altering the natural history of the disease with continued benefit after discontinuation of therapy. There are various means to educate patients. These involve detailed discussions in the clinic with documentation of education in the medical record. Patient education may be supplemented by patient handouts and educational materials which should be written in layman's terms in order to facilitate appropriate understanding by patients (**Figure 2**). Patient education should be informed by the available evidence which is reviewed here. Multiple systematic reviews, MAs, randomized controlled clinical trials, CPGs as well as observational studies have investigated this topic.

Immunotherapy-induced immunological changes

In contrast to other treatments for AR, AIT (both SCIT and SLIT) has been shown to induce sustained immunological changes which likely underlie observed sustained clinical benefits. These include a reduction in mast cell and basophil degranulation; an initial increase then decrease in serum-specific IgE (sIgE) and increase in allergen-specific IgG (sIgG) blocking antibodies; generation of allergen-specific regulatory T and B cells and suppression of allergen-specific effector T cell subsets and innate lymphoid cells; and reduction in tissue mast cells and eosinophils accompanied by a decrease in type I skin test reactivity.[152,153]

Potential benefit of AIT in reducing new allergen sensitization

There is mixed evidence to support the fact that AIT is effective in reducing the likelihood of developing new allergen sensitizations in patients. In a systematic review of 18 studies involving 1049 children and 10,057 adults, Di Bona et al noted that 10/18 studies showed evidence that AIT prevents the onset of new sensitizations compared to placebo treatment. Six out of the ten positive studies were performed in children and the highest benefit was most obvious in small studies and those with shorter follow-up.[154,155] This effect was not statistically significant. For children at high hereditary risk of atopy (≥2 first-degree relatives with allergic disease), the use of SLIT-Aq with HDM in early life (starting treatment when children were less than 1 year of age) led to a significant reduction in sensitization to any common allergen in the active group compared to placebo.[156] The evidence for the prevention of new sensitizations by AIT is limited to pediatric studies likely because the rate of new sensitizations is higher earlier in life.

Potential benefits of AIT in preventing the development of asthma

A 3-year observational study demonstrated that the use of AIT in children with AR suppressed the development of asthma, and the suppression was preserved for 7 years after the end of AIT.[157] Valovirta et al performed a randomized, double-blind, placebo-controlled trial in 812 children with AR and no medical history or signs of asthma with the aim of evaluating the effect of AIT on the risk of developing asthma.[158] The children were treated with grass SLIT-T or placebo for 3 years and followed for 2 years after cessation of therapy. There was no difference in time to the onset of asthma, defined by prespecified asthma criteria relying on documented reversible impairment of lung function (primary endpoint). However, treatment with SLIT-T significantly reduced the risk of experiencing asthma symptoms or using asthma medication at the end of trial (odds ratio = 0.66, $P < .036$), during the entire 5-year period and the 2-year posttreatment follow-up. The number needed to treat (NNT) to prevent an additional child from both having asthma symptoms and using asthma medication was 10. However, the younger the children were at treatment start, the greater the benefit, thus the NNT to prevent 1 additional child from having asthma symptoms and asthma medication use was NNT = 6 for children aged 5 and NNT = 20 for children aged 12.[158-161] Furthermore, a small double-blind placebo-controlled study investigated the prevention of asthma using HDM AIT and demonstrated that early-life administration might reduce the onset of childhood asthma.[162] In addition to these individual studies, a 2017 MA of 32 studies evaluated the preventive effects of AIT (SCIT and SLIT) in the prevention of new allergic diseases.[70] Random-effects MA of 6 RCTs that evaluated the new onset of asthma in patients with AR demonstrated a significant reduction in the risk of developing asthma at the end of the trials (2-year duration) with relative risk (RR) = 0.40 (95% confidence interval [CI]: 0.30-0.54). There was no conclusive evidence that this benefit was maintained over the longer term. In 2022, Farraia et al performed a systematic review (24 studies) and MA (18 studies) and showed a significant 25% decrease in the risk of developing asthma following AIT (SCIT and SLIT).[163] However, after excluding studies with high risk of bias the result did not remain significant. Upon subgroup analysis, there was a remarkable preventive effect of AIT in children (RR, 95% CI: 0.71, 0.53-0.96), when completing 3 years of therapy (RR, 95% CI: 0.64, 0.47-0.88), and in mono-sensitized patients (RR, 95% CI: 0.49, 0.39-0.61) supporting a protective effect when certain criteria are met. Therefore, the use of AIT for patients with AR may reduce the onset of asthma and reduce asthma symptoms and medication use and the effect seems most robust in children.

Continued symptomatic benefit after discontinuation of AIT

AIT is a disease-modifying treatment and may include preventive effects beyond AIT cessation. The use of AIT for

CLINICAL PRACTICE GUIDELINES

PATIENT INFORMATION

Frequently Asked Questions (FAQs) About Allergen Immunotherapy

WHAT IS ALLERGEN IMMUNOTHERAPY AND HOW DOES IT WORK?

Allergen immunotherapy (AIT) is a type of treatment used to reduce allergy symptoms and improve quality of life. This is done by giving regular and repeated doses of an allergen (a substance that causes allergies) or allergens. Examples of allergens that you can inhale include pet dander, pollen, ragweed, grass, and dust mites. By taking gradually increasing doses of these allergens, your immune system builds up a tolerance and becomes less sensitive.

WHO SHOULD GET ALLERGEN IMMUNOTHERAPY?

If you are 5 years and older, experience symptoms from allergic rhinitis, and have positive allergy test results, you may be a candidate for AIT. Allergic rhinitis (hay fever) is a condition in which the inside of the nose becomes inflamed and irritated. This happens when your body's immune system reacts to an allergen. Symptoms can include sneezing, itchy or runny nose, and nasal congestion (blockage). If you are unable to manage your symptoms with regular medication and prefer a treatment with lasting benefits, AIT may be the right treatment option for you.

WHAT ARE THE DIFFERENT IMMUNOTHERAPY TREATMENT OPTIONS?

For inhalant allergens, AIT is usually administered using one of two methods:

- Subcutaneous immunotherapy (SCIT), which involves placing allergens under the skin with a needle
- Sublingual immunotherapy (SLIT), which involves using drops or tablets placed under the tongue

Both treatment options have differences in associated risks, benefits, efficacy, convenience, and cost. Your health care providers should discuss the available options to determine what works best for you.

WHAT ARE THE BENEFITS COMPARED TO OTHER TREATMENT OPTIONS?

Unlike other treatments, AIT can lead to lasting benefits even after stopping treatment. This is because it changes the way your body reacts to allergens. This can reduce the need to take other medications which provides cost savings and convenience. There is also evidence that AIT can prevent the onset of new allergies, asthma, and reduce asthma symptoms.

HOW DO YOU DETERMINE WHICH ALLERGENS TO TREAT?

Your health care provider will identify allergens based on an assessment of several factors. This includes your symptoms, medical history, the season of symptoms, and allergy test results. Based on these factors, your health care provider will determine which allergens to include in your treatment regimen that deliver the best possible results.

WHAT IF I HAVE MULTIPLE ALLERGIES?

You can take AIT to treat multiple allergies at the same time. Your health care provider may choose to treat one or a few allergens or multiple allergens. Studies show that both methods are safe and effective. Treating with even a few allergens can change your body's response to other allergens. There is currently no evidence that show if one method is better than the other.

HOW LONG DOES IT TAKE TO SEE THE BENEFITS?

You can expect to see a decrease in symptoms in the first year of AIT. It is generally recommended to continue taking doses for at least three years for maximal benefit. This period of time is believed to induce benefits that continue for at least one year after stopping treatment. Currently, there are a limited number of studies that show how long you should stay on AIT and if you will stay symptom-free after stopping treatment. The decision to continue or stop as well as the associated risks and benefits should be discussed with your health care provider.

WHAT ARE THE RISKS?

Both SCIT (shots) and SLIT (tablets or drops) are considered safe and effective treatment options. However, they can induce a severe and potentially life-threatening reaction - called anaphylaxis – on rare occasions. Anaphylaxis can affect different parts of your body. Signs and symptoms can range from mild to severe. Your healthcare provider should know how to recognize and treat this rare side effect if it happens.

Before receiving AIT, your health care provider should assess your asthma status and discuss all potential risks. This includes the signs and symptoms of anaphylaxis and how to use epinephrine, which is the main treatment for anaphylaxis.

WHO SHOULD NOT GET ALLERGEN IMMUNOTHERAPY?

There are specific situations where AIT may not be suitable due to increased risks of adverse events. Before starting or continuing AIT, you should discuss with your health care provider if you:

- Are pregnant
- Have uncontrolled asthma
- Are unable to tolerate injectable epinephrine
- Use beta-blockers
- Have a history of anaphylaxis
- Have a weakened immune system
- Have eosinophilic esophagitis (EoE). Worsening of EoE is a concern only for SLIT (tablets or drops).

Gurgel RK, Baroody, FM, Damask, CC, et al. Clinical Practice Guideline: Immunotherapy for Inhalant Allergy. *Otolaryngology–Head and Neck Surgery*. 2024;170(S1):S1-S42.

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Figure 2. Patient information sheet for frequently asked questions (FAQs) about allergen immunotherapy. AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

patients with seasonal AR due to grass and/or cedar pollen or HDMs resulted in a sustained reduction in symptoms and medication use that lasted 3 to 5 years after discontinuation supporting the alteration of the natural history of the disease with AIT.[164-167] The potential to discontinue medications for AR after successful AIT adds the benefit of cost savings and convenience to the patient.

In summary, the potential benefits of immunotherapy in preventing new sensitization and the development of asthma as well as maintaining clinical benefit for AR symptoms should be part of AIT patient education.

Statement 6: Pre-/Co-seasonal Therapy

Clinicians who administer SLIT to patients with seasonal AR should offer pre-/co-seasonal immunotherapy.

Evidence Strength: Recommendation based on MAs and RCTs with a preponderance of benefit over harm.

Action Statement Profile: 6

- Quality improvement opportunity: Increase utilization for patients with seasonal AR; increases patients' options for therapy
  (National Quality Strategy Domains: Prevention and Treatment of Leading Causes of Morbidity and Mortality, Making Quality Care More Affordable)
- Aggregate evidence quality: Grade A/B, based on placebo-controlled RCT and MAs for efficacy of pre-/co-seasonal therapy and comparison of efficacy between the 2 treatment models
- Level of confidence in the evidence: High
- Benefits: Decreased cost; patient convenience; no need to be on therapy all year-long; patient safety
- Risks, harms, costs: Unclear if it alters the natural history of the disease or if it imparts prolonged benefit; possible undertreatment in the polysensitized patient; costs
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Not all options are being presented to patients; there is concern about financial bias in the education provided
- Intentional vagueness: None
- Role of patient preferences: None for offering; high for patients regarding treatment selection
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

Efficacy of Pre-/Co-Seasonal SLIT

There is evidence to support the efficacy of pre-/co-seasonal (refer to definitions in **Table 1**) and continuous SLIT on allergic respiratory disease. Multiple double-blind, placebo-controlled, randomized trials of pre-/co-seasonal administration have shown efficacy for both tablets and SLIT-Aq. Pollen SLIT-Aq has shown improvement in AR symptoms (vs. placebo) using birch[168] and ragweed extracts.[169,170] For SLIT-T, efficacy and safety have also been shown using 5-grass pollen SLIT-T[171-173] and ragweed SLIT-T.[174,175] A study showed that initiation of SLIT using pollen tablets must be done at least 8 weeks prior to grass pollen season in order to observe clinical efficacy (**Figure 3**).[176] A pre-seasonal treatment period longer than 8 weeks improves the clinical efficacy (relative to placebo) during the grass pollen season.[176,177] The magnitude of reductions in AR symptoms and medication scores increased with duration of preseasonal treatment with 4 months being optimal.[176]

Comparison of Pre-/Co-Seasonal Versus Continuous SLIT Regimens

There are few studies examining head-to-head comparisons between pre-/co-seasonal and continuous regimens for seasonal AR. Indirect comparison by MA of co-seasonal versus continuous SLIT and comparison of standard titration versus ultrarush titration of pollen extracts each showed improvements in AR symptoms and medication-use scores as compared to placebo.[178,179] In these studies, no differences in efficacy were found between regimens. A 3-year open randomized clinical trial comparing co-seasonal versus continuous regimen in children showed equivalent improvement in AR symptoms and medication use scores.[180] Another study of 60 children, using both pre-/co-seasonal and continuous regimens demonstrated improvement in overall AR symptoms and medication use scores.[181] However, the pre-/co-seasonal group had significantly improved nasal symptoms of rhinorrhea, sneezing, itching, and nasal congestion as compared to the continuous regimen group. A small, open-label, non-blinded, head-to-head study comparing pre-seasonal (10-week pre-/co-seasonal, n = 11) vs continuous (n = 10) regimen of pollen extract demonstrated no difference in efficacy in AR symptoms as measured by visual analog scales between the 2 regimens.[182] In addition, pre-/co-seasonal regimens are hypothesized to have better economic and compliance benefits relative to continuous regimens by virtue of their

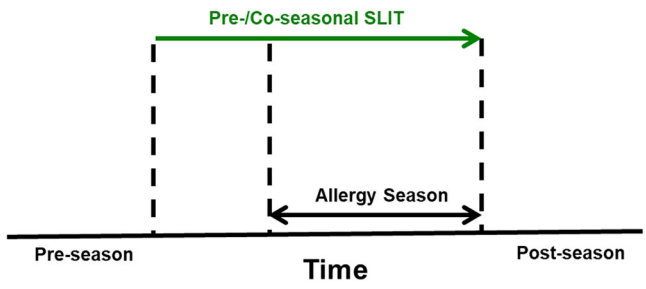

Figure 3. Time course of sublingual immunotherapy (SLIT) administration. Pre-/co-seasonal SLIT is initiated optimally at 8 weeks prior to onset of allergy season and continues until the end of season. This figure demonstrates the timing of pre-/co-seasonal treatment in relation to the allergy season. Figure is created by the clinical practice guideline development group.

shorter duration of treatment.[183] Again, head-to-head studies are lacking.

Evidence for Disease Modification by SLIT

The evidence of persistent disease modification using pre-/co-seasonal administration has not been well studied. Presently, only pre-/co-seasonal SLIT for grass has evidence of sustained posttreatment efficacy.[171,183,184] A pre-/co-seasonal grass tablet study[171,172] reported sustained improvement in medication use and symptoms scores during years 4 and 5 after 3 years of pre-/co-seasonal therapy (Refer to KAS 10 for details). There is a multi-institutional, placebo-controlled trial, of pre-/co-seasonal SLIT droplet extract of mixed grass pollens (treatment was given for 4 months a year) treatment for 3 years duration which resulted in reduction of AR symptoms and 2.5 fold reduction in the development of asthma.[185]

Safety

There are no head-to-head studies comparing the adverse effects of pre-/co-seasonal versus continuous SLIT.

In summary, pre-/co-seasonal SLIT has been shown to be a safe and effective option for controlling seasonal AR and should be included in discussions with patients to allow for shared decision-making.

Statement 7: Selecting Clinically Relevant Allergens

Clinicians prescribing AIT should limit treatment to only those clinically relevant allergens that correlate with the patient's history and are confirmed by testing.

Evidence Strength: Recommendation based on cohort studies and expert opinion with a preponderance of benefit over harm.

Action Statement Profile: 7

- Quality improvement opportunity: There may be overtreatment (treating for more allergens than needed) which could lead to unnecessary use of resources
  (National Quality Strategy Domain: Making Quality Care More Affordable, Coordination of Care, Prevention and Treatment of Leading Causes of Morbidity and Mortality)
- Aggregate evidence quality: Grade D, based on expert opinion for how well clinicians can correlate symptoms and specific test results; Grade C, based on cohort studies for evidence that positive allergens on testing may not be associated with cause of symptoms
- Level of confidence in the evidence: Medium
- Benefits: Preventing overtreatment, cost effective; decrease risk of adverse reactions; socioeconomic costs (including time)
- Risks, harms, costs: Undertreatment; choosing clinically insignificant allergens; no improvement if choosing the wrong allergen(s); potential for adverse events or side effects; time; inconvenience; and cost to repeat AIT with different allergens
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Clinicians are not correlating test results with symptoms and are treating for positive results of allergens that don't cause symptoms
- Intentional vagueness: The use of the terms "relevant" and "correlate" was intentionally vague as there may be overlap of symptoms between allergens; the GDG wanted to leave this discretion to the prescribing clinician; the use of the term clinically relevant was used because of the difficulty in linking symptoms to a specific allergen and requires a combination of history; testing and knowledge of exposures
- Role of patient preferences: None
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to avoid selecting allergens for AIT treatment that are unlikely to benefit the patient. The presence of a positive allergy test (sensitization) does not always indicate clinical AR. Clinical assessment of allergy patients is currently the best way to select which allergens are most relevant to a patient's symptoms. Additionally, most of the SCIT and SLIT studies demonstrating efficacy were performed using 1 to a few selected allergens (Refer to KAS 8). There may be a range of acceptable allergen selections used in AIT as history and physical findings for AR may not be specific for the causative allergen(s), but clinical assessment including the season of symptoms, triggering exposures, and knowledge of allergens should be combined with allergy test results to select allergens for immunotherapy.

The Centers for Disease Control and Prevention has conducted allergy testing on representative samples of the US population (independent of clinical allergy) for both allergy skin testing and sIgE allergen testing. They found 54% of the population were positive to at least 1 allergy skin prick test[186] and 43.7% were positive to at least 1 sIgE test.[187] European cohorts diagnosing AR by history and allergy testing have estimated clinically significant AR in around 15% of the population.[15-17] While the percentage of the population that has clinical AR varies markedly across regions and epidemiologic studies,[11,12] positive allergy tests appear to be substantially more common than the combination of positive allergy testing and clinical symptoms of AR. Positive allergy tests in the absence of clinical allergy are also seen in food allergy[188] and venom allergy.[189]

Studies that have tried to associate an allergy test result with clinical allergic history specific for a particular allergen have not consistently shown a strong correlation.[190,191] In a study of pregnant women the positive predictive value for a positive allergy test for cat or ragweed was only 44.7 and 50.3, respectively.[192] These women were not selected for bothersome AR, and the association maybe stronger when symptoms are more bothersome (such as in those considering AIT). Allergy testing in the absence of correlating allergy symptoms may be unreliable.

Patients reporting allergy symptoms may have negative testing. This may be due to the overlap of symptoms with non-AR or other nasal pathology. Also, some patients have been found to have allergen-sIgE present in the nasal tissue and AR symptoms, when skin tests or serum sIgE tests are negative.[193] This is often called "local allergy." How to best evaluate and treat patients with local allergies is still evolving in the medical literature.[9]

There are conflicting studies about whether AIT is specific to the allergen used or if AIT also down regulates allergic inflammation through nonallergen-specific mechanisms. A few studies have shown that AIT benefit is specific only to the allergens used in immunotherapy,[194-196] but there are also studies showing similar benefits in both single-sensitized and poly-sensitized patients during single or limited AIT (Refer to KAS 8).[197-202] The mechanism of AIT is not fully deciphered, but allergen-sIgG and IgE changes (B lymphocyte-mediated) and allergen-nonspecific mechanisms (T lymphocyte-mediated) have been observed.[203]

Studies looking at allergen selection variances tend to show more allergens selected for SCIT in the United States and fewer allergens selected in Europe, Canada, and SLIT. One survey found 4 times as many allergens used in US patients (18 allergens) than in Canadian patients (4 allergens).[204] These variances suggest that limiting treatment allergens to those most associated with symptoms may yield similar benefits. Preferentially selecting standardized allergens (less variability in antigenicity) and allergens known to cause symptoms in a higher portion of the allergic population also seems reasonable when the clinical assessment is less specific. Clinician knowledge of local pollens and allergic exposures also can benefit choosing allergens for effective immunotherapy. The effective dose varies among allergens and varies between SCIT, SLIT-T, and SLIT-Aq which should be included in shared decision-making with the patient on AIT formulations. Both allergy testing results and formulation/prescription for SCIT and SLIT should be documented in the medical record.

In conclusion, selecting allergens for immunotherapy should be informed by the patient's history, exam, and allergy test results. Shared decision-making between the provider and immunotherapy patient should be utilized in selecting allergens for AIT.

Statement 8: Treating Polysensitized Patients With Limited Allergens

Clinicians may treat polysensitized patients with a limited number of allergens.

Evidence Strength: Option based on post hoc observational studies of RCTs with a balance of benefits and harms.

Action Statement Profile: 8

- Quality improvement opportunity: Reduce cost, patient convenience; reduce risk of adverse events and improve patient safety
  (National Quality Strategy Domain: Prevention and Treatment of Leading Causes of Morbidity and Mortality, Making Quality Care More Affordable, Coordination of Care)
- Aggregate evidence quality: Grade C, based on post hoc observational studies of RCT trial patients
- Level of confidence in the evidence: Medium
- Benefits: Lower cost; reduce unnecessary treatment; option of tablet or SLIT-Aq; improved patient safety; reduced adverse events
- Risks, harms, costs: Not achieving optimal control (undertreatment); undertreatment could require additional or prolonged treatment; cost may be less if effective; cost and time may be more if not effective
- Benefits-harm assessment: Balance of benefits and harms
- Value judgments: Potentially, not all clinically relevant allergens need to be treated
- Intentional vagueness: None
- Role of patient preferences: Moderate, discussion about not needing to treat all positive test results
- Exceptions: None
- Policy level: Option
- Differences of opinion: None

Supporting Text

The purpose of this statement is to address whether every, or even most, positive and relevant allergens identified in patient allergy testing should be included in an allergy treatment regimen.

Definitions

- "Monotherapy" describes treating a patient with AIT, either by sublingual route or by subcutaneous injection, with the use of only 1 allergen.
- "Pauci-therapy" is a term used for treating allergic patients with limited AIT using less than the number of positive allergy tests. A precise number is not specified. The prefix "pauci" is derived from the Latin word for "few."[205]

In the years following the early 20th-century advent of AIT, different patterns have emerged relating to the treatment of polysensitized patients. One variation in care

is how many of the allergens identified by testing are utilized in AIT (Refer to KAS 7). The most notable difference has been choosing how many of the positive allergens to include in AIT. One philosophy, popular in Europe and other locations, is to select 1 or very few of the positive allergens for therapy.[206,207] Alternatively, other allergists, commonly in the United States, will treat all, or nearly all, allergens showing a positive response on allergy testing and potentially associated with allergic symptoms.[194,195,204,208] Both practice patterns have demonstrated clinical benefits with an acceptable safety profile over the years. No definitive head-to-head trial exists. In the absence of data showing clear superiority, this dichotomy has continued to the present day.

The arrival of US FDA-approved SLIT tablets has reenergized this discussion. SLIT tablets are available in the US for grass, ragweed, and HDMs. SLIT-Aq allows for the administration of treatment with multiple allergens simultaneously. However, SLIT-Aq is not FDA approved, and thus "off-label" in the United States. As a result, it will usually be "out of pocket" and not covered by most commercial or government insurance providers. Therefore, additional allergens administered would incur additional costs. This has precipitated increased interest in the use of 1 or very few allergens in the treatment of polyallergic patients. Presently, evidence indicates that in some populations, single-agent immunotherapy such as HDM or grass is sufficient to provide satisfactory control of symptoms in polyallergic patients.[197-201]

In the absence of robust prospective studies, evaluation of mono- or pauci- AIT compared to multiallergen AIT (use of all significant positive and relevant allergenic responses) relies upon post hoc evaluations, MAs, and studies related to assessment of SLIT-T.[209-211]

Pauci-immunotherapy may work by non-specific down-regulation of allergic inflammation through mediators such as interleukin-10 or T-regulatory lymphocytes. Cross-reactivity between allergens may also play a role.

Cross-reactivity refers to different species causing allergies through the same or very similar IgE binding sites. Specific examples have been described, such as the birch allergen providing "cross-reactive" immune relief to certain related tree species.[211] Cross-reactivity may partially explain why single- or few-allergen therapy decreases overall symptoms. Further information and guidance on this topic may be forthcoming as testing mechanisms for component-resolved diagnostics (CRD) becomes more available in clinical medicine.[212,213]

At this time, there is satisfactory evidence to support the use of multiple AIT, and also evidence in favor of using 1 or a few allergens as therapy by subcutaneous or sublingual routes. There is insufficient and conflicting evidence to suggest that 1 format is superior. It is considered a reasonable option to offer single, or a few selected allergens for immunotherapy to patients as an alternative to multi-AIT, when based upon a patient's clinical picture and the results of allergy testing.

Statement 9: LRs and AIT Escalation

Clinicians administering AIT should continue escalation or maintenance dosing when patients have LRs to AIT.

Evidence Strength: Recommendation based on prospective case-controlled studies, with a preponderance of benefit over harm.

Action Statement Profile: 9

- Quality improvement opportunity: Delay in getting to effective dosing
  (National Quality Strategy Domain: Patient Safety)
- Aggregate evidence quality: Grade B, based on prospective case-controlled studies
- Level of confidence in the evidence: High
- Benefits: No delay in optimal treatment dosage; patient does not have to undergo additional injections; cost savings; saves on additional resources; improved compliance
- Risks, harms, costs: Localized discomfort; may discontinue therapy due to anxiety related to LRs; emotional stress to clinician and patient
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Clinicians may misinterpret the role of dose adjustment based on LRs as precursors to SRs
- Intentional vagueness: When referring to AIT in the KAS, The GDG did not specifically refer to SCIT or SLIT. While the literature profile is primarily derived from SCIT, the GDG agreed that this applies to all AIT. Size of the LR was not defined
- Role of patient preferences: Low. While the patient should have little input on dose adjustments, some patients may opt to discontinue therapy based on LRs
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: There was some difference of opinion in which a member of the panel would hold off escalating dosing with large LRs (LLRs), but did not have literature to cite in this regard

Supporting Text

Adverse reactions to SCIT include LR and SRs. LRs are defined as any swelling located at or near the injection site following an allergen injection.[214] Many different size definitions have been used to differentiate an LR from an LLR. LLRs have been variously defined as (1) induration of >25 mm or 12-hour duration, (2) >20 mm or >24-hour duration, (3) >40 mm, and (4) larger than the size of the patient's palm (8-10 cm).[214,215]

Historically, textbooks of allergy recommended dosage adjustments secondary to LLRs.[216] Adjustments were recommended as LLRs were considered to foretell a future SR should the SCIT dosage be increased. This mindset was the likely basis for the practice of dosage adjustments for LLRs until subsequent literature and studies demonstrated that this was not the case.[214] This changing paradigm represents an opportunity for quality improvement.

The 1988 World Health Organization (WHO) position paper on SCIT referenced 2 articles that both demonstrated that the occurrence of an LR was not predictive of a future SR and that LLRs usually did not precede SRs, respectively.[217,218] In 2000, the WHO maintained the position that LRs were not predictive of an increased risk of anaphylaxis and that LRs did not require subsequent dose adjustments.[219]

Tankersley et al,[220] in 2000, studied the rates of LRs and SRs over an 18-month period at a single-site allergy clinic. During the second 9 months, no dose adjustments were made secondary to LRs unless the reaction was larger than the patient's palm (adult; 8-10 cm) or resulted in significant patient discomfort. They found no differences in SR rates, LR rates in patients experiencing SRs, or LR rates preceding SRs when the SCIT dosages were adjusted because of LRs. They concluded that dose adjustments for LRs were unnecessary, delayed progression to maintenance, potentially increased administration errors, and resulted in additional injections and visits which impacted compliance and resulted in increased costs.

Eliminating dosage adjustments secondary to LRs results in the same rate of SRs to SCIT as making dosage adjustments, however, eliminating dose adjustments resulted in fewer delays in reaching maintenance, increased patient compliance, and decreased costs.[221,222] In 2009, Calabria et al[223] found that LRs are not predictive of subsequent LRs at the next SCIT injection and also concluded that LRs should not be used to make SCIT dose adjustments.

There have been 2 studies that have evaluated the association between an increased frequency of LLRs and SRs while on SCIT.[224,225] These studies demonstrated that LLRs are not predictive of SRs, however, a subgroup of patients with LLRs do experience a higher frequency of SRs during their SCIT course. This association occurs irrespective of dosage adjustments.

In conclusion, LRs are not predictive of SRs and routine dosage adjustments for LRs are not supported by the literature. Moreover, the association of frequent LRs and increased frequency of SRs occurs whether or not dose adjustments are made. Patients should be counseled that escalating dosage after an LR does not increase the risk of subsequent LR or SR.

Statement 10: Anaphylaxis Identification and Management

The clinician performing allergy skin testing or administering AIT must be able to diagnose and manage anaphylaxis.

Evidence Strength: Strong recommendation based on systematic reviews, randomized-controlled studies, and CPGs with a preponderance of benefit over harm.

Action Statement Profile: 10

- Quality improvement opportunity: Missing signs of anaphylaxis; discharging a patient from health care setting too soon after administering AIT; staff is not adequately trained to monitor patients after testing or immunotherapy
  (National Quality Strategy Domain: Patient safety, Prevention and treatment of leading causes of morbidity and mortality)
- Aggregate evidence quality: Grade A based on systematic reviews, RCTs, and CPG
- Level of confidence in the evidence: High
- Benefits: Prevent morbidity and mortality
- Risks, harms, costs: Misidentification of anaphylaxis, misdiagnosis, cost for emergency room and medical treatment, patient anxiety
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: The clinician who does not routinely administer AIT does not always identify anaphylaxis effectively or may misidentify anaphylaxis. If a clinician is administering AIT or performing allergy skin testing, patient monitoring is important. Only clinicians appropriately trained in the identification and management of anaphylaxis should be performing skin testing and administering AIT
- Intentional vagueness: None
- Role of patient preferences: None
- Exceptions: None
- Policy level: Strong recommendation
- Differences of opinion: None

Supporting Text

The clinician performing skin testing or administering AIT should be able to identify and treat anaphylaxis associated with allergy skin testing and AIT administration.

SCIT is a safe and unique method for managing patients with AR, ARC, and AA. Although systemic and fatal reactions are rare, they are of primary concern when administering AIT. A surveillance study of SRs from SCIT injections in North America estimates that the incidence of fatal reactions is 1 in every 7.2 million injection visits, with asthma consistently noted as a comorbid condition in patients with fatal reactions.[83] While there are anecdotal reports of anaphylaxis to SLIT with FDA-approved tablets or SLIT-Aq, none were fatal.[226] Clinicians administering AIT must remain vigilant, should be familiar with recognizing the signs and symptoms of anaphylaxis, and be prepared to render emergency management. Similarly, patients should also be educated to recognize the signs and symptoms of

anaphylaxis as well as being educated on how to administer epinephrine.

Anaphylaxis is a systemic, potentially life-threatening syndrome typically with multiorgan involvement.[93] The signs and symptoms of anaphylaxis can vary from mild to severe, including hives, swelling, itching, respiratory distress, chest pain, abdominal pain, and hypotension. The most severe form of anaphylaxis can lead to cardiovascular collapse and death. Over the years, there have been various definitions/criteria for diagnosis of anaphylaxis with similarities and differences being most notably between the 2006 NIAID and 2020 WAO anaphylaxis criteria (Refer to **Figure 4**).[227,228]

Most severe reactions occur within 30 minutes, informing the recommendations that clinicians should monitor patients for at least 30 minutes after administering SCIT.[3,50,229,230] Among practices monitoring patients for at least 30 minutes after SCIT, approximately 15% of SRs occur later than 30 minutes after injection,[50] and reactions extending up to 2 hours postinjection have been reported.[231,232] Members of the ACAAI and the AAAAI complete an annual survey of SCIT-related SRs with strategies to enforce postinjection waiting times and to reduce risks from asthma/severe asthma. In the 2008 to 2018 survey, it was noted that practices that tracked the time after injections and required checking out with office personnel had significantly lower total Grades 3 and 4 SRs (Refer to **Table 2**).[83]

Differentiating between vasovagal syncope and anaphylaxis can be challenging, as both can present with similar symptoms. Vasovagal syncope may present with prodromal symptoms of nausea and diaphoresis, while anaphylaxis is commonly associated with urticaria and respiratory distress. The lack of pruritus in the presence of

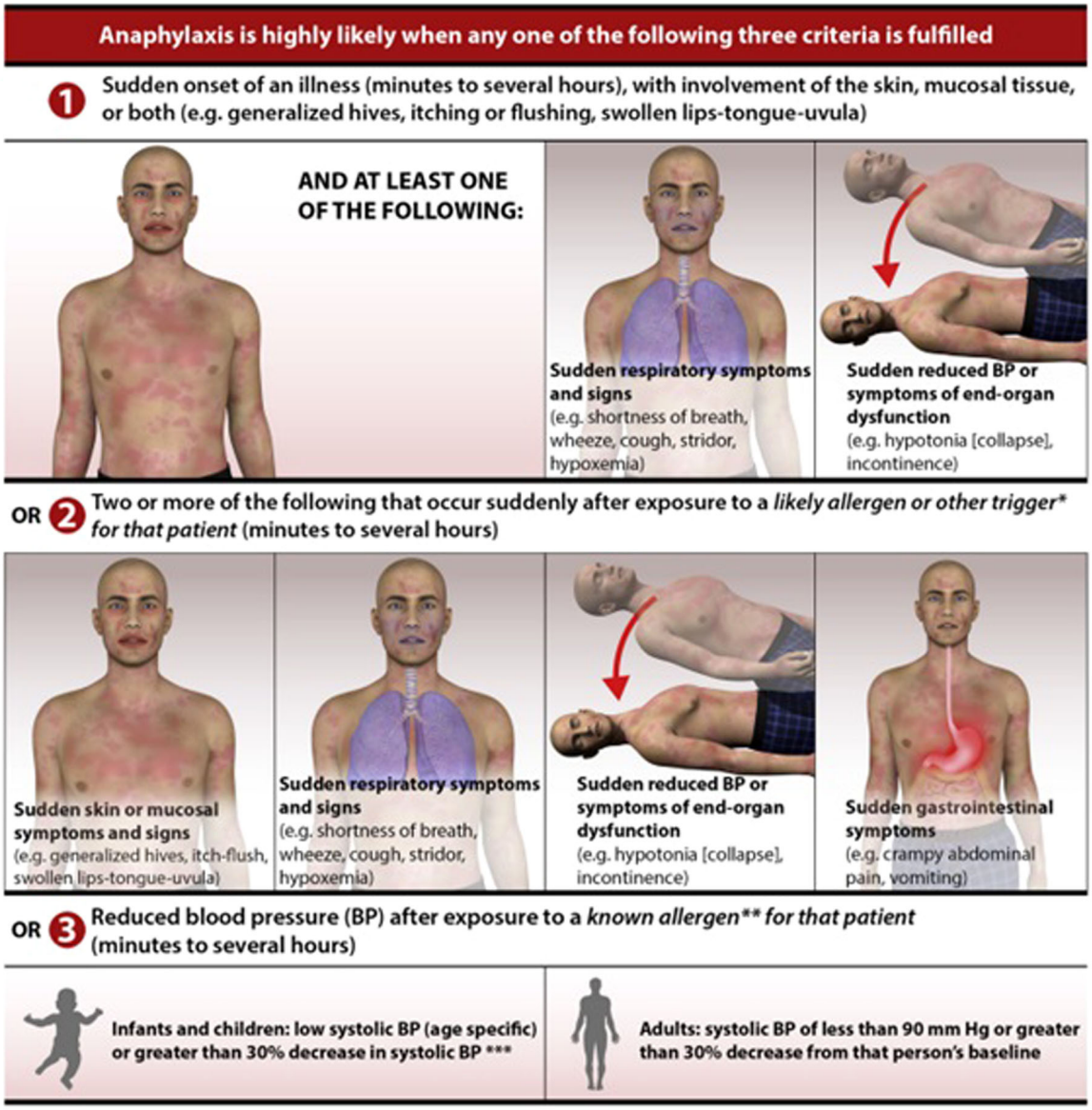

Figure 4. Anaphylaxis diagnostic criteria. Reproduced from Shaker et al,[89] copyright 2020, with permission from Elsevier.

Table 8. Differentiating Between Vasovagal and Anaphylaxis

	Vasovagal	Anaphylaxis
Onset	Immediate, usually within minutes	Typically within 30 minutes
Neurologic	Fainting sensation, light headedness, dizziness	Sense of severe anxiety and distress
Respiratory	Normal breathing, no cough, no hoarseness	Dyspnea, wheezing, stridor, hypoxemia, inability to maintain airway patency, persistent cough, throat clearing
Cardiovascular	Bradycardia, hypotension	Tachycardia, hypotensive
Gastrointestinal	Nausea, vomiting	Abdominal cramps, diarrhea, nausea, vomiting
Skin	Generalized pallor, cool, clammy skin, absence of urticaria and angioedema	Pruritis, generalized erythema, urticaria, angioedema

bradycardia and hypotension can aid in distinguishing a vasovagal attack from anaphylaxis (Refer to **Table 8**).

Clinicians should educate patients and their caregivers about the signs and symptoms of anaphylaxis. An emergency action plan that includes instructions for using epinephrine should be reviewed with patients on AIT. This discussion should be part of the informed consent surrounding AIT and documented in the patient's medical record. Epinephrine is an effective first-line treatment of all systemic symptoms and should be used early when treating SRs.[233-236] Epinephrine is universally recommended as the first-line treatment for anaphylaxis administered intramuscularly into the vastus lateralis (antero-lateral thigh).[89] Intramuscular epinephrine should be given at a dose of 0.01 mg/kg of 1 mg/mL (1:1000), up to 0.5 mg in adults and 0.3 mg in children and teenagers. There are no absolute contraindications to its use for anaphylaxis.[89,227] Clinicians should administer additional doses of intramuscular epinephrine every 5 to 15 minutes if anaphylaxis signs or symptoms persist.[234,237-239]

Additional emergency management includes placing the patient in a supine position if their presentation is mainly cardiovascular, monitoring vital signs, and administration of oxygen to patients with respiratory distress and those receiving further doses of epinephrine.[234,237-239] Intravenous fluids are to be administered early with the first epinephrine dose to patients with cardiovascular involvement and should be repeated if lack of response. Intravenous fluids, such as normal saline, should also be given in severe anaphylaxis with a respiratory presentation if a second dose of intramuscular epinephrine is required.[234] Patients with lower respiratory symptoms (eg, chest tightness, wheezing, shortness of breath) should receive inhaled beta-2 agonists following initial treatment with epinephrine (Refer to **Figure 5**).[3,89,227,234,237,238,240]

Biphasic anaphylaxis is a recurrence of anaphylaxis after appropriate treatment. The "Anaphylaxis—A 2020 Practice Parameter Update" suggests that clinicians incorporate severity of anaphylaxis presentation and/or the administration of >1 dose of epinephrine for the treatment of initial anaphylaxis as a guide to determining a patient's risk for developing biphasic anaphylaxis.[89] Additional predictors of biphasic reactions have included wide pulse pressure, unknown anaphylaxis trigger, skin/mucosal signs and symptoms, and drug trigger in children.[89,241] Extended clinical observation is suggested in a setting capable of managing anaphylaxis (to detect a biphasic reaction) for patients with resolved severe anaphylaxis and/or those who need >1 dose of epinephrine.[89]

Antihistamines are often included as adjunctive therapy for cutaneous signs and symptoms associated with anaphylaxis, but they should not be administered before, or in place of, epinephrine. Similarly, glucocorticoids are also frequently used as adjunctive therapy in the treatment of anaphylaxis but also should not be administered prior to, or in place of, epinephrine as they have no proven role in the treatment of an acute reaction due to their slow onset of action.[240,242] Antihistamines and/or glucocorticoids are not reliable interventions to prevent biphasic anaphylaxis. The "Anaphylaxis—A 2020 Practice Parameter Update" recommended against the use of antihistamines and glucocorticoids to prevent biphasic anaphylaxis in adults.[89]

Statement 11: Retesting During AIT

Clinicians should avoid repeat allergy testing as an assessment of the efficacy of ongoing AIT unless there is a change in environmental exposures or a loss of control of symptoms.

Evidence Strength: Recommendation based on CPG, placebo-controlled, and randomized clinical trials with a preponderance of benefit over harm.

Action Statement Profile: 11

- Quality improvement opportunity: Reducing unnecessary testing; making quality care more affordable (National Quality Strategy Domain: Prevention and Treatment of Leading Causes of Morbidity and Mortality, Making Quality Care More Affordable)
- Aggregate evidence quality: Grade B, based on CPGs, placebo-controlled RCTs
- Level of confidence in the evidence: Low for correlation of testing during AIT and clinical response; high for immunomodulation of testing during AIT

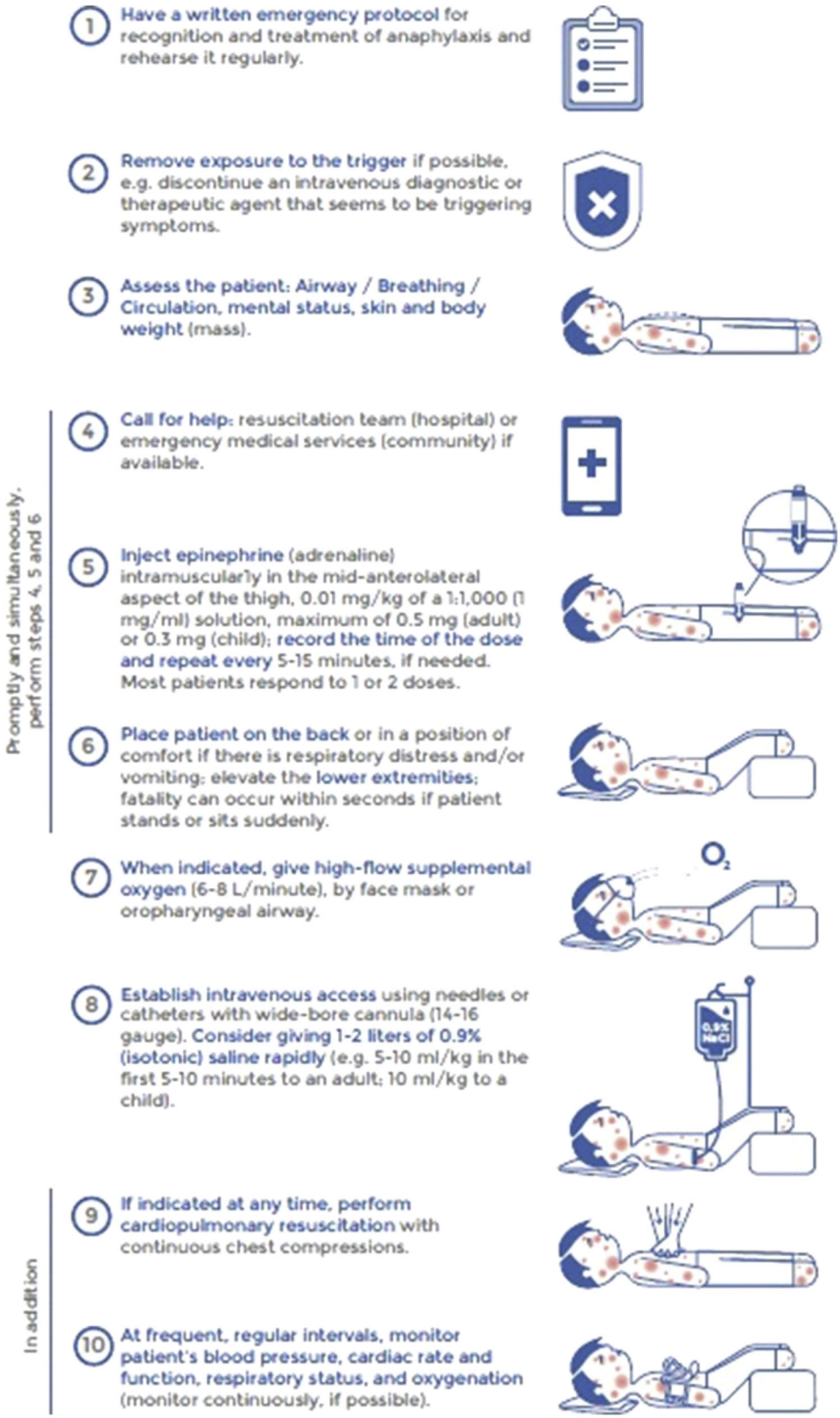

Figure 5. Management of anaphylaxis Reproduced from Cardona et al,[227] published under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

- Benefits: Reducing unnecessary testing; reducing resources including cost; time; decreased patient anxiety from testing
- Risks, harms, costs: Low risk of missing new sensitizations; undertreatment; money; time
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Allergy testing is performed without evidence of usefulness during AIT. Allergy testing is not useful to assess the efficacy of AIT
- Intentional vagueness: None
- Role of patient preferences: None
- Exceptions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to reduce or eliminate the routine use of repeat allergy testing to assess the efficacy of AIT during treatment without a loss of control of symptoms, or after the conclusion of therapy. It is recommended that clinicians avoid repeat allergy testing as an assessment of the efficacy of AIT and also repeat allergy testing should be avoided in decision-making about when to discontinue AIT (Refer to KAS 12).[3]

The clinical outcome of AIT is typically assessed by clinicians by obtaining a patient's report of a decrease in the severity of symptoms and a decrease in the need for concomitant medication.[243] Although objective measures such as spirometry, provocation tests (nasal, dermal, conjunctival, bronchial), and skin test titration have been used in research settings to assess response to AIT, they have not been shown to add benefit in routine clinical use.[244,245]

Skin testing or serum sIgE antibody testing of patients during treatment is not recommended because it has not been demonstrated that skin test reactivity (to a single dilution) or sIgE levels correlate closely with symptoms.[3] The level of sIgE does not reliably monitor the clinical response to AIT.[246] An early initial increase in sIgE levels has been demonstrated during both SCIT[247] and SLIT.[248] This increase during the escalation phase of treatment is followed by blunting of seasonal increases in sIgE levels.[246] Although long-term studies of SCIT demonstrated a gradual decrease in sIgE levels over several years,[249] there was no clear association between changes in sIgE levels and the magnitude of the clinical response.[250,251] IgG antibodies compete with IgE for the same epitopes with a resulting inhibition of degranulating cell activation.[252] IgG1 antibodies, produced mostly upon natural exposure to allergens, may play a protective role. AIT induces allergen-specific IgG4 antibodies. The blocking capacity of IgG4 antibodies has been postulated as one of the major mechanisms underlying the efficacy of AIT in respiratory allergies.[253-255] However, the increase in serum-specific IgG4 levels has not been confirmed as a biomarker of AIT efficacy at the individual patient level.[255] The testing of IgG4 antibodies is not recommended for the assessment of AIT efficacy in clinical practice.

To determine efficacy of treatment, clinicians typically utilize subjective reports from the patient that their allergy symptoms are satisfactorily controlled. These subjective assessments, however, may not be reliable. A more objective measure of efficacy is the use of clinical symptoms scores and assessment of the number of medications required for symptom control.[256,257] Several of these instruments have been validated. A commonly used scoring in AIT clinical trials is a 4-point rating scale (from 0 absent to 3 severe) for obstruction, sneezing, rhinorrhea, nasal itching and ocular itching. Rescue allergy medication (usually an oral antihistamine) use can also be a marker of AR control. It is recommended that clinical improvement of AR be monitored as evidence of efficacy of AIT. This is based on symptom and/or medication scores which have been utilized as the primary outcome measures in clinical trials.[256,257]

In summary, although allergy retesting is utilized in research settings to demonstrate immunotherapy-induced immunomodulation, it is unnecessary for clinicians to order serial allergy testing to assess response to treatment, as it does not correlate with a patient's clinical response. Awareness by clinicians who provide AIT that clinical symptoms and medication use are better markers of effective AIT than repeat allergy testing both reduces unhelpful testing and eliminates the continued administration of AIT inappropriately based on persistently positive allergy tests.

Statement 12: Duration for AIT

For patients who are experiencing symptomatic control with AIT, clinicians should treat for a minimum duration of 3 years, with ongoing treatment duration based on patient response to treatment.

Evidence Strength: Recommendation based on systematic reviews, international consensus guideline, and RCTs with a preponderance of benefit over harm.

Action Statement Profile: 12

- Quality improvement opportunity: Preventing overtreatment and undertreatment
  (National Quality Strategy Domain: Patient Safety, Prevention and Treatment of Leading Causes of Morbidity and Mortality)
- Aggregate evidence quality: Grade B, based on systematic reviews, international consensus guideline, RCT
- Level of confidence in the evidence: High confidence in minimal duration of 3 years; low confidence in more than 5 years of treatment
- Benefits: Avoid overtreatment; reduce rate of relapse associated with early discontinuation; conserve resources

- Risks, harms, costs: Overtreatment and undertreatment; overuse of resources; side effects of treatment with duration beyond effective range; societal waste
- Benefits-harm assessment: Preponderance of benefit over harm
- Value judgments: Patients are both under- and overtreated; there is an assumption that patients have been on maintenance dosing at the time when a clinician would consider discontinuing therapy
- Intentional vagueness: Maximal duration of treatment. While the GDG agreed that 3-5 years is the typical maximal duration, there are clinical scenarios that warrant even longer treatment; patient benefits are not defined; did not differentiate SLIT or SCIT
- Role of patient preferences: Moderate for patients who have undergone 3-5 years of treatment; low for patients who have been treated for at least 5 years
- Exceptions: Patients treated with co-seasonal therapy (seasonal tablets)
- Policy level: Recommendation
- Differences of opinion: Some (4) panel members felt like a specific range of 3-5 years should have been recommended as there is little evidence to justify treatment beyond 5 years. Some of the literature looked at a 3-year duration, while other literature looked at 5-year duration, so the optimal duration of treatment is unclear

Supporting Text

The purpose of this statement is to provide guidance for appropriate duration for administration of AIT. Immunotherapy is both a treatment for disease and an intervention that can potentially modify allergic disease and produce long-term clinical remission. The optimal duration of AIT is not well defined, with a limited number of studies specifically designed to evaluate the duration of immunotherapy efficacy. Maintenance doses for both SCIT and SLIT have traditionally been recommended to be continued for at least 3 years.[3,78,132] This amount of time has been reported as necessary to induce clinical and immunological allergen-specific tolerance, defined as the persistence of clinical benefit for at least 1 year after cessation of treatment, accompanied by altered antigen-specific T-cell and/or B-cell responses.[64,258]

Only a few double-blind, randomized controlled studies assessed efficacy for at least 12 months after cessation of immunotherapy. Most studies that have evaluated the duration of SCIT efficacy have been in patients with seasonal pollen allergies. In a 7-year trial, Durham et al[167] randomized 40 adults with severe AR to receive SCIT (n = 21) consisting of maintenance monthly injections of 20 μg of Phl p 5 or placebo (n = 19) injections for a year. One group completed 1 year and then an additional 3 years of active treatment, and a second group received 1 year of placebo and then active treatment for 3 years. Therefore, subjects received either 3 or 4 years of immunotherapy with efficacy parameters being monitored during the subsequent 3 years of therapy. In the 2 groups that received active immunotherapy, there were no significant differences in any of the symptom scores throughout the 3-year period. Furthermore, scores for seasonal symptoms and the use of rescue medication remained low after the discontinuation of immunotherapy.[259] This trial demonstrated under double-blind conditions, that 3 to 4 years of grass pollen AIT resulted in persistent efficacy for at least 3 years after the discontinuation of AIT.

Naclerio et al[260] conducted a double-blind, controlled trial of ragweed AR patients on AIT. Twenty patients who had received maintenance ragweed SCIT (12 μg of Amb a1) for a minimum of 3 years were then randomized to continue SCIT or placebo injections for an additional year. Nasal allergen challenge (NAC) was performed before initiation of AIT and after 1 year. After the initial 3-year open phase of AIT, NAC revealed decreases in the number of sneezes in all participants. However, after the final additional year of treatment, the clinical response to NAC remained entirely suppressed in the group that remained on active treatment, whereas the group on placebo showed a partial recrudescence of response to NAC with median number of sneezes increasing from 2 to 4.

Together, these studies, although only including small samples of participants per group, suggest that a long-term tolerogenic effect of SCIT can be achieved following 3 years of treatment, but that this effect is not absolute, and might differ depending on the allergen used. The Durham et al trial suggests no difference in symptom score or rescue medications with longer courses of treatment, while the data on clinical response to NAC by Naclerio et al suggest the possibility that the treatment effect may begin to diminish as early as 1 year off treatment.

A larger (n = 634) 5-year double-blind, placebo-controlled, randomized trial,[166,261,262] consisting of a 3-year treatment phase (SLIT-T) followed by 2 years of blinded follow-up in adults with a history of moderate-to-severe grass pollen ARC resulted in a reduction in mean symptom scores of 25% to 36% and reduction in medication scores by 20% to 45% in the AIT group over the 5 consecutive grass pollen seasons.

Another long-term efficacy trial of grass pollen SLIT-T in adults with grass pollen ARC randomized 633 adults to 3 treatment arms: placebo group, 5-grass SLIT-T initiated 2 months prior to the expected start of the pollen season group (2-month SLIT group), and 5-grass SLIT-T initiated 4 months prior to the expected start of the pollen season group (4-month SLIT group).[171,172] Treatment was continued daily throughout the season and for the next 3 consecutive years (pre-/co-seasonally).

All 3 arms had blinded follow-up after 3 years of treatment or placebo for years 4 and 5. The least squares (LS) for the mean daily combined score (DCS) were reduced by 16% to 38% in the 4-month SLIT group compared with placebo during the 5 pollen seasons covered by the trial. The daily ARC total symptom score was reduced by 11% to 39% and the daily rescue medication score reduced by 23% to 38% in the 4-month SLIT group compared with placebo. During the first and second off-treatment years, a statistically significant difference (25% and 28%, respectively) was observed in LS mean DCS in the 4-month SLIT group compared with placebo. These 2 SLIT tablet trials provide robust evidence for the induction of lasting tolerance after 3 years of grass pollen SLIT.

Scadding et al[132] demonstrated that 2 years of either SCIT or SLIT were insufficient to maintain tolerance to grass pollen NAC at 1 year after treatment discontinuation. This was a double-blind, placebo-controlled, randomized, 3-parallel-group study in adults with moderate to severe seasonal AR. The groups consisted of 36 participants who received 2 years of SLIT (daily tablets containing 15 μg of major allergen Phl p 5 and monthly placebo injections), 36 who received SCIT (monthly injections containing 20 μg of Phl p 5 and daily placebo tablets) and 34 who received matched double-placebo. NAC was performed before treatment, at 1 and 2 years of treatment, and at 3 years (1 year after treatment discontinuation). The study demonstrated that AIT given for periods shorter than 3 years may be associated with relapse of symptoms after 1 year of treatment cessation, compared to trials in which treatment was given for at least 3 years. It is therefore recommended that patients complete at least 3 years of AIT in order to achieve disease modification and long-term clinical and immunological tolerance.

A small, prospective controlled study by Des Roches et al[263] was designed to examine the immunotherapy relapse rate during the 3 years after discontinuation of AIT in 40 asthmatic patients who had been treated with AIT with standardized dust mite (Der p) extract for 12 to 96 months. A patient was considered to have relapsed when symptoms of asthma and/or rhinitis occurred and/or when pulmonary function tests were impaired with 55% of the patients relapsing in this study. The duration of efficacy of AIT after its cessation in this study appeared to depend upon the duration of AIT with relapse rate of 62% in the group treated for less than 35 months compared with 48% in the group treated for greater than 36 months. Overall 45% of the patients did not experience relapse during the 3 years after discontinuation of AIT. Some patients experience prolonged remission, but others might relapse after discontinuation of AIT. Therefore, the decision to continue or stop immunotherapy must be individualized.

A clinical improvement (both in terms of decreased symptoms and reduction in medication usage) can be reasonably expected in the first year of AIT.[3,264] The patient's response to AIT should be evaluated on a regular basis. If a patient is not demonstrating benefit, potential causes should be considered. Potential causes may include incorrect diagnosis, too short a duration of AIT, inadequate dosage, and inadequate adherence. Once a clinical benefit is ascertained, maintenance AIT should be continued for a period of at least 3 years. Patients might experience sustained clinical remission of their allergic disease after discontinuing AIT, but some might relapse. The severity of disease, benefits sustained from treatment, and convenience of treatment are all factors that should be considered through shared decision-making in determining whether to continue or stop AIT for any individual patient.[3,264] If AIT is effective, maintenance treatment might be continued for longer than 3 years, depending on the patient's ongoing response to treatment.

There are a limited number of trials that were specifically designed to evaluate the duration of immunotherapy efficacy, and even fewer studies have looked for biomarkers or other clinical predictors to identify patients who will remain in prolonged clinical remission after discontinuation of AIT. Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained prolonged clinical remission after discontinuing AIT. Therefore, the duration of AIT beyond the recommended minimum duration of 3 years should be determined through a shared decision-making process after educating on the benefits and risks associated with discontinuing or continuing inhalant AIT.

Implementation Considerations

The complete guideline is published as a supplement to *Otolaryngology–Head and Neck Surgery* to facilitate reference and distribution. An executive summary of the recommendations will be published to present the KASs more concisely to clinicians. The guideline will be presented as a panel presentation to American Academy of Otolaryngology–Head and Neck Surgery members and attendees at the AAO-HNSF 2024 Annual Meeting & OTO Experience. A full-text version of the guideline will be accessible free of charge at www.entnet.org. A plain language summary will be available as well, aimed at patients, as well as parents and caregivers of children, for whom initiation of immunotherapy is being considered. Additionally, pertinent educational materials will be developed in conjunction with the GDG's patient advocate including a patient handout with a comparison of SCIT and SLIT.

Implementation challenges are numerous when trying to reduce variation in practices, especially when some are long-established and without evidence. To facilitate change and clarify expectations, this guideline provides tables and figures that (1) categorize the WAO SCIT SR grading system; (2) highlight clinical trials involving SLIT versus SCIT; (3) provide a quick-reference summary

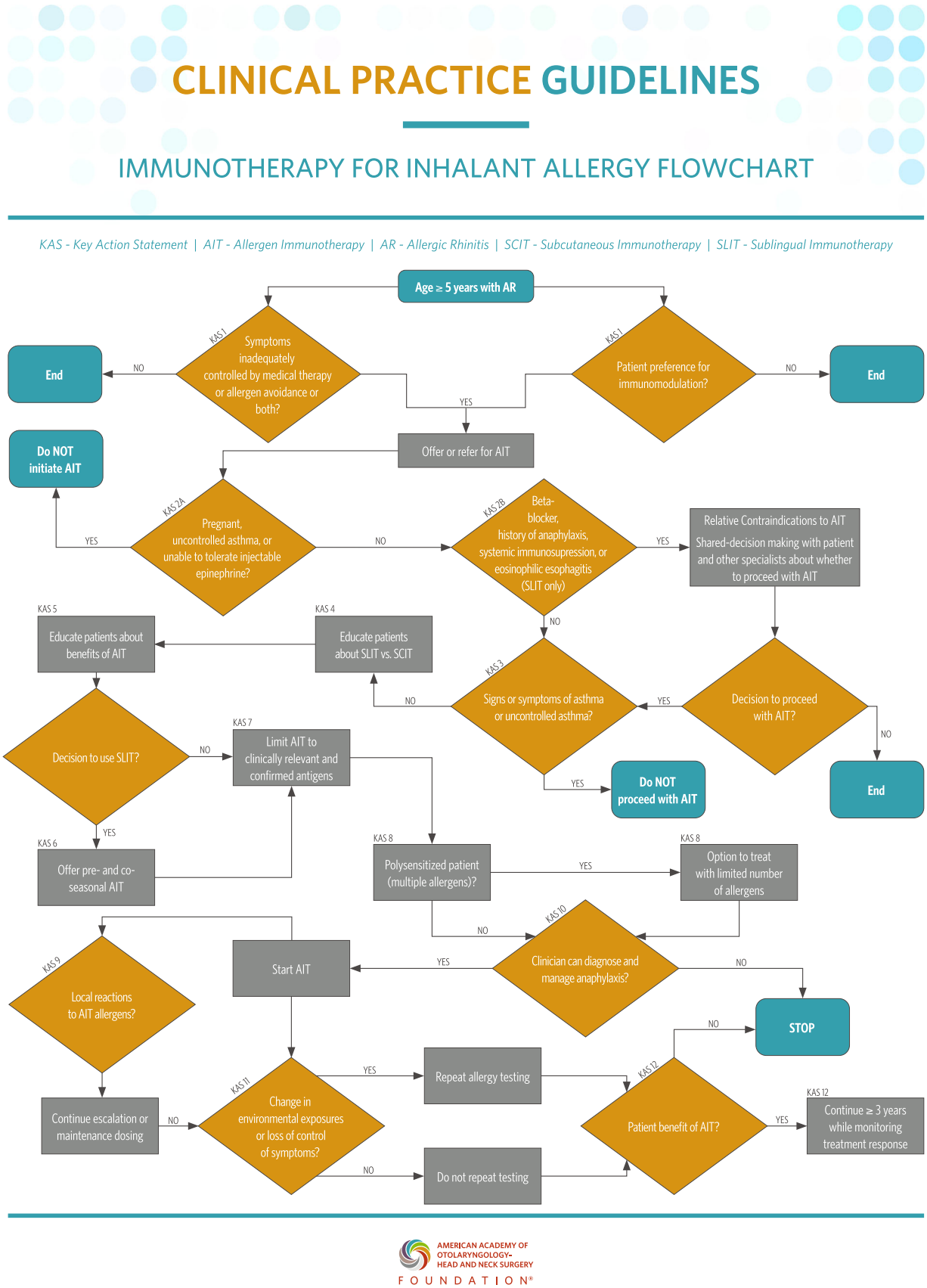

Figure 6. Flowchart showing key action statements and process of care.

comparing SCIT versus SLIT as modalities for treatment for AR; (4) offer a graphical representation explaining pre-/co-seasonal SLIT time course; (5) differentiate between vasovagal reactions and anaphylaxis; and (6) graphically highlight the management of anaphylaxis. The guideline contains supplemental materials including FAQs about AIT, a handout comparing SCIT and SLIT as treatment options, and flowchart for anaphylaxis treatment

Given the importance of patient and caregiver engagement and education in choosing AIT as a treatment modality, the GDG developed a plain language summary of this guideline, published concurrently with the full guideline, available for download at https://www.entnet.org/content/clinical-practice-guidelines. We will also explore foreign language versions of the guideline and supporting materials to facilitate communication with diverse families and stakeholders.

Implementation of the proposed recommendations contained in the guideline will need additional written and online resources, ideally integrated within electronic medical records and decision support tools. These tools, which include performance measures derived from guideline recommendation statements, will need to educate clinicians about the importance of assessing for the presence of co-morbid asthma prior to skin testing and assessing asthma control prior to each immunotherapy injection or initiation of SLIT-T or SLIT-Aq. The routine practice of adjusting SCIT dose after an LLR is commonplace now, as is retesting patients at the conclusion of AIT, and the recommendation against these practices will need to be disseminated, with analysis of outcomes as practices change.

The guideline includes a flowchart of the guideline KASs in **Figure 6**. The flowchart facilitates more rapid understanding of the guideline logic, sequence of action statements, and the interrelationship of key recommendations and options. The flowchart can be adopted as a quick reference guide to support the implementation of the guideline recommendations.

Research Needs

This guideline was developed based on the current body of evidence regarding immunotherapy for inhalant allergy. As determined by the GDG's review of the literature, assessment of current clinical practices, and determination of evidence gaps, research needs were determined as follows:

1. How is local nasal allergy (negative testing, nasal IgE presence, and allergic symptoms) assessed and treated?
2. Does the correlation between symptom triggers and testing affect the efficacy of AIT?
3. Is it safe to continue AIT in pregnancy or initiate it in pregnant patients?
4. How safe is AIT when a patient is on a nonselective or selective beta-blocker?
5. What specific markers of asthma severity reflect lack of control and make AIT unsafe?
6. What constitutes an effective dose of nonstandardized allergens in SCIT?
7. What are the effective allergen doses in SLIT-Aq?
8. Which allergens should be selected in SLIT-Aq?
9. What is the difference in efficacy between SCIT and SLIT in polysensitized patients?
10. Does recurrent pre-/co-seasonal AIT confer immunomodulation?
11. Do the preventive benefits of immunotherapy (reduced sensitization and prevention of asthma) warrant expanding the candidacy for immunotherapy in children?
12. How many allergens are necessary for optimal treatment in AIT for the polyallergic patient?
13. How should we manage patients with AIT when initiating biologics for Type 2 disease (chronic rhinosinusitis with nasal polyps, asthma, eczema)
14. Do LRs during AIT have any predictive significance for future reactions in identifiable subsets of AIT patients?
15. What are the barriers to treating anaphylaxis with epinephrine during AIT?
16. Are there reliable clinical or biologic markers for when to stop successful AIT?
17. What is the optimal duration of treatment for successful AIT?
18. How long should AIT continue if symptoms are not successfully controlled?
19. Which social determinants of health play a role in efficacy and safety of AIT in patients with asthma?

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Author Contributions

Richard K. Gurgel, writer, chair; **Fuad M. Baroody**, writer, assistant chair; **Cecelia C. Damask,** writer, assistant chair; **James "Whit" Mims**, writer, assistant chair; **Stacey L. Ishman**, writer, methodologist; **Dole P. Baker**, writer; **Kevin J. Contrera**, writer; **Fariha S. Farid**, writer; **John A. Fornadley**, writer; **Donna D. Gardner**, writer; **LaKeisha R. Henry**, writer; **Jean Kim**, writer; **Joshua M. Levy**, writer; **Christine M. Reger**, writer; **Howard J. Ritz**, writer; **Robert J. Stachler**, writer; **Tulio A. Valdez**, writer; **Joe Reyes**, writer, AAO-HNSF staff liaison; **Nui Dhepyasuwan**, writer, AAO-HNSF staff liaison.

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Disclaimer

This guideline is not intended as the sole source of guidance regarding immunotherapy for inhalant allergy. Rather, it is designed to assist clinicians by providing an evidence-based framework for decision-making strategies. The guideline is not intended to replace clinical judgment or establish a protocol for this condition/treatment and may not provide the only appropriate approach to managing this problem. As medical knowledge expands, and technology advances, clinical indicators and guidelines are promoted as conditional and provisional proposals of what is recommended under specific conditions but are not absolute. Guidelines are not mandates. These do not and should not purport to be a legal standard of care. The responsible physician, in light of all circumstances presented by the individual patient, must determine the appropriate treatment. Adherence to these guidelines will not ensure successful patient outcomes in every situation. The AAO-HNSF emphasizes that these clinical guidelines should not be deemed to include all proper treatment decisions or methods of care, or to exclude other treatment decisions or methods of care reasonably directed to obtaining the same results.

ORCID iD

Joe Reyes http://orcid.org/0009-0008-7157-9247

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