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Clinical Practice Guideline: Allergic Rhinitis

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Abstract

Objective. Allergic rhinitis (AR) is one of the most common diseases affecting adults. It is the most common chronic disease in children in the United States today and the fifth most common chronic disease in the United States overall. AR is estimated to affect nearly 1 in every 6 Americans and generates $2 to $5 billion in direct health expenditures annually. It can impair quality of life and, through loss of work and school attendance, is responsible for as much as $2 to $4 billion in lost productivity annually. Not surprisingly, myriad diagnostic tests and treatments are used in managing this disorder, yet there is considerable variation in their use. This clinical practice guideline was undertaken to optimize the care of patients with AR by addressing quality improvement opportunities through an evaluation of the available evidence and an assessment of the harm-benefit balance of various diagnostic and management options.

Purpose. The primary purpose of this guideline is to address quality improvement opportunities for all clinicians, in any setting, who are likely to manage patients with AR as well as to optimize patient care, promote effective diagnosis and therapy, and reduce harmful or unnecessary variations in care. The guideline is intended to be applicable for both pediatric and adult patients with AR. Children under the age of 2 years were excluded from the clinical practice guideline because rhinitis in this population may be different than in older patients and is not informed by the same evidence base. The guideline is intended to focus on a limited number of quality improvement opportunities deemed most important by the working group and is not intended to be a comprehensive reference for diagnosing and managing AR. The recommendations outlined in the guideline are not intended to represent the standard of care for patient management, nor are the recommendations intended to limit treatment or care provided to individual patients.

Action Statements. The development group made a *strong recommendation* that clinicians recommend intranasal steroids for patients with a clinical diagnosis of AR whose symptoms affect their quality of life. The development group also made a *strong recommendation* that clinicians recommend oral second-generation/less sedating antihistamines for patients with AR and primary complaints of sneezing and itching. The panel made the following *recommendations*: (1) Clinicians should make the clinical diagnosis of AR when patients present with a history and physical examination consistent with an allergic cause and 1 or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red and watery eyes. (2) Clinicians should perform and interpret, or refer to a clinician who can perform and interpret, specific IgE (skin or blood) allergy testing for patients with a clinical diagnosis of AR who do not respond to empiric treatment, or when the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy. (3) Clinicians should assess patients with a clinical diagnosis of AR for, and document in the medical record, the presence of associated conditions such as asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis, and otitis media. (4) Clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.

The panel *recommended against* (1) clinicians routinely performing sinonasal imaging in patients presenting with symptoms consistent with a diagnosis of AR and (2) clinicians offering

oral leukotriene receptor antagonists as primary therapy for patients with AR.

The panel group made the following options: (1) Clinicians may advise avoidance of known allergens or may advise environmental controls (ie, removal of pets; the use of air filtration systems, bed covers, and acaricides [chemical agents formulated to kill dust mites]) in patients with AR who have identified allergens that correlate with clinical symptoms. (2) Clinicians may offer intranasal antihistamines for patients with seasonal, perennial, or episodic AR. (3) Clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy. (4) Clinicians may offer, or refer to a surgeon who can offer, inferior turbinate reduction in patients with AR with nasal airway obstruction and enlarged inferior turbinates who have failed medical management. (5) Clinicians may offer acupuncture, or refer to a clinician who can offer acupuncture, for patients with AR who are interested in nonpharmacologic therapy. The development group provided *no recommendation* regarding the use of herbal therapy for patients with AR.

Keywords

allergic rhinitis, allergic rhinitis immunotherapy, surgical management of allergic rhinitis, medical management of allergic rhinitis, allergic rhinitis and steroid use/antihistamine use/decongestant use, allergic rhinitis and complementary/alternative/integrative medicine, acupuncture, herbal therapies, diagnosis of allergic rhinitis, nasal allergies, hay fever, atopic rhinitis, atrophic rhinitis, pollinosis, catarrh

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Introduction

Allergic rhinitis (AR) is one of the most common diseases affecting adults.[1] It is the most common chronic disease in children in the United States today[2] and is the fifth most common chronic disease in the United States overall.[3] AR is estimated to affect nearly 1 in every 6 Americans and generates $2 to $5 billion in direct health expenditures annually.[4,5] It can impair quality of life and, through loss of work and school attendance, is responsible for as much as $2 to $4 billion in lost productivity annually.[4,5] Not surprisingly, myriad diagnostic tests and treatments are used in managing patients with this disorder, yet there is considerable variation in their use. This clinical practice guideline was undertaken to optimize the care of patients with AR by addressing quality improvement opportunities through an evaluation of the available evidence and an assessment of the harm-benefit balance of various diagnostic and management options.

For the purpose of this guideline, AR is defined as an immunoglobulin E (IgE)–mediated inflammatory response of the nasal mucous membranes after exposure to inhaled allergens. Symptoms include rhinorrhea (anterior or post nasal drip), nasal congestion, nasal itching, and sneezing. AR can be seasonal or perennial, with symptoms being intermittent or persistent. **Table 1** summarizes the common terms used for this guideline.

Defining Allergic Rhinitis

AR is an inflammatory, IgE-mediated disease characterized by nasal congestion, rhinorrhea (nasal drainage), sneezing, and/or nasal itching. It can also be defined as inflammation of the inside lining of the nose that occurs when a person inhales something he or she is allergic to, such as animal dander or pollen; examples of the symptoms of AR are sneezing, stuffy nose, runny nose, post nasal drip, and itchy nose.

AR may be classified by (1) the temporal pattern of exposure to a triggering allergen, such as *seasonal* (eg, pollens), *perennial/year-round* (eg, dust mites), or *episodic* (environmental from exposures not normally encountered in the patient's environment, eg, visiting a home with pets); (2) frequency of symptoms; and (3) severity of symptoms. Classifying AR in this manner may assist in choosing the most appropriate treatment strategies for an individual patient.

In the United States, AR has traditionally been viewed as either seasonal or perennial, and this is the classification system that the Food and Drug Administration (FDA) uses when approving new medications for AR. However, it is recognized that this classification system has limitations, as the length of the aeroallergen pollen season is dependent on geographic location and climatic conditions. When the pollen season is year-round, as in tropical locations, it can be very difficult based on history to distinguish allergic symptoms provoked

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Table 1. Abbreviations and Definitions of Common Terms.

Term	Definition
Allergic rhinitis (AR)	Disease caused by an IgE-mediated inflammatory response of the nasal mucous membranes after exposure to inhaled allergens. Symptoms include rhinorrhea (anterior or posterior nasal drainage), nasal congestion, nasal itching, and sneezing.
Seasonal allergic rhinitis (SAR)	Disease caused by an IgE-mediated inflammatory response to seasonal aeroallergens. The length of seasonal exposure to these allergens is dependent on geographic location and climatic conditions.
Perennial allergic rhinitis (PAR)	Disease caused by an IgE-mediated inflammatory response to year-round environmental aeroallergens. These may include dust mites, mold, animal allergens, or certain occupational allergens.
Intermittent allergic rhinitis	Disease caused by an IgE-mediated inflammatory response and characterized by frequency of exposure or symptoms (<4 days per week or <4 weeks per year).
Persistent allergic rhinitis	Disease caused by an IgE-mediated inflammatory response and characterized by persistent symptoms (>4 days per week and >4 weeks per year).
Episodic allergic rhinitis	Disease caused by an IgE-mediated inflammatory response that can occur if an individual is in contact with an exposure that is not normally a part of the individual's environment. (ie, a cat at a friend's house).

by exposure to pollen from symptoms caused by exposure to allergens that are perennial in temperate zones (eg, dust mites). Mold has been considered to be both a seasonal and a perennial allergen.[6] Furthermore, it is recognized that many patients with AR have perennial AR exacerbated by seasonal pollen exposure, and many patients are polysensitized so the clinical implications of seasonal versus perennial are not as clear.[6]

Classifying a patient's symptoms by frequency and severity allows for more appropriate treatment selection. AR symptom frequency has been divided into *intermittent* (<4 days per week or <4 weeks per year) and *persistent* (>4 days per week and >4 weeks per year).[6] However, this classification of symptom frequency has limitations. For example, the patient who has symptoms 3 days per week year-round would be classified as "intermittent" even though she or he would more closely resemble a "persistent" patient. It may be advantageous for the patient and the provider to determine which frequency category is most appropriate and would best guide the treatment plan. Based on these definitions, it is possible that a patient may have intermittent symptoms with perennial AR or persistent symptoms with seasonal AR.

AR severity can be classified as being *mild* (when symptoms are present but are not interfering with quality of life) or *more severe* (when symptoms are bad enough to interfere with quality of life).[6,7] Factors that may lead to a more severe classification include exacerbation of coexisting asthma; sleep disturbance; impairment of daily activities, leisure, and/or sport; and impairment of school performance or work.

Guideline Purpose

The primary purpose of this guideline is to address quality improvement opportunities for all clinicians, in any setting, who are likely to manage patients with AR, as well as to optimize patient care, promote effective diagnosis and therapy, and reduce harmful or unnecessary variations in care. The guideline is intended to be applicable for both pediatric and adult patients with AR. Children under the age of 2 years were excluded in this clinical practice guideline because rhinitis in this population may be different than in older patients and is not informed by the same evidence base.

The guideline is intended to focus on a select number of quality improvement opportunities deemed most important by the working group and is not intended to be a comprehensive reference for diagnosing and managing AR. The recommendations outlined in the guideline are not intended be an all-inclusive guide for patient management, nor are the recommendations intended to limit treatment or care provided to individual patients. The guideline is not intended to replace individualized patient care or clinical judgment. Its goal is to create a multidisciplinary guideline with a specific set of focused recommendations based upon an established and transparent process that considers levels of evidence, harm-benefit balance, and expert consensus to resolve gaps in evidence.[8] These specific recommendations may then be used to develop performance measures and identify avenues for quality improvement. **Table 2** highlights the topics and issues considered in the development of this guideline.

Healthcare Burden

Incidence and Prevalence

Allergic rhinitis is a worldwide health problem that affects adults and children. In the United States, AR is the 16th most common primary diagnosis for outpatient office visits.[9] Large epidemiologic studies consistently show a significantly higher percentage of the population with rhinitis symptoms than those with rhinitis symptoms and positive allergy tests.[10] In the 2005-2006 National Health and Nutritional Examination Survey (NHANES), a sample of 7398 people (selected to represent the United States population age 6 years and older) were surveyed for "hay fever," "current allergies," and "current rhinitis" and tested for IgE specific to 19 inhalant allergens. One in 3 participants reported rhinitis symptoms within the last 12 months not associated with an upper respiratory infection. Of those with rhinitis, 52.7% demonstrated at least 1 positive allergy test.[10] By this standard, IgE-mediated AR may affect 1 in 6 persons within the United States. The United States population is most commonly sensitized to grass pollen, dust mites, and ragweed pollen.[10]

The International Study of Asthma and Allergies in Childhood (ISAAC), a worldwide study of allergies in

Table 2. Topics and Issues Considered in Allergic Rhinitis (AR) Guideline Development.[a]

Diagnosis/Testing	Treatment	Prevention/Education/ Risk Factors	Other Therapies	Outcomes
• Diagnosis of AR • Differentiating nonallergic nasal conditions from AR • When should a patient be referred to an allergy specialist? • Differentiating perennial or seasonal AR • Identifying and treating comorbidities • When is it acceptable to test for allergic component(s), and what type of test should be performed? • Accuracy of self-diagnosis • Accuracy of clinician diagnosis based on clinical assessment • Children age 2 and older with a diagnosis of allergies, since age 2 is the earliest age to consider allergy testing • Role and appropriate use of imaging • Role of nasal endoscopy • Accurate use of instruments to measure symptoms/objective testing for baseline • When is it necessary to perform specific allergy testing and/or IgE test?	• First-line therapy upon diagnosis • When does combining 2 different classes of allergy pharmacology benefit the patient? • Pharmacology and the different medication classes that offer additive vs negative effects • Self-directed therapy or over-the-counter medications vs physician-directed or prescription medications • Use and safety of nasal, oral, topical steroids • When is it acceptable to add a second or third medication? • Treatment of allergic conjunctivitis • Role of surgical management • Managing chronic inflammation of lung, sinus, skin, and ears • Role of immunotherapy • Efficacy of different antihistamines • Measuring response to therapy and identifying further need for therapy • Role of environmental controls	• Methods for preventing the development of AR • Role of patient education • When is it appropriate to manage symptoms over the phone (or internet)? • Role of dietary modifications • Value of pollen counts in determining symptom severity and self-guidance • Role of stress management in the creation of, or exacerbation of, AR symptoms • Identification of risk factors for the development of AR	• Role of acupuncture • Role of herbal medicines • Role of homeopathy • Role of nasal rinses • Role of capsaicin • Role of antibiotics	• Initial evaluation of the patient • Improvement in accuracy of diagnosis; avoidance of unnecessary testing • Reduction in care variation and unnecessary radiation exposure from sinonasal imaging • Expenditure reduction for ineffective environmental measures • Increased treatment optimization and reduced complications from comorbidities • Optimization of proven effective therapy • Avoidance of sedating antihistamine and promotion of direct therapy • Improved awareness of the different classes of medication for effective treatment of AR • Reduction in the use of a less effective first-line agent • Improved symptom control and reduction in care variation • Increased awareness and appropriate use of immunotherapy and reduction in care variation • Improved nasal breathing and quality of life • Increased awareness of acupuncture as a treatment option • Increased awareness of herbal therapy as a treatment option

[a]This list was created by the Guideline Development Group to refine content and prioritize action statements; not all items listed were ultimately included in the guideline.

children, found a large variation in the prevalence of AR between countries, with the lowest rate reported at 1.5% in Iran and the highest at 39.7% in Nigeria.[11] The prevalence of AR varies with genetics, epigenetics, and environmental exposure in complex ways we do not fully understand. Allergic rhinitis is a heterogenic condition in many respects, so the epidemiologic variance is not unexpected. Despite the variation, the majority of centers found an increasing prevalence of AR

in children over time. In the United States, over an 8-year time period ending in 2002, the prevalence of AR in 2422 children ages 13 to 14 years increased from 13% to 19%.[11] These results illustrate that AR is both a common and growing global concern.

Costs, Quality of Life, and Productivity

The financial impact associated with the management of AR is substantial. Most estimates of the annual direct cost of AR range from US$2 to $5 billion,[4,5] with more than half of AR direct costs likely coming from prescription medications.[4] Data from the 2007 Medical Expenditure Panel Survey suggest that clinic visits and the number of prescriptions filled for patients with AR are approximately twice the number of those for patients without AR.[12] There are also considerable costs associated with managing the comorbidities of AR, such as sinusitis and asthma, which are classified as "hidden" direct costs.[5]

In addition to imposing direct costs, AR exacts a considerable toll on patients' quality of life, cognitive function, decision making, and self-perception.[13] Indirect costs of AR in adults include costs associated with decreased work productivity and days absent due to illness. In the United States, AR results in a loss of 800,000 to 3.5 million workdays per year.[14,15] From a cohort of 8267 US employees at 47 employer locations, Lamb et al[16] reported that AR caused greater loss of productivity than any other illness and accounted for nearly one-quarter of all lost productivity. Lost productivity from AR has been estimated to cost $2 to $4 billion annually in the United States.[4,5] In children, AR and its associated comorbidities are responsible for 800,000 to 2 million lost school days annually.[14,15] Children with AR have also been shown to have increased disorders of learning performance, behavior, and attention, especially when common comorbidities such as sleep-disordered breathing and asthma are present.[17-20]

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 benefit and harm.[21] The Guideline Development Group consisted of 20 panel members representing experts in otolaryngology, allergy and immunology, internal medicine, family medicine, pediatrics, sleep medicine, advanced practice nursing, complementary and alternative medicine (acupuncture and herbal therapies), and consumer advocacy.

Literature Search

An information specialist conducted 2 literature searches from June 2013 through November 2013, using a validated filter strategy, to identify clinical practice guidelines, systematic reviews, and randomized controlled trials (RCTs). The search terms used were ((Nasal Allergy[TW] OR Nasal Allergies[TW] OR Nose Allergy[TW] OR Pollinosis[TW] OR Pollinoses[TW] OR Catarrh[TW] OR Catarrhs[TW]) OR (Allergic Rhinitis[TW]) OR ((("Rhinitis, Allergic, Perennial"[MESH]) OR "Rhinitis, Allergic, Seasonal"[MESH]) OR "Rhinitis, Atrophic"[MESH]) AND (("1980/01/01"[PDAT]: "2013/12/31"[PDAT]) AND English[LANG])) AND ((Clinical Trial*[PT] AND (Randomized[TW] OR Randomised[TW])) OR ("Randomized Controlled Trial"[PUBLICATION TYPE] OR Randomized Controlled Trial[TW] OR Randomized Controlled Trial[TW])). These search terms were used to capture all evidence on the population, incorporating all relevant treatments and outcomes.

The English-language searches were performed in multiple databases including the Cochrane Library, EMBASE, PubMed, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). In certain instances, targeted searches for lower level evidence were performed by panel members to address gaps from the systematic searches identified in writing the guideline from December 2013 through May 2014.

1. Clinical practice guidelines were identified by a PubMed search using *guideline* as a publication type or title word. The initial search identified 54 guidelines. Articles were excluded if they (1) were not on the topic of the guideline, (2) were not available in English, (3) did not meet the panel's quality criteria (eg, the review had a clear objective and method), (4) did not possess an explicit search strategy, and/or (5) did not have valid data extraction methods. After duplicates, irrelevant references, and non-English-language articles were removed, the final tally was 31 guidelines.
2. Systematic reviews were identified through, EMBASE, the Cochrane Library, CINAHL, and PubMed. The initial data set included 759 systematic reviews or meta-analyses that were distributed to the panel members. Articles were excluded if they (1) were not on the topic of the guideline, (2) were not available in English, (3) did not meet the panel's quality criteria (eg, the review had a clear objective and method), (4) did not possess an explicit search strategy, and/or (5) did not have valid data extraction methods. The final data set retained was 390 systematic reviews or meta-analyses.
3. The initial set of RCTs identified through PubMed, EMBASE, CINAHL, and the Cochrane Library totaled 2446 RCTs articles. These were distributed among panel members for review. Articles were excluded if they (1) were unpublished RCTs, duplicate articles, and articles with unavailable abstracts (2) were not on the topic of the guideline, (3) were not available in English, (4) did not meet the panel's quality criteria (eg, the review had a clear objective and method), (5) did not possess an explicit search strategy, and/or (6) did not have valid data extraction methods. The total final data set retained after the panel review was 1605 RCT articles.

The 31 clinical practice guidelines, 390 systematic reviews, and 1605 RCTs were broken down into the 14 key action statement categories. This material was supplemented, as

Table 3. Evidence Levels for Grades of Evidence.[a]

Grade	Evidence Quality for Diagnosis	Evidence Quality for Treatment and Harm
A	Systematic review of cross-sectional studies with consistently applied reference standard and blinding	Well-designed randomized controlled trials performed on a population similar to the guideline's target population
B	Individual cross-sectional studies with consistently applied reference standard and blinding	Randomized controlled trials; overwhelmingly consistent evidence from observational studies
C	Nonconsecutive studies, case-control studies, or studies with poor, nonindependent, or inconsistently applied reference standards	Observational studies (case control and cohort design)
D	Mechanism-based reasoning or case reports	
X	Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit over harm	

[a]American Academy of Pediatrics classification scheme[25] updated for consistency with current level of evidence definitions.[26]

needed, with targeted searches to address specific needs identified in writing the guideline through February 2014. After assessing quality and relevance, we retained 9 of the clinical practice guidelines, 81 of the systematic reviews, and 177 of the RCTs.

In a series of conference calls, the working group defined the scope and objectives of the proposed guideline. During the 12 months devoted to guideline development ending in March 2014, the group met twice, with in-person meetings following the format previously described,[21] using electronic decision-support (BRIDGE-Wiz, Yale Center for Medical Informatics, CT) software to facilitate creating actionable recommendations and evidence profiles.[22] Internal electronic review and feedback on each guideline draft were used to ensure accuracy of content and consistency with standardized criteria for reporting clinical practice guidelines.[23]

American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) staff used the Guideline Implementability Appraisal and Extractor (GLIA) to appraise adherence of the draft guideline to methodological standards, to improve clarity of recommendations, and to predict potential obstacles to implementation.[24] Guideline panel members received summary appraisals in April 2014 and modified an advanced draft of the guideline.

The final guideline draft underwent extensive external peer review. Comments were compiled and reviewed by the panel's chair and co-chairs, and a modified version of the guideline was distributed and approved by the guideline development panel. The recommendations contained in the guideline are based on the best available data published through May 2014. Where data were lacking, a combination of clinical experience and expert consensus was used. A scheduled review process will occur at 5 years from publication, or sooner if new compelling evidence warrants earlier consideration.

Classification of Evidence-Based Statements

Guidelines are intended to produce optimal health outcomes for patients, to minimize harms, and to reduce inappropriate variations in clinical care. The evidence-based approach to guideline development requires that 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. The definitions for evidence-based statements are listed in **Tables 3**[25] and **4**.[25] Because much of the guideline dealt with evidence relating to diagnostic tests, **Table 3** was adapted to include current recommendations from the Oxford Centre for Evidence-Based Medicine.[26]

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.[25] Clinicians should always act and decide in a way that they believe will best serve their patients' interests and needs, regardless of guideline recommendations. Clinicians 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.[25]

Making recommendations about health practices involves value judgments on the desirability of various outcomes associated with management options. Values applied by the guideline panel 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, including travel expenses of all panel members, 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,[27] the panel 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. Last, panelists were reminded that conflicts of interest extend beyond financial

Table 4. Guideline Definitions for Evidence-Based Statements.

Statement	Definition	Implication
Strong Recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B).[a] 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.	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 that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C).[a] 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.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	An option means that either the quality of evidence that exists is suspect (Grade D)[a] or that well-done studies (Grade A, B, or C)[a] show little clear advantage to one approach versus another.	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.
No Recommendation	No recommendation means there is both a lack of pertinent evidence (Grade D)[a] and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

[a]American Academy of Pediatrics classification scheme.[25]

relationships and may include personal experiences, how a participant earns a living, and the participant's previously established "stake" in an issue.[28]

Guideline Key Action Statements

Each evidence-based statement is organized in a similar fashion: an evidence-based key action statement in bold, followed by the strength of the recommendation in italics. Each key action statement is followed by an "action statement profile" of aggregate evidence quality, level of confidence in the evidence, benefit-harm assessment, and statement of costs. Additionally, there is an explicit statement 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 base supporting the statement. An overview of each evidence-based statement in this guideline can be found in **Table 5**.

The role of patient preference in making decisions deserves further clarification. For some statements, where the evidence base demonstrates clear benefit, although the role of patient preference for a range of treatments may not be relevant (such as with intraoperative decision making), clinicians should provide patients with clear and comprehensible information on the benefits to facilitate patient understanding and shared decision making, which in turn leads to better patient adherence and outcomes. 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 in decisions regarding treatment and care.[29] In cases where evidence is weak or benefits are unclear, the practice of shared decision making—again where the management decision is made by a collaborative effort between the clinician and an informed patient—is extremely useful. Factors related to patient preference include (but are not limited to) absolute benefits (numbers needed to treat), adverse effects (number needed to harm), cost of drugs or procedures, and frequency and duration of treatment.

STATEMENT 1. PATIENT HISTORY AND PHYSICAL EXAMINATION: Clinicians should make the clinical diagnosis of AR when patients present with a history and physical examination consistent with an allergic cause and 1 or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red and watery eyes. *Recommendation based on observational studies, with a preponderance of benefit over harm.*

Table 5. Summary of Guideline Action Statements.

Statement	Action	Strength
1. Patient history and physical examination	Clinicians should make the clinical diagnosis of AR when patients present with a history and physical examination consistent with an allergic cause and 1 or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red and watery eyes.	Recommendation
2. Allergy testing	Clinicians should perform and interpret, or refer to a clinician who can perform and interpret, specific IgE (skin or blood) allergy testing for patients with a clinical diagnosis of AR who do not respond to empiric treatment, or when the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy.	Recommendation
3. Imaging	Clinicians should not routinely perform sinonasal imaging in patients presenting with symptoms consistent with a diagnosis of AR.	Recommendation (against)
4. Environmental factors	Clinicians may advise avoidance of known allergens or may advise environmental controls (eg, removal of pets, the use of air filtration systems, bed covers, and acaricides [chemical agents that kill dust mites]) in AR patients who have identified allergens that correlate with clinical symptoms.	Option
5. Chronic conditions and comorbidities	Clinicians should assess patients with a clinical diagnosis of AR for, and document in the medical record, the presence of associated conditions such as asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis, and otitis media.	Recommendation
6. Topical steroids	Clinicians should recommend intranasal steroids for patients with a clinical diagnosis of AR whose symptoms affect their quality of life.	Strong recommendation
7. Oral antihistamines	Clinicians should recommend oral second-generation/less sedating antihistamines for patients with AR and primary complaints of sneezing and itching.	Strong recommendation
8. Intranasal antihistamines	Clinicians may offer intranasal antihistamines for patients with seasonal, perennial, or episodic AR.	Option
9. Oral leukotriene receptor antagonists (LTRAs)	Clinicians should not offer oral leukotriene receptor antagonists as primary therapy for patients with AR.	Recommendation (against)
10. Combination therapy	Clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy.	Option
11. Immunotherapy	Clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.	Recommendation
12. Inferior turbinate reduction	Clinicians may offer, or refer to a surgeon who can offer, inferior turbinate reduction in patients with AR with nasal airway obstruction and enlarged inferior turbinates who have failed medical management.	Option
13. Acupuncture	Clinicians may offer acupuncture, or refer to a clinician who can offer acupuncture, for patients with AR who are interested in nonpharmacologic therapy.	Option
14. Herbal therapy	No recommendation regarding the use of herbal therapy for patients with AR.	No recommendation

Abbreviations: AR, allergic rhinitis; IgE, immunoglobulin E.

Action Statement Profile

- Quality improvement opportunity: To promote a consistent and systematic approach to initial evaluation of the patient with AR
- Aggregate evidence quality: Grade C, based on observational studies
- Level of confidence in evidence: High
- Benefits: Avoid unnecessary treatment or testing, time referrals appropriately, institute a specific therapy, improve quality of life and productivity, improve accurate diagnosis
- Risks, harms, costs: Inappropriate treatment, potential misdiagnosis from using history and physical alone
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Although the Guideline Development Group recognized that a conclusive diagnosis of AR is difficult without diagnostic testing, making a presumptive diagnosis of AR based on history and physical examination alone is reasonable.
- Intentional vagueness: The use of the words "clinical diagnosis" acknowledges that this is a presumptive diagnosis not confirmed with testing. The

use of the words "when patients present with a history and physical examination consistent with an allergic cause" assumes that a clinician will know how to make an appropriate diagnosis of AR. Specifics of what constitutes a history and physical examination consistent with an allergic cause are provided in the supporting text.

- Role of patient preferences: Limited—Patient may request that additional testing be conducted before deciding on initiation of treatment.
- Exclusions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to provide guidance for the initial clinical diagnosis of AR when a patient first presents to a health care provider. Since rhinitis is an extremely frequent complaint, and since this complaint will often be heard first in the primary care setting, it is important that primary care providers be able to make an initial, if provisional, diagnosis, especially since first-line, effective, readily available therapies for AR may differ from those used for nonallergic rhinitis.[30]

Key elements of the history in patients presenting with AR include seasonal, perennial or episodic, exposure-associated itching of the nose, palate, or eyes, sneezing, nasal congestion, sniffling, clear rhinorrhea, and postnasal drip.[31] Children may only complain of malaise or fatigue, often associated with a cough, and the history must include specific questions about rhinorrhea and nasal and ocular itch in order to elicit these complaints.[32] Seasonal disease may be caused by exposure to outdoor fungal spores or plant pollens, which vary seasonally in their appearance; perennial symptoms tend to be associated with sensitization to indoor allergens, such as dust mites, cockroaches, animal dander, and other molds,[33] but may also be attributed to persistent pollen exposure in some climates. Associated exposures to specific identifiable allergens, such as animals, in connection with the sudden appearance and clearing of symptoms should also be sought. Alternatively, symptoms that develop on exposure to irritants such as smoke, fumes, and chemicals are less likely to represent AR. Symptoms of other sinonasal diseases such as sinusitis, vasomotor rhinitis, and granulomatous diseases can overlap with AR symptoms and should be differentiated from AR. Less typical symptoms, such as epistaxis, unilateral rhinorrhea, unilateral nasal blockage, severe headache, or anosmia, suggest alternative diagnoses and should be investigated further. These symptoms could indicate a more concerning diagnosis, such as cerebrospinal fluid (CSF) rhinorrhea, sinonasal tumors, or chronic rhinosinusitis. Less typical symptoms such as epistaxis, unilateral nasal symptoms, severe headache, or anosmia suggest alternative diagnoses. Viral upper respiratory infections may produce similar symptoms but tend to be of a shorter duration and often include other symptoms such as fever and myalgia. Clinicians should pay attention to a patient's medications, such as antihypertensive drugs, psychotropic agents, and topical decongestants, that may cause nasal symptoms.[34] Moreover, a family history of AR, asthma, or atopic dermatitis strengthens the diagnosis of AR in patients with compatible symptoms.[35,36] Finally, the severity of symptoms should be assessed to help guide treatment decisions.

Findings on physical examination that support the diagnosis of AR include several classic findings, such as clear rhinorrhea and pale pink or bluish swelling of the nasal turbinate mucosa. Ocular findings are common and include watery eye discharge, swelling of the conjunctivae and, especially in children, the "allergic shiner," with darkening and puffiness of the lower eyelids, reflecting venous pooling in the lid vessels. Persistent adenoids may contribute to nasal symptoms and should be evaluated, especially in children. Frequent throat clearing is often present as well, reflecting postnasal drip. These symptoms are nonspecific to AR, and if a patient has them, clinicians should also rule out other causes, such as laryngopharyngeal reflux. Chronic AR symptoms can lead to frequent rubbing of the nose (the "allergic salute") and the development of an "allergic crease" across the nasal bridge. When nasal congestion is present from AR, patients, especially children, may develop "adenoid facies" from chronic mouth breathing. While many of these findings are, in themselves, nonspecific, their presence in a patient with the appropriate history lends further support to the diagnosis of AR.[32] The physical examination should also eliminate other nonallergic causes of nasal obstruction and rhinorrhea, such as foreign bodies, CSF leak, nasal polyps (which can be associated with AR but may have other infectious or chronic inflammatory origins), tumors, and infection.

Although definitive diagnosis depends on the finding of an IgE-mediated response to a specific allergen, detected through cutaneous or blood testing in most patients, it is reasonable to make an initial diagnosis and begin therapy based on the history and physical examination. This is especially important in those patients whose school or work performance and quality of life are compromised by their symptoms.[37] A good response to avoidance of suspected allergens or appropriate empiric therapy supports the diagnosis of AR and may preclude the need for further testing.[30] **Table 6** highlights the history and physical findings in AR.

STATEMENT 2. ALLERGY TESTING: Clinicians should perform and interpret, or refer to a clinician who can perform and interpret, specific IgE (skin or blood) allergy testing for patients with a clinical diagnosis of AR who do not respond to empiric treatment, or when the diagnosis is uncertain, or when knowledge of the specific causative allergen is needed to target therapy. *Recommendation based on RCTs and systematic reviews, with a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Improve accurate diagnosis and avoid unnecessary testing
- Aggregate evidence quality: Grade B, based on randomized controlled trials and systematic reviews
- Level of confidence in evidence: High

Table 6. History and Physical Findings in AR.

Presenting Symptoms	Historical Findings	Physical Findings
Nasal congestion • Sneezing • Rhinorrhea (clear or colored may exist, although colored rhinorrhea may indicate a comorbid disease process with AR) • Itching of nose, eyes, palate • Postnasal drip • Frequent throat clearing • Cough • Malaise (may be presenting complaint in children) • Fatigue (may be presenting complaint in children)	• Seasonal vs perennial nature of symptoms • Symptoms on exposure to particular agent (animals, particular plants) • Current medications • Family history of atopic or allergic disease • Symptoms on exposure to irritants (makes allergic origin less likely) • Symptoms of upper respiratory infection (makes allergic origin less likely)	• Clear rhinorrhea (clear or colored may exist, although colored rhinorrhea may indicate a comorbid disease process with AR) • Bluish or pale swelling of nasal mucosa • Ocular findings (watery discharge, swollen conjunctivae, scleral injection) • Frequent throat clearing • Allergic shiners • Nasal crease • Absence of foreign body, tumor, purulence suggesting infection

- Benefits: Confirming diagnosis, directing pharmacologic therapy, directing immunotherapy, avoidance strategies, avoidance of ineffective therapy, reduce cost of unnecessary testing
- Risks, harms, costs: Cost of testing, adverse events from testing, misinterpretation of results, inaccurate test results (false positives and negatives)
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: Patients may benefit from identification of specific allergic cause.
- Intentional vagueness: We did not specify which specific IgE test (blood or skin) to order. We also did not specify which allergens to test, as that was beyond the scope of this guideline. We did not specify what constitutes empiric treatment, although this is generally treatment that is initiated prior to confirmatory, IgE-specific testing and could include recommending environmental controls, allergen avoidance, or medical management. Lack of response to empiric treatment is not defined to allow the clinician to exercise judgment in making this determination but is generally thought to include patients with persistent symptoms despite therapy.
- Role of patient preferences: Moderate—Shared decision making in discussion of harms and benefits of testing; clinicians and patients should discuss potential costs, benefits, and adverse effects of additional testing, and type of testing, either skin or blood, if neither is contraindicated.
- Exclusions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to help clinicians decide when to use IgE-specific allergy testing and to define the types of testing that may be useful. While a presumptive diagnosis of AR can be made based on a history and physical examination, the presence of a specific IgE antibody to a specific inhalant allergen(s) to which the patient has reported symptoms helps confirm the diagnosis of AR.

Many patients with symptoms of AR can be successfully treated empirically based solely on history and physical examination, without confirmation of IgE allergy. Empiric treatment is defined as treatment that is initiated prior to IgE-specific testing and could include environmental controls, allergen avoidance, or medical management. There are, however, clinical scenarios when confirmatory testing is warranted. These include when patients do not respond to empiric treatment, when the diagnosis of AR is uncertain, when identification of the specific allergen could affect therapy decisions, or to aid in titration of therapy. According to guidelines from the World Health Organization (WHO), allergy testing can be considered as well as other treatment measures such as immunotherapy in patients in whom antihistamines and moderate-dose intranasal steroids (INS) insufficiently control symptoms, with an adequate trial of medications being 2 to 4 weeks in duration.[6] In these scenarios, the results of specific IgE testing (either skin or blood) (see **Table 7**) provide additional information that can guide targeted therapy or alter treatment by the clinician.

As AR is an IgE-mediated disease, testing for non-IgE antibodies (ie, IgG) when trying to identify specific allergen triggers is not beneficial. Measurement of total IgE also has limited diagnostic value in the diagnosis of AR.[38] There are 2 main categories of useful IgE-specific tests: skin and blood testing. Further discussion of these modalities follows.

Skin Testing

Skin testing is a bioassay performed by introducing a specific allergen into the patient's skin. Skin testing allows for direct observation of the body's reaction to a specific antigen. The antigen rapidly activates cutaneous mast cells by interacting with IgE antibodies on the surface of those cells. This leads to the release of chemical substances such as histamine from mast cell granules and results in the development of a wheal and flare reaction within 15 to 20 minutes.[39,40]

Table 7. Immunoglobulin E (IgE)–Specific Tests.

	Recommendation	Advantages	Disadvantages
Skin tests Skin prick, or intradermal	Recommend	• Allows for direct observation of the body's reaction to a specific antigen • Considered more sensitive than blood testing • Intradermal can be used when additional sensitivity is required or skin prick negative • Less expensive than blood testing	• Possible systemic allergic reaction (anaphylaxis) • May be affected by patient medications
Blood	Recommend	• No risk of anaphylaxis • Not affected by patient's medications • Can be used for patients with skin conditions such as dermatographism or severe eczema • Can be used for patients on β-blockers or with comorbid medical conditions that preclude skin testing	• Requires reliable laboratory, potential for laboratory errors
IgG or total IgE	Recommend against		Does not yield information helpful for management of allergic rhinitis
Other nonspecific tests Acoustic rhinometry Olfactory testing Microarray testing Nasal nitric oxide measurements Nasal allergen challenges	No recommendation for or against		

Skin testing is primarily done by either the skin prick/puncture technique or by the intradermal/intracutaneous technique. Skin prick testing has been shown to be highly sensitive and specific, typically over 80% for both.[38,41,42] Scratch testing, a form of puncture technique, is rarely done now due to reduced sensitivity and specificity, poor reproducibility, and greater patient discomfort.[38,43] Intradermal and intradermal dilutional tests are other forms of skin testing that are used for identifying IgE-specific allergens.[44] Intradermal skin tests are particularly helpful when the prick test is negative and there is a high clinical suspicion for allergic sensitization to a particular allergen or if increased sensitivity is required.[38,45] Provocation-neutralization testing is a form of intradermal testing that is primarily of historical interest for inhalant allergy testing, as it has been shown to produce unreliable results.[38]

Skin testing can be used in patients of any age. While infants may have small wheals with both positive controls and allergens, prick/puncture tests can be performed with a high degree of reliability. Although the prevalence of positive skin tests is known to be lower after age 50, significant positive skin tests can still be detected in the older population.[38,42,46,47] Skin testing may be contraindicated when coexistent uncontrolled or severe asthma is present. Skin disease such as eczema can be a relative contraindication. Other contraindications may include coexisting medical conditions that would likely compromise survival should skin testing-induced anaphylaxis develop: for example, severe and unstable cardiovascular disease, concurrent use of β-blockers.

While adverse reactions such as immediate and delayed local swelling, redness, pain, and itching have been reported with skin testing, serious adverse events such as anaphylaxis and death are extremely rare. There have been no fatalities reported as a result of prick inhalant testing and 6 fatalities from intradermal inhalant testing, with 5 of these being asthmatic patients for whom prick testing did not precede intradermal testing.[38,48] There is considerable variation in clinical practice in (1) the number of skin tests performed, (2) the allergen extract concentration used for testing, (3) selection of skin testing devices, (4) interpretation and documentation of results, and (5) quality assurance procedures used.[41,49] When performing prick or intracutaneous skin testing, the clinician should use standardized allergen extracts when available and

should record measurements of wheal and erythema for allergen and positive and negative controls at 15 to 20 minutes after placement. The clinician should also list all medications the patient has taken within the past week, as many medications, such as antihistamines and some antidepressants (eg, tricyclics), may suppress the skin test response.[38,42,50]

Blood Testing

Allergen-specific IgE can be determined by testing the patient's serum with an in vitro test. Using an immunoassay, allergen-specific IgE in serum is detected by incubating the serum with the suspected allergen, which has been absorbed on a solid phase (eg, plastic disc or bead). The bound specific IgE is then measured by the addition of an anti-IgE antibody for this specific allergen, which has a label, such as an enzyme, attached to allow for detection. Anti-IgE antibodies tagged to radioactive tags, (radioallergosorbent tests, aka RAST) are seldom used today, making the term *RAST* an anachronism.[43]

Advantages of using immunoassays for allergy testing include the ability to test for sensitivity to specific antigens without concern about adverse reactions, including anaphylaxis. Antihistamines and other medications (eg, tricyclic antidepressants and β-blockers) do not need to be withheld. Using blood allergy testing instead of skin testing may be preferred when special skin conditions, such as dermatographism ("skin writing" with reddened and raised skin lines produced by scratching or stroking) or severe eczema, are present, in that these conditions may make skin test interpretation very difficult.[38]

While both skin prick and serum-specific IgE tests have similar diagnostic properties, the skin prick test is generally considered to be more sensitive.[38,51,52] Another potential advantage of skin testing is that it is less expensive than blood testing,[53] and patients are able to see the tangible results of their testing. Clinicians should use their best judgment when deciding which method of IgE-specific testing to use for a given patient. Given the lack of conclusive evidence of superiority of one test over another, in the absence of contraindications to one form of testing, patient preference for and the availability of skin or blood testing should play a role in deciding which test to use. Clinicians should always be aware that detection of sensitization to an allergen is not equivalent to a clinical diagnosis of an allergy to a specific allergen. In the absence of clinical symptoms, positive skin or blood testing does not mean that the patient has an allergy to that allergen.

Other Tests

Other diagnostic tests are used to evaluate patients with suspected AR. Those tests include acoustic rhinometry, olfactory testing, microarray testing, nasal nitric oxide measurements, testing for food allergy, and nasal allergen challenges. Nasal smears to evaluate nasal eosinophilia have been used by some clinicians, although general agreement on their usefulness is lacking.[7,54-56] There is insufficient evidence to make recommendations for or against the use of these tests. As a final point, the provider's knowledge of the patient's history, local allergens, qualities of allergen extracts, and how allergen immunotherapy is prepared may reasonably lead to the use of different IgE-specific testing modalities including skin prick testing, blood or serum testing, intradermal testing, intradermal dilutional testing, or combinations thereof. **Table 7** lists the various types of testing for AR and the advantages and disadvantages of the different tests.

STATEMENT 3. IMAGING: Clinicians should not routinely perform sinonasal imaging in patients presenting with symptoms consistent with a diagnosis of AR. *Recommendation against based on observational studies, with a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Reduction of variation of care, reduction of potential harm from unnecessary radiation exposure
- Aggregate evidence quality: Grade C, based on observational studies
- Level of confidence in evidence: High
- Benefits: Avoiding unnecessary radiation exposure, reduction of cost, reducing variation in care
- Risks, harms, costs: Inaccurate or missed diagnosis of pathology with similar presenting symptoms.
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: None
- Intentional vagueness: The word *routine* was used to allow for circumstances where the patient history may warrant imaging for evaluation of another problem besides AR
- Role of patient preferences: None
- Exclusions: None
- Policy level: Recommendation
- Differences of opinions: None

Supporting Text

The purpose of this statement is to discourage the routine use of diagnostic imaging for patients with AR. History, physical examination, and allergy testing are the key aspects of making the diagnosis of AR. Specific IgE-mediated allergen diagnostic testing is confirmatory. There are no radiological findings specifically diagnostic for AR. The utility of imaging procedures in AR is undocumented, and no articles were found regarding the diagnostic yield of imaging studies with AR.

Radiographic imaging is unwarranted in patients who already meet clinical criteria for the diagnosis of AR. Potential significant adverse events and unnecessary costs preclude any benefits of routine imaging. Plain film radiographs and computed tomography (CT) scans expose patients to ionizing radiation, which may result in future radiation-induced cancers.[57,58] Iodinated contrast carries the risk of allergic anaphylactic reactions and nephrotoxicity.[59]

Radiographic testing may have a role in the diagnosis if the clinical presentation points to potential sequelae of AR, such as rhinosinusitis, nasal polyposis, or concerns of a suspected

neoplasm. In contrast to AR, which only affects the nasal mucosa, rhinosinusitis is defined as inflammation of the nasal cavity and adjacent paranasal sinuses. Complicated sinusitis implies spread of infection into adjacent structures, which can result in orbital or intracranial complications, such as orbital abscess and meningitis.[60] Diagnosis of most cases of uncomplicated acute and subacute rhinosinusitis is based on clinical findings. Sinonasal imaging, specifically CT scans without contrast, may be indicated in patients who demonstrate signs and symptoms of recurrent acute rhinosinusitis, nasal polyposis, chronic rhinosinusitis, or complicated rhinosinusitis or to define sinus anatomy prior to surgery.[61] In patients with a suspected sinonasal neoplasm, sinus CT and magnetic resonance imaging (MRI) may be indicated for further evaluation. CT scans will define the bony anatomy of the sinuses and patterns of bone destruction as well as any formation of cartilaginous or bone matrix. MRI with and without contrast can differentiate soft-tissue densities from postobstructive secretions and will delineate evidence of perineural, orbital, skull base, or intracranial extension of tumor.[62,63]

In summary, the diagnosis of AR is based on clinical presentation, and there is no role for radiographic imaging. Potential significant costs and possible side effects of imaging modalities outweigh their utility in the routine evaluation of a patient with AR.

STATEMENT 4. ENVIRONMENTAL FACTORS: Clinicians may advise avoidance of known allergens or may advise environmental controls (eg, removal of pets; the use of air filtration systems, bed covers, and acaricides [chemical agents that kill dust mites]) in AR patients who have identified allergens that correlate with clinical symptoms. *Option based on RCTs with minor limitations and observational studies, with equilibrium of benefit and harm.*

Action Statement Profile

- Quality improvement opportunity: Reduce expenditures on environmental measures that do not improve symptoms
- Aggregate evidence quality: Grade B, based on randomized controlled trials with minor limitations and observational studies
- Level of confidence in evidence: Moderate—with the exception of studies on house dust mites, the majority of the studies were small
- Benefits: Decreased allergen levels and possible reduction in symptoms
- Risks, harms, costs: Cost of environmental controls, emotional effect (eg, recommending animal avoidance in pet lovers), cost of ineffective recommendation
- Benefit-harm assessment: Equilibrium
- Value judgments: Many studies have demonstrated a reduction in allergen levels with environmental controls; however, benefits in alleviating symptoms are limited. Use of multiple avoidance techniques may be more effective than individual measures.
- Intentional vagueness: None
- Role of patient preferences: Large—Shared decision making in discussion of evidence for effectiveness of possible controls and the need to weigh the costs and benefits
- Exclusions: None
- Policy level: Option
- Difference of opinion: None

Supporting Text

The purpose of this statement is to reduce symptoms of AR and improve quality of life through environmental controls that efficiently and effectively reduce allergen exposure while avoiding measures that are costly, are impractical, and have not been shown to be beneficial. The term "environmental control" refers to implementing one or more interventions to reduce or eliminate allergens and irritants in the environment and improve health outcomes for patients with AR. These control measures focus on preventing the development of sensitization, progression of disease, allergens triggering symptoms, and medication use.[64] The use of environmental control measures is a means of actively engaging patients in treatment strategies designed to reduce exposure to specific allergens and improve allergy symptoms. The risks and benefits of the various methods need to be discussed with patients in order for them to make informed decisions about measures that would be most beneficial and cost-effective over time. Findings from these studies suggest that an environmental control program comprised of multiple strategies may reduce exposure to allergens and improve symptoms.

As an environmental control, the protective effect of exclusively breastfeeding infants in the first 3 to 6 months of life on the development of AR remains inconclusive. A meta-analysis of 6 prospective studies with a combined sample of 3303 participants found no significant association between breastfeeding infants and protection from developing AR in later childhood.[65] Kramer[66] summarized findings from systematic reviews and meta-analyses on the effects of breastfeeding and the development of allergic disease. The evidence revealed no reduction in the risk of developing AR in breastfed infants. Methodological challenges in designing prospective studies along with limited follow-up times make it difficult to adequately study the effect of breastfeeding on AR. The inability to conduct randomized, double-blind studies limits methodology to observational designs biased by maternal preferences related to breastfeeding.[67] Inconsistencies in diagnosing AR by health care providers as well as misclassification of infant feeding methods and duration further contribute to the challenges faced by investigators.[66] Thus, breastfeeding continues to be recommended in the literature although its benefits in preventing the development of AR remain unsubstantiated.

Avoidance measures such as removal of pets from the environment can reduce allergen exposure but are often difficult for patients to adhere to. Several studies have examined measures to reduce animal dander. One study by Hodson and colleagues[68] examined the effectiveness of washing dogs to reduce Can f1 allergen levels in dog hair and dander as well as in homes. Can f1 allergen levels were significantly reduced

when the animals were washed with shampoo for 5 minutes and then blown dry. However, prewashed levels of Can f1 returned by days 3 to 4. Thus, in order to be effective in reducing dog allergen, the dog should be washed at least twice a week. A collective review of studies on washing cats weekly revealed a reduction in Fel d1 levels; however, these lower levels were not maintained at 1 week and there was little change in airborne levels of allergen in the home.[64] Thus, the clinical benefits of washing cats remain unsubstantiated by current research findings. Although frequent washing of pets may help reduce these allergens on the animal and in the home, prewashed levels quickly returned (less than a week) and the benefit in reducing symptoms of AR has not been demonstrated in the studies. Findings from a randomized trial,[69] a meta-analysis study of 11 birth cohorts[70] and a literature review[71] on the role of pet ownership in the early years of life as either contributing to the development of atopy (a genetic predisposition to produce elevated levels of IgE to allergens) or possibly protecting against sensitization were inconclusive.

The most recent Cochrane review[72] on avoidance measures for house dust mites (HDMs) updated the original Cochrane review[73] and reviews that were published in 2003[74] and 2007.[75] The 2010 review[72] evaluated 9 RCTs that investigated the effectiveness of measures to decrease exposures to HDMs, including use of impermeable covers, air filtration (high-efficacy particulate air [HEPA] filters), acaricides (chemical agents formulated to kill dust mites), or a combination of treatments.[76] Only 2 of the 9 studies met Cochrane inclusion criteria. Acaricides were found to be most efficacious as both single therapy and in combination with other environmental control methods in reducing dust mite exposure and improving symptoms of AR.[76] Acaricides are insecticides that are sprayed on furniture, rugs, and bedding. When acaricides are used, only products appropriate for indoor use should be applied in the home and patients should read specific instructions for proper application. In a randomized, placebo-controlled trial on the efficacy of impermeable bed covers in HDM-sensitized patients with AR, researchers found significant reduction in dust mite levels in mattresses with impermeable covers versus permeable bedding.[77] However, this change in dust mite exposure was not associated with any improvement in patient symptoms. The protective effects of mite-impermeable mattress covers on the development of HDM sensitization in newborns was evaluated in a large randomized controlled European birth cohort study. Infants in the intervention group slept on mite-impermeable encased mattresses. At 24 months of age (a young age that may be a potential limitation of the study), there were no differences in development of HDM sensitization between infants in the intervention group versus those in the control group.[78] A randomized study[79] of 30 patients with AR secondary to HDMs examined the effect of extensive environmental control measures in the bedroom, such as using vinyl mattress covers, washing bedding biweekly in hot water (55°C), removing upholstered furniture, and washing floors daily. After 1 month, this combination of bedroom environmental control methods significantly reduced dust mite levels in the bedroom. Additionally, patients in the intervention group reported a significant improvement in nasal symptoms compared with those in the control group.

The effectiveness of HEPA filtration in reducing symptoms of AR and medication use was examined in a randomized double-blind study.[80] Thirty-two patients with positive sensitization to HDM used high air filtration in the bedroom for 8 weeks: 4 weeks with HEPA filtration and 4 weeks with placebo filtration. Comparative analysis between the 2 filtration periods found a reduction in particulate matter in the bedrooms when HEPA filters were used but no improvement in allergy symptoms or medication use. However, when the researchers compared the last 2 weeks of each 4-week period, there were significant reductions in symptom scores in the HEPA filtration group, indicating some benefit. In another study,[81] 35 patients with perennial allergic rhinoconjunctivitis sensitized to dust mite, cat, or dog allergens participated in a randomized, double-blind, placebo-controlled crossover design to determine the effectiveness of a combined therapy using dust-mite barrier bed pillow encasings and localized HEPA air filtration. Participants were assigned to either the active filtration group or the placebo group for 2 weeks followed by a 1-week washout period before switching groups for a second 2-week period. Dust samples collected around and under the bed showed a reduction of 99% in the active filtration group compared with a reduction of only 7% in the placebo group. Overnight nasal and ocular symptoms of AR were significantly reduced in the active group compared with the placebo group; however, no changes in daytime symptoms were found.

Use of multiple strategies may help reduce dust mite exposure and nasal symptoms in HDM-sensitive patients, although a single intervention such as using HDM-impermeable covers on bedding or HEPA filtration has not been shown to be effective.[72,77,82] Based on the limited quality of evidence on dust mite avoidance measures, further research is needed to better understand the effectiveness of these approaches. **Table 8** lists the environmental control measures that can be used to possibly reduce allergen levels and symptoms.

STATEMENT 5. CHRONIC CONDITIONS AND COMORBIDITIES: Clinicians should assess patients with a clinical diagnosis of AR for, and document in the medical record, the presence of associated conditions such as asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis, and otitis media. *Recommendation based on randomized trials with some heterogeneity and a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Identification of significant comorbid conditions or complications, potential for treatment optimization
- Aggregate evidence quality: Grade B, based on randomized trials with some heterogeneity
- Level of confidence in the evidence: High

Table 8. Environmental Control Measures to Reduce Allergen Levels and Symptoms.

	Evidence Supports Reduction in Allergen Level		Evidence Supports Reduction in Symptoms	
Environmental Control Measure	Yes	No	Yes	No
Removal of pets	X		X	
Washing pets twice a week	X			X
Acaricides to kill dust mites	X		X	
Impermeable covers for bedding	X			X
Air filtration	X			X
Combined use of multiple control measures	X		X	

- Benefits: Increased awareness of these conditions; identification of treatable conditions; knowledge of these conditions may alter recommendations for AR treatment as comorbid conditions can alter response to treatment.
- Risks, harms, costs: Potential erroneous diagnosis of comorbid conditions
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: None
- Intentional vagueness: None
- Role of patient preferences: None
- Exclusions: None
- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to increase awareness of the medical conditions that are associated with AR and emphasize the importance of diagnosing and treating these comorbidities, which include atopic disorders, sleep-disordered breathing, otitis media, and rhinosinusitis.

There is a well-established epidemiologic association among the atopic disorders, asthma, eczema, and AR, which share many pathophysiologic mechanisms. Over half of patients with asthma have AR,[83] and 10% to 40% of patients with AR have asthma. The association between asthma and AR is especially strong when asthma is documented to have an allergic cause, a situation where the absence of AR would be distinctly unusual.[84] In children, the risk of asthma is related to the severity and duration of the patient's rhinitis.[85,86] Childhood AR not only predisposes to the development of asthma in childhood but also increases the risk of asthma persisting into adulthood and the onset of allergic asthma in middle age. In contrast, adult-onset, nonallergic asthma is not necessarily associated with AR.[87] Moreover, the presence of food-associated atopic dermatitis before age 4 is associated with the development of asthma and AR later in childhood (after age 7)[88]; this is a consistent observation that has been referred to as the "allergic march." In one study, 57.6% of children with early childhood eczema developed AR, 34.1% became asthmatic, and the likelihood of developing the respiratory disorders was related to the severity of the dermatitis.[89] The connection between the skin inflammation and later respiratory disease may be due in part to sensitization to airborne allergens by contact with the skin surface.[90] Allergic conjunctivitis can also be seen in conjunction with AR and can be treated concurrently.

Recognition of the connections among these atopic diseases has implications for both diagnosis and therapy. A history of atopic eczema or asthma makes an allergic origin more likely in a patient presenting with persistent or recurrent nasal symptoms. Evaluation of a patient with AR should always include an assessment for asthma; inquiry about typical symptoms such as difficulty breathing, cough, wheezing, and ability to exercise; and examination of the chest. This evaluation should be repeated on follow-up visits, particularly in children, and spirometry should be performed whenever asthma is suspected. Treatment of AR in patients with concurrent asthma should be individualized; the use of oral antihistamines[91,92] and especially INS[93,94] has been shown to reduce bronchial hyperreactivity and improve asthma control.[86,95-97] In addition, leukotriene receptor antagonists may be an appropriate choice for patients with both asthma and AR[98] even though they are not first-line therapy for independent AR (see Statement 9 on LTRAs). Immunotherapy can also benefit both conditions,[99-102] and there is evidence that treatment of children with AR with allergen-specific immunotherapy may prevent the development of asthma[103] and sensitivity to new allergens.[104] There is also emerging evidence that immunotherapy for AR may improve control of atopic dermatitis.[105]

Nasal blockage and impaired mucociliary clearance[106] may predispose patients with AR to sinus infection; however, a definite relationship between these disorders is not well established. Adenoid hypertrophy must also be considered in children with AR or sinonasal disease.

There may be an association between AR and otitis media with effusion,[107] with reports of comorbidity varying widely from 16.3 to 89%.[108] In a review of patients with both conditions, allergy treatment using INS, with or without antibiotics, was found to hasten resolution of otitis media with effusion.[109] This effect may be related to reversing underlying Eustachian tube dysfunction. AR has been associated with sleep-disordered

breathing[110] as well as decreased sleep quality and daytime fatigue and sleepiness.[20,111] While no study has clearly established a causal relationship between AR and sleep-disordered breathing, evidence supports the treatment of AR to improve both AR and sleep-disordered breathing.[112] This association may be due to adenoid hypertrophy, but appropriate treatment of AR has been shown to improve sleep quality and reduce daytime somnolence in both children and adults.[113-116] Although nasal blockage is not usually the primary causative factor in obstructive sleep apnea, patients treated for coexistent AR can benefit from mild reductions in the apnea hypopnea index and reduction in daytime sleepiness.[117]

STATEMENT 6. TOPICAL STEROIDS: Clinicians should recommend intranasal steroids for patients with a clinical diagnosis of AR whose symptoms affect their quality of life. *Strong recommendation based on RCTs with minor limitations and a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Optimizing the use of proven effective therapy
- Aggregate evidence quality: Grade A, based on randomized controlled trials with minor limitations
- Level of confidence in the evidence: High
- Benefits: Improved symptom control, improved quality of life, better sleep, potential cost saving with monotherapy, targeted local effect
- Risks, harms, costs: Topical side effects, epistaxis, drug side effects, potential growth concerns in children, septal perforation, and the cost of medication
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: None
- Intentional vagueness: None
- Role of patient preferences: Large—There are multiple classes of effective therapy with differing risks, adverse effects, costs, and benefits. The clinician should use his or her expertise in assisting patients to evaluate the best treatment and to ensure patient compliance.
- Exclusions: None
- Policy level: Strong recommendation
- Differences of opinions: Minor. There were some differences of opinion regarding the best therapy for mild or intermittent symptoms, as oral or nasal antihistamines may be adequate therapy for those patients.

Supporting Text

The purpose of this statement is to encourage clinicians to use INS for AR based on their efficacy, superiority over other therapies, and good safety record.

Intranasal steroids are very effective for the treatment of AR. With potent anti-inflammatory properties, INS directly modulate the pathophysiology of AR. In nasal allergen challenge models, pretreatment with INS results in significant reduction in mediator and cytokine release along with a significant inhibition in the recruitment of basophils, eosinophils, neutrophils, and mononuclear cells to nasal secretions.[118-120] Moreover, use of these agents in seasonal disease leads to a reduction in inflammatory cells and cytokines within the nasal mucosa and secretions of patients with AR.[121,122] INS also reduce the antigen-induced hyperresponsiveness of the nasal mucosa to subsequent challenge by antigen[123] and histamine release.[124,125]

Placebo-controlled clinical trials demonstrate the effectiveness of INS in the reduction of nasal symptoms including sneezing, itching, rhinorrhea, and congestion in adults and children with AR.[126-129] By reducing nasal symptoms, INS significantly improve the quality of life[126,127,130] and sleep[115,131-134] of patients with AR. There are no significant differences in efficacy between the available agents.[126] Onset of action starts at time points ranging from 3-5 hours to 36 hours after first dosing.[135-139] The continuous use of INS is recommended and more efficacious than intermittent use[140,141] However, studies of as-needed use of intranasal fluticasone have shown that intermittent use is better than placebo.[142,143]

As far as duration of therapy before INS are considered ineffective, onset of action starts at time points ranging from 3-5 hours to 36 hours after the first dose, as mentioned above. The studies suggest that once efficacy is reached after the first dose, it is maintained for the duration of these trials. Although there seems to be more reduction in some of these parameters over the length of therapy, these changes are not statistically significant compared with the time points when active drugs reached statistically significant benefit. Therefore, based on the above data, it is reasonable to assume that efficacy would be reached after 1 week of therapy at the most and, if none is observed, the treatment might be considered ineffective.

Along with diminished nasal symptoms, INS have beneficial effects on allergic eye symptoms including itching, tearing, redness, and puffiness.[144,145] These symptoms are thought to occur from the direct effects of allergen on the conjunctiva and reflexes originating in the nose after allergen exposure. The reflex response is reduced by INS.[146] Some studies have also suggested that INS improve asthma control in patients suffering from both AR and asthma[97,147] (see Statement 5 on chronic conditions and comorbidities). Hypertrophic adenoids can also be reduced in size with INS use.

Comparative studies have shown that INS are superior to oral H_1 antihistamines in controlling nasal symptoms, including nasal congestion, with no significant difference in the relief of ocular symptoms.[148-150] INS are more effective than leukotriene receptor antagonists across the range of allergy symptoms.[150,151] However, intranasal antihistamines have a more rapid onset of action than INS in comparison studies.[152,153]

Different preparations of INS are comparable in efficacy, making sensory attributes an important factor in patient preference and adherence to therapy.[154] These sensory attributes include aftertaste, nose runout, throat rundown, and smell. To address some of these concerns, nonaqueous intranasal preparations with hydrofluoroalkane aerosol are now approved for the treatment of AR in the United States.[155-158]

The most common side effects of INS are a result of local irritation and include dryness, burning, stinging, blood tinged

secretions, and epistaxis. The incidence of epistaxis with different preparations ranges from 4% to 8% over short treatment periods ranging from 2 to 12 weeks with no differences between placebo and active therapy.[159,160] Higher incidences of epistaxis (reaching 20%) are reported in studies carried over a year.[161,162] Epistaxis can be minimized with proper INS positioning and administration, generally pointed away from the septum within each side of the nose. Septal perforations, although rare, have been reported.[163] Biopsy specimens from the nasal mucosa of patients with perennial rhinitis who have been treated with INS continuously for 1 to 5 years showed no evidence of atrophy.[164-171] Studies in adults and children evaluating the effects of INS on the hypothalamic-pituitary axis using morning cortisol concentrations, cosyntropin stimulation, and 24-hour urinary free cortisol excretion show no adverse effects.[162,172-183] There is some evidence of hypothalamic-pituitary-adrenal axis suppression with betamethasone nasal spray specifically.[184,185] Patients with HIV may absorb INS at a higher rate and need to use caution when using INS or find an alternative treatment.[186-188] Although there have been reports of an association between the use of INS and the development of posterior subcapsular cataracts,[189] later work did not corroborate these concerns.[190,191] Studies with INS given over several months have failed to show development of posterior subcapsular cataracts, significant increases in intraocular pressure, or glaucoma.[162,172,180,192]

The effect of INS on growth in children has been investigated in controlled studies using both knemometry (a technique able to measure short-term growth by estimating the distance between heel and knee of the sitting child with an accuracy of 0.09-0.16 mm) in short-term studies and stadiometry (the accurate measurement of height using an instrument that provides a direct digital reading of height that is accurate to the nearest millimeter) in yearlong, placebo-controlled studies where height is measured monthly. In knemometry studies, intranasal budesonide reduced lower leg growth rate in 2 studies, but the difference was statistically significant in only one of them.[193,194] In placebo-controlled studies, fluticasone furoate, triamcinolone acetonide (in 2 doses), and fluticasone propionate for 2 weeks did not affect lower leg growth rate compared with placebo.[195,196] In the yearlong studies using stadiometry, intranasal beclomethasone dipropionate, at twice the recommended daily dosage, resulted in growth suppression, but fluticasone propionate and mometasone furoate showed no effects on growth compared with placebo.[197,198] In a small, nonrandomized, open-label study, children were followed for 2 years while receiving triamcinolone acetonide nasal spray, and their height was measured by stadiometry and compared with predicted values; no significant difference was shown between measured and predicted heights.[199] Therefore, in clinical practice, it seems prudent to use the intranasal steroid preparations that have not been shown to have any negative impact on growth in children, as detailed above.

Short courses of systemic corticosteroids are often used clinically for patients with severe AR but have not been shown to be superior to INS.[7,200] In nasal challenge studies, systemic steroids are effective in reducing AR symptoms, mediator release, and eosinophil influx during the late phase response.[119,201] An open-label study evaluated the effect of 3 different therapies in patients with seasonal AR: oral loratadine, oral loratadine with mometasone furoate nasal spray, and oral antihistamine with oral betamethasone.[200] Results showed that both groups with steroid therapy had significantly higher symptomatic improvements in sneezing, nasal obstruction, watery nasal discharge, and nasal itching over the 7 days of therapy than the group with loratadine alone, with no significant difference between the 2 steroid groups. While oral corticosteroids have potent anti-inflammatory effects, they are not recommended for the routine treatment of AR due to known significant systemic side effects and lack of superiority to INS.

INS are strongly recommended for the treatment of AR by virtue of their superior efficacy in controlling nasal congestion and other symptoms of this inflammatory condition. Prophylactic treatment with INS is best initiated several days before the pollen season in subjects with known seasonal AR. Beginning treatment at the recommended dose is suggested followed by evaluation of the patient's response on follow-up. During this visit, the nose should be examined for signs of local irritation due to the drug or mechanical trauma from the applicator itself, and the treatment regimen should be modified according to the patient's response. A list of FDA-approved INS, by patient age, can be found in **Table 9**.

STATEMENT 7. ORAL ANTIHISTAMINES: Clinicians should recommend oral second-generation/less sedating antihistamines for patients with AR and primary complaints of sneezing and itching. *Strong recommendation based on RCTs with minor limitations and a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Avoidance of sedating antihistamine use and promotion of use of effective symptom-directed therapy
- Aggregate evidence quality: Grade A, based on randomized controlled trials with minor limitations
- Level of confidence in evidence: High
- Benefits: Rapid onset of action, oral administration, relief of symptoms, over-the-counter availability, potential cost saving (generic brand), relief of eye symptoms
- Risks, harms, costs: Systemic side effects (sedation), dry eyes, urinary retention
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: None
- Intentional vagueness: None
- Role of patient preferences: Large—Shared decision making in considering the benefits, harms, costs, and evaluation of the best treatment options. Clinicians should offer a comparison of evidence for the effectiveness of oral versus nasal administration of

Table 9. Intranasal Steroids.

Name	Formulation	FDA Indications	Contraindications	Age Approved	Dosing	Common Side Effects	OTC or Prescription
Triamcinolone acetonide[a] (Nasacort Allergy 24HR), 55 µg per spray	Propellant, aqueous	Seasonal and perennial AR	History of hypersensitivity to medication or components	≥2 y	Age 2-5 y: 1 spray per nostril every day Age 6-11 y: 2 sprays per nostril every day Age ≥12 y: 2 sprays per nostril 1 or 2 times per day	Pharyngitis, epistaxis, cough	OTC
Budesonide (Rhinocort AQ) 32 µg per spray	Propellant	AR and nonallergic rhinitis	History of hypersensitivity to medication or components	≥6 y	Age ≥6 y: 2 sprays per nostril twice a day or 4 sprays per nostril in the morning	Epistaxis, pharyngitis, bronchospasm, coughing, nasal irritation	Prescription
Flunisolide[b] (Nasalide or Nasarel), 25 µg per spray	0.025% solution	Seasonal and perennial AR	History of hypersensitivity to medication or components	≥6 y	Age 6-14 y: 1 spray per nostril 3 times per day or 2 sprays per nostril twice a day Age >14 y: 2 sprays per nostril 2 or 3 times per day	Epistaxis, pharyngitis, cough, aftertaste, nasal burning or stinging	Prescription
Fluticasone propionate[b] (Flonase), 50 µg per spray	0.05% nasal spray (aqueous)	AR and nonallergic rhinitis	History of hypersensitivity to medication or components	≥4 y	Age 4 y to adult: 1 spray per nostril every day Adult: 2 sprays per nostril every day	Headache, pharyngitis, epistaxis, nasal burning or irritation, nausea or vomiting, asthma symptoms, cough	Prescription
Mometasone furoate (Nasonex), 50 µg per spray	Aqueous	Seasonal and perennial AR, nasal polyps	History of hypersensitivity to medication or components	≥2 y	Age 2-11 y: 1 spray per nostril every day Age ≥12 y: 2 sprays per nostril every day Age ≥18 y with polyps: 2 sprays per nostril twice a day	Headache, viral infection, pharyngitis, epistaxis, cough	Prescription
Ciclesonide (Omnaris), 50 µg per spray	Aqueous suspension	Seasonal and perennial AR	History of hypersensitivity to medication or components	≥6 y	Age ≥6 y: 2 sprays per nostril every day	Epistaxis, headache, nasopharyngitis, ear pain, pharyngolaryngeal pain	Prescription
Fluticasone furoate (Veramyst), 27.5 µg per spray	Suspension	Seasonal and perennial AR	History of hypersensitivity to medication or components	≥2 y	Age 2-11 y: 1-2 sprays per nostril every day Age >11 y: 2 sprays per nostril every day	Epistaxis, headache, pharyngolaryngeal pain, nasal ulceration, back pain, pyrexia, cough	Prescription
(Qnasl), 80 µg per spray	HFA nonaqueous aerosol	Seasonal and perennial AR	History of hypersensitivity to medication or components	≥12 y	Age ≥12 y: 2 sprays per nostril every day	Nasal discomfort, epistaxis, headache	Prescription
Ciclesonide (Zetonna), 37 µg per spray	HFA-propelled aerosol	Seasonal and perennial AR	History of hypersensitivity to medication or components	≥12 y	Age ≥12 y: 1 spray per nostril every day	Nasal discomfort, epistaxis, headache	Prescription

Abbreviations: AR, allergic rhinitis; HFA, hydrofluoroalkane; OTC, over the counter.
[a]Only preparation available OTC.
[b]Available in generic form.

antihistamines and nasal steroids that will provide good patient adherence and treatment efficacy.
- Exclusions: None
- Policy level: Strong recommendation
- Differences of opinions: None

Supporting Text

The purpose of this statement is to define the role and encourage the use of oral antihistamines in the treatment of AR. These agents have been in use since the 1940s, and numerous controlled clinical studies have established their effectiveness, in both children and adults, for relief of symptoms including rhinorrhea, sneezing, itching, and nasal blockage as well as associated ocular complaints.[202-206] While these agents may not be as effective as INS, they are adequate for many patients with mild to moderate disease and have the advantage of lower cost, rapid onset of action, and effectiveness for intermittent symptoms.

Oral antihistamines, which block the action of histamine on the H_1 receptor, have numerous anti-inflammatory effects[206] and can be broadly categorized as first- or second-generation agents. Older first-generation agents, which are lipophilic and cross the blood-brain barrier, also have antimuscarinic effects. Newer second-generation agents are highly selective for the H_1 receptor and have limited penetration of the central nervous system. Examples of first-generation medications include diphenhydramine, chlorpheniramine, and hydroxyzine. The use of first-generation agents is limited by the side effects of sedation and mucosal dryness. It is important to recognize that performance impairment may occur even when patients have no obvious perception of drowsiness.[207,208] Commonly used second-generation drugs include fexofenadine, cetirizine, levocetirizine, loratadine, and desloratadine. In almost all situations, second-generation antihistamines are preferred. There are relatively few comparative studies among the various compounds of second-generation antihistamines, but data indicate that cetirizine and its active enantiomer, levocetirizine, are the most potent[209-212] but carry a modest risk of sedation not seen with other drugs in this class.[208,213,214]

Advantages of oral antihistamines include rapid onset of action,[215,216] once-daily dosing, maintenance of effectiveness with regular use, and the availability of some drugs without a prescription. Some patients who fail to improve with one agent may respond to an alternative drug in this category.[217,218] Maximum benefit is seen with continuous use,[219,220] but use on an as-needed basis can provide significant symptom relief and is appropriate for some patients, especially those with intermittent symptoms.[221]

Although most studies have shown that INS, used on a continuous basis, is superior to oral antihistamines for treatment of AR, especially for symptoms of nasal congestion,[150,222-226] an antihistamine, used as a single agent either intermittently or continuously, may provide adequate relief for many individuals. Oral antihistamines usually produce no further improvement when added to treatment with INS, although the addition of as-needed INS to a regularly taken oral antihistamine is a viable strategy.[227,228] The decision to use oral agents rather than intranasal sprays is often a matter of patient preference, and consideration of this preference may promote better adherence to therapy. **Table 10** provides a list of FDA-approved oral antihistamine medications for AR, including contraindications, common side effects, approval age, and availability (over the counter or prescription).

STATEMENT 8. INTRANASAL ANTIHISTAMINES: Clinicians may offer intranasal antihistamines for patients with seasonal, perennial, or episodic AR. *Option based on RCTs with minor limitations and observational studies, with equilibrium of benefit and harm.*

Action Statement Profile

- Quality improvement opportunity: Improve awareness of this class of medications as another effective treatment for AR that may be an alternative to other medication classes
- Aggregate evidence quality: Grade A, based on randomized controlled trials with minor limitations and observational studies
- Level of confidence in evidence: High, but most of the trials were of short duration
- Benefits: Rapid onset, increased effectiveness over oral antihistamines for nasal congestion
- Risks, harms, costs: Increased cost relative to oral antihistamines, poor taste, sedation, more frequent dosing, epistaxis, local side effects
- Benefit-harm assessment: Equilibrium
- Value judgments: The Guideline Development Group felt that in general this class of medications would represent second-line therapy after failure of nasal steroids or oral antihistamines due to poor acceptance, taste, and cost but that there may be specific patients in whom this class would be an appropriate first-line therapy.
- Intentional vagueness: None
- Role of patient preferences: Large—There is equilibrium of benefits to risks when using intranasal antihistamine. Shared decision making may help ensure that the patient understands the potential benefits versus harms of undergoing this treatment, while also promoting patient compliance with medication.
- Exclusions: Not approved for children younger than 5 years.
- Policy level: Option
- Differences of opinion: Minor; there are reasonable data supporting their use, but there was some debate regarding the harm-benefit ratio leading this to be an option. Several panel members thought these should be recommended at the same level as oral antihistamines.

Supporting Text

The purpose of this statement is to address the use of intranasal antihistamines for patients with AR. Antihistamine allergy medications are H_1-receptor antagonists, and 2 intranasal antihistamines are currently approved by the US FDA for

Table 10. Allergic Rhinitis Oral Antihistamines.

Medication	FDA Indications (Seasonal, Perennial)	Contraindications	Approved Ages	Common Side Effects	Dosing	OTC or Prescription
Cetirizine (Zyrtec)	Both	Hypersensitivity to cetirizine, levocetirizine, or hydroxyzine	≥6 months	Occasional sedation, mucosal dryness, urinary retention	Age 2-5 y: 2.5 mg 1 or 2 times per day Age 6-12 y: 5-10 mg/d Age 12-65 y: 10 mg/d Age 66-76 y: 5-10 mg/d Age ≥77 y: 5 mg/d	OTC
Levocetirizine (Xyzal)	Both	Hypersensitivity to levocetirizine, cetirizine, or hydroxyzine	≥6 months	Occasional sedation, mucosal dryness, urinary retention	Age 2-5 y, 1.25 mg/d Age 6-11 y, 2.5 mg/d Age ≥12 y, 2.5-5.0 mg/d	Prescription
Fexofenadine (Allegra)	Seasonal	Hypersensitivity to fexofenadine	≥2 years	Occasional headache	Age 2-11 y, 30 mg twice a day Age ≥12 y, 60 mg twice a day or 180 mg/d	OTC
Loratadine (Claritin, Alavert)	Both	Hypersensitivity to loratadine or desloratadine	≥2 years	Possible sedation with higher than usual doses	Age 2-5 y, 5 mg/d Age ≥6 y, 10 mg/d	OTC
Desloratadine (Clarinex)	Both	Hypersensitivity to desloratadine or loratadine	≥6 months	Possible sedation with higher than usual doses	Age 2-5 y, 1.25 mg/d Age 6-11 y, 2.5 mg/d Age ≥12 y, 5 mg/d	Prescription

Abbreviation: OTC, over the counter.

treatment of AR. Azelastine and olopatadine are both second-generation H_1-receptor antagonists and have equal efficacy in head-to-head, placebo-controlled comparison studies.[229] The formulations of these 2 antihistamines are listed in **Table 11**.

One of the benefits of intranasal application is targeted delivery and increased dosage to nasal tissues while limiting systemic effects.[230] For the treatment of nasal symptoms, intranasal antihistamines have shown equality or superiority to oral antihistamines in numerous well-designed randomized, controlled, and blinded studies.[231-233] Intranasal antihistamines show benefit even in patients who fail oral antihistamine treatment.[233,234] Specifically with regard to nasal congestion, intranasal antihistamines are more efficacious than oral preparations.[232,235,236] Intranasal antihistamines also have the advantage of rapid onset of action in the range of 15 to 30 minutes, which is much faster than in the oral route (average onset 150 minutes).[231,237] Numerous studies have compared INS to intranasal antihistamines. The results are conflicting, with some showing equality[238-240] and some showing superiority of INS.[149,241] Heterogeneity, lack of standardized dosing, lack of validated outcome metrics, and short-term follow-up limit the applicability of these comparisons.

Formulations and recommended doses for the available intranasal antihistamines are shown in **Table 11**. Olopatadine is FDA approved for treatment of seasonal AR in adults and in children 6 years and older. Azelastine 0.1% is approved for age 6 years and older. The azelastine 0.15% solution plus sorbitol and sucralose (added to improve taste) formulation is approved for both seasonal and perennial AR in adults and in children 6 years and older.

The most common adverse events related to intranasal antihistamine use are bitter taste, epistaxis, headache, somnolence, and nasal burning. Bitter taste occurs in 2% to 18% of patients using intranasal antihistamines[229,240,242,243] compared with 0% to 0.2% of patients using INS[240,243] and may reduce patient compliance. While taste aversion has been demonstrated to all intranasal antihistamines, taste varies between formulations. Therefore, a trial of a second formulation may be preferred in patients who have had symptomatic benefit. While early studies quoted somnolence rates around 11%,[232] more recent studies have found rates of 0.4% to 3%, which were equal or only slightly greater than in placebo groups.[7,233,234,243,244] In side-by-side comparisons, the somnolence rates of inhaled antihistamines, inhaled nasal steroids, and

Table 11. Allergic Rhinitis (AR) Intranasal Antihistamines.

Medication	FDA Indications	Contraindications	Approved Ages	Dosing	Common Side Effects	OTC or Prescription
Olopatadine (Patanase) (as HCl) 0.6% (665 µg per spray); aqueous nasal spray	Seasonal AR	None	≥6 y	Age 6-11 y: 1 spray twice a day Age ≥12 y: 2 sprays twice a day	• Bitter taste • Epistaxis • somnolence • Headache	Prescription
Azelastine (Astelin) 0.1% solution (137 µg per spray)	Seasonal AR, vasomotor rhinitis	None	≥6 y	Age 6-11 y: 1 spray twice a day Age ≥12 y: 1-2 sprays twice a day or 2 sprays daily	• Bitter taste • Epistaxis • Somnolence • Headache	Prescription
Azelastine (Astepro) 0.15% solution (205.5 µg per spray)	Seasonal AR, perennial AR	None	≥6 y	Age 6-11 y: 1 spray twice a day Age ≥12 y: 1-2 sprays twice a day or 2 sprays daily	• Bitter taste • Epistaxis • Somnolence • Headache	Prescription
Azelastine plus fluticasone (Dymista) (137 µg of azelastine, 50 µg of fluticasone per spray)	Seasonal AR	None	≥12 y	1 spray per nostril twice a day	• Bitter taste • Epistaxis • Somnolence • Headache	Prescription

placebo have been equivalent.[240,243] Somnolence rate ranges of intranasal antihistamines (0.9%-11.5%), oral antihistamines (1.3%-14%), and placebo (0.3%-10%) overlap as well.[7,232,234] Caution should be taken at the initiation of intranasal antihistamines for signs of somnolence, and follow-up with a clinician is advised to assess response and side effects. Intranasal antihistamines are an effective treatment for AR and can be used as first- or second-line therapy. Due to the rapid onset of action and targeted delivery of intranasal antihistamines, they are especially useful in patients with episodic nasal symptoms or as a pretreatment prior to nasal allergen exposure. The need for twice-daily dosing and the side effects of somnolence and bitter taste, however, may lead clinicians and/or patients to prefer initial treatment with a different class of medication. **Table 11** summarizes a list of FDA-approved intranasal antihistamine medications for AR which includes contraindications, common side effects, approval age, and availability (over the counter or prescription). An AR medication recommendation guideline is summarized in **Table 12**.

STATEMENT 9. ORAL LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRAs):Clinicians should not offer LTRAs as primary therapy for patients with AR. *Recommendation against based on RCTs and systematic reviews, with a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Reduced use of a less effective agent for initial therapy
- Aggregate evidence quality: Grade A, based on randomized controlled trials and systematic reviews
- Level of confidence in evidence: High
- Benefits: Avoid ineffective or less effective therapy, cost saving, decreased variations in care
- Risks, harms, costs: There may be a subset of patients who would benefit from this medication (eg, patients with both AR and asthma).
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: The panel was concerned with the cost of this medication in combination with the evidence that it is less effective than first-line medications.
- Intentional vagueness: None
- Role of patient preferences: Low—Rare patients with intolerance of intranasal therapy and concerns regarding somnolence may benefit from consideration of use of this class of medicine.
- Exclusions: Patient with concurrent diagnosis of asthma. These patients may benefit from oral leukotriene receptor antagonists as a first-line therapy.

Table 12. Guideline Medication Recommendations.[a]

Medication Class	Recommendations for Symptoms				Recommendations for Exposure to Allergen			Recommendations for Symptom Frequency		Recommendations for Symptom Severity		
	Congestion	Rhinorrhea	Sneezing	Nasal Itching	Seasonal	Perennial	Episodic	Intermittent	Persistent	Mild	Severe	Patient Preference
Intranasal steroids	+++	+++	+++	+++	++	++	+	++	++	++	++	Large
Oral antihistamines	+	++	++	++	+	+	+	++	+	+	No	Large
Intranasal antihistamines	++	++	++	++	++	+[b]	++	++	+[b]	++	+	Large
Leukotriene receptor antagonist	+	+	+	+	+	+	No	No	Yes	Yes	Not as monotherapy	Low

[a]The plus symbols indicate the relative effectiveness for each medication class for the various symptoms: for example, most effective for congestion (+++) but also effective for each of the other symptoms (+).
[b]One of the intranasal antihistamines available in the United States (Astepro) is indicated for perennial/persistent AR.

- Policy level: Recommendation
- Differences of opinion: None

Supporting Text

The purpose of this statement is to reduce the use of a more expensive, less effective agent as first-line treatment of AR.

The LTRA montelukast is FDA-approved for treatment of symptoms of seasonal AR in adults and pediatric patients 2 years of age and older and perennial AR in adults and pediatric patients 6 months of age and older. While several other LTRAs are available in the United States, montelukast is the only LTRA approved by the FDA for AR. Systematic literature reviews and meta-analyses (predominantly based on controlled studies of montelukast in adults with seasonal AR) conclude that LTRAs are more effective at controlling symptoms and improving quality of life than placebo.[245-248] While some studies have shown that LTRAs are as effective as oral antihistamines,[151,245,247,248] others have shown that LTRAs are less effective[246] than oral antihistamines and INS.[151,245-248] In a single randomized, double-blind study, montelukast had a similar effect to pseudoephedrine in reducing symptoms of AR except the symptom of nasal congestion, for which pseudoephedrine was more effective.[249] In patients having both AR and asthma, montelukast improves both conditions.[250-253]

Montelukast is generally well tolerated and is not associated with drowsiness.[254] In placebo-controlled trials, behavior-related adverse events were infrequent.[255] However, some postmarketing reports have demonstrated rare drug-induced neuropsychiatric events (including aggression, depression, suicidal thinking, and behavior).[256] Suicidal ideation was reported in 1 of 9929 patients (0.01%) in clinical trials treated with montelukast.[257]

Montelukast has traditionally been more expensive than oral antihistamines,[258] although the cost differential has been lessened with the introduction of generic montelukast. Because montelukast is currently more expensive and equally as effective as or less effective than oral antihistamines for AR, and because it is less effective than INS, clinicians should not routinely offer an LTRA as primary therapy for patients with AR. However, there may be a subset of patient who have AR and asthma who may benefit from this medication.

STATEMENT 10. COMBINATION THERAPY: Clinicians may offer combination pharmacologic therapy in patients with AR who have inadequate response to pharmacologic monotherapy. *Option based on RCTs with minor limitations and observational studies, with equilibrium of benefit and harm.*

Action Statement Profile

- Quality improvement opportunity: Reduce variations in care, improve symptom control
- Aggregate evidence quality: Grade A, based on randomized controlled trials with minor limitations and observational studies
- Level of confidence in evidence: High. There is strong evidence supporting the use of some combinations and the ineffectiveness of other combinations.

- Benefits: Improved effectiveness and symptom control of combined therapy
- Risks, harms, costs: Increased cost, overuse of medication, use of ineffective combinations, multiple medication side effects, drug interactions
- Benefit-harm assessment: Equilibrium
- Value judgments: None
- Intentional vagueness: The term "combination therapy" is nonspecific as there are multiple different combinations. The details are elaborated in the supporting text. The term "inadequate response to monotherapy" also allows for some interpretation by clinicians and patients.
- Role of patient preferences: Moderate—Shared decision making in consideration of evidence for benefits, harms and cost of combinations, effective dosing, and potential medication interactions to assist the patient in more effective treatment compliance.
- Exclusions: Decongestants that are part of some combined products are not approved for children under the age of 4 years.
- Policy level: Option
- Differences of opinion: None

Supporting Text

The purpose of this statement is to promote the use of effective and decrease the use of ineffective pharmacologic combinations for the treatment of AR. When initial therapy with an INS does not lead to adequate control of allergic nasal symptoms, or the patient cannot tolerate INS, the practitioner may choose combination therapies, of which the most effective additive to an INS is an intranasal antihistamine. In severe nasal obstruction, adding topical oxymetazoline to INS for a few days has proven benefit, but due to concerns about nasal rebound, topical oxymetazoline use should be limited to a few days. If nasal sprays are disliked or not tolerated, combination therapy of an oral antihistamine and decongestant is the next most effective pharmacotherapy for AR. The selection of effective pharmacotherapy for AR may be influenced by coexisting conditions of allergic conjunctivitis or asthma. While oral antihistamines and INS are common selections for primary monotherapy, their combination does not offer much clinical benefit.

Intranasal Steroids and Oral Antihistamines

When patients have no response to INS or incomplete control of nasal symptoms with an INS, oral antihistamines should not be routinely used as additive therapy. The largest trials have shown no benefit of taking an INS plus oral antihistamine compared with INS plus placebo in adults.[259,260]

A Cochrane review including only one study of adequate quality found no evidence to support this combination in children.[261]

Oral Antihistamines and Oral Decongestants

Oral antihistamines and oral decongestant combinations control AR symptoms better than either oral antihistamine or oral decongestant alone. This benefit has been consistently demonstrated in multiple randomized, placebo-controlled trials, each with more than 500 subjects enrolled.[262-270] Adding an oral decongestant to a second-generation antihistamine increases side effects of insomnia, headache, dry mouth, and nervousness.[263,264,267] Additionally, the potential for tolerance from chronic use of oral decongestants may be seen.

In one study, 24-hour extended-release pseudoephedrine (240 mg) caused less insomnia than 12-hour extended-release pseudoephedrine (120 mg) taken twice daily (4% vs 15%, $P < .01$).[271] A 2005 meta-analysis concluded that "pseudoephedrine caused a small but significant increase in systolic blood pressure (0.99 mm Hg; 95% CI, 0.08 to 1.90) and heart rate (2.83 beats/min; 95% CI, 2.0 to 3.6), with no effect on diastolic blood pressure (0.63 mm Hg, 95% CI, –0.10 to 1.35)."[272] Oral decongestant use is not recommended for patients under 4 years of age, and the extended-release, 120-mg, 12-hour dose is not recommended for patients under 12 years of age.

Oral Antihistamines and Leukotriene Receptor Antagonists

There is conflicting evidence as to whether combined treatment with oral antihistamine and LTRA is superior to either as single treatment, and therefore routine use of combined therapy is not recommended. Combinations of oral antihistamines and LTRAs were equivalent to oral antihistamine alone within arms of several studies.[273-277] Alternatively, some trials showed that oral antihistamine plus LTRA was superior to oral antihistamine alone[278-280] or LTRA alone[278,279] for AR symptoms. Other studies showed a benefit when combining oral antihistamine and LTRA compared with oral antihistamine or LTRA in preventing symptoms,[281] in patients who had poor control with LTRA monotherapy,[282] and specifically in nighttime symptoms.[276] Combination of oral antihistamine and LTRA is either inferior to[273,283-285] or less likely equivalent to[277] INS monotherapy in control of AR symptoms.

Intranasal Steroids and Leukotriene Receptor Antagonists

LTRAs should not routinely be used as additive therapy for patients benefiting from INS for AR.[283,286,287] Three studies with arms that compared INS to INS + LTRA did not show a significant benefit to adding LTRA for their primary outcome. The largest trial enrolled 102 patients.[287]

Intranasal Steroids and Intranasal Antihistamines

The combination of INS and intranasal antihistamine is more effective than INS or intranasal antihistamine monotherapy for AR.[243,288-290] This benefit has been demonstrated across multiple symptoms of AR and in patients with moderate to severe symptoms.[290] In patients who tolerate INS or intranasal antihistamine spray and have inadequate control of AR symptoms with a single agent, combined INS + intranasal antihistamine is an effective option.[243,288-290]

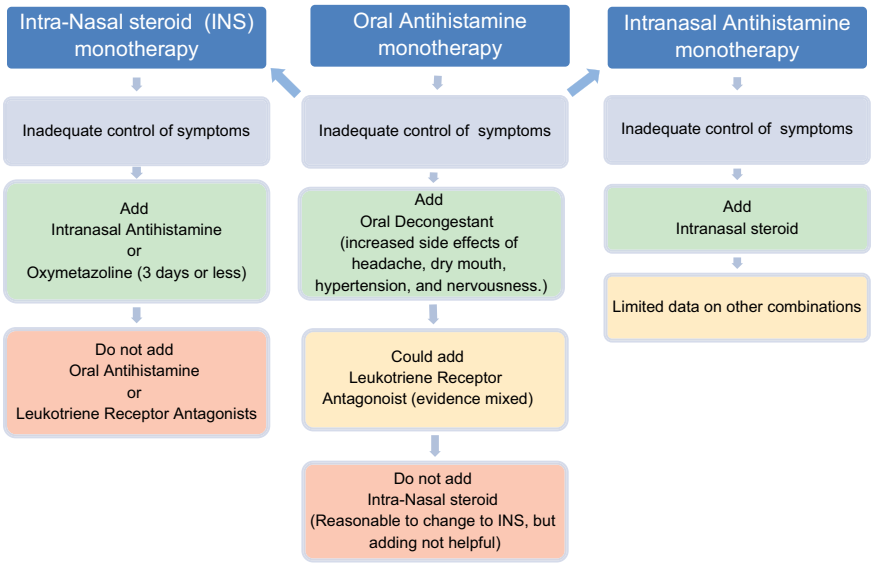

Figure 1. Recommendations for adding a second medication to treat allergic rhinitis.

Intranasal Steroids and Intranasal Oxymetazoline

The combination of INS and intranasal oxymetazoline is more effective in controlling AR symptoms than either monotherapy.[291-294] The development of rhinitis medicamentosa (rebound nasal congestion from overuse of intranasal oxymetazoline) is a concern. The sizes and lengths of the currently available studies are insufficient to draw conclusions about the risk of rhinitis medicamentosa. Short-term use (<3 days) of this combination in cases of severe nasal congestion is recommended. **Figure 1** illustrates the recommendations for adding a second medication to treat allergic rhinitis.

STATEMENT 11. IMMUNOTHERAPY: Clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls. *Recommendation based on RCTs and systematic reviews, with a preponderance of benefit over harm.*

Action Statement Profile

- Opportunity for quality improvement: Increased appropriate use of immunotherapy and reduced variation in care; increased awareness of immunotherapy
- Aggregate evidence quality: Grade A, based on randomized controlled trials and systematic reviews
- Level of confidence in evidence: High
- Benefits: Altered natural history, improved symptom control, decreased need for medical therapy, long-term cost-effectiveness, may improve or prevent asthma or other comorbidities, and may prevent new sensitizations
- Risks, harms, costs: Local reactions, systemic reactions including anaphylaxis, increased initial cost, frequency of treatment (logistics), pain of injection, delayed onset of symptom control (months)
- Benefit-harm assessment: Preponderance of benefit over harm
- Value judgments: None
- Intentional vagueness: We elected to use the term "inadequate response to medical therapy" as there are circumstances where immunotherapy may be beneficial for symptom control even if there is some response to medical therapy since immunotherapy addresses the underlying pathophysiology of atopy.
- Role of patient preferences: Large—There are potential risks, harms, and costs associated with the use of immunotherapy and a delayed onset. Shared decision making may help the patient understand the potential harms of undergoing this treatment. In addition, the efficacy of using this mode of therapy depends on patient compliance with frequency and duration of treatment as well as delay in onset of effect with immunotherapy.
- Exclusions: Uncontrolled asthma
- Policy Level: Recommendation
- Differences of opinion: Minor; some panel members felt that immunotherapy could be offered as first-line treatment to patients who elect not to use medical therapy.

Supporting Text

The purpose of this statement is to increase the awareness of immunotherapy as a treatment for AR, promote its appropriate use, and reduce unnecessary or harmful variation in care.

Allergen-specific immunotherapy (SIT) involves controlled, repetitive dosing of allergen(s) in patients diagnosed with IgE-mediated AR by history and confirmed with specific allergy testing in order to increase immune tolerance to the offending allergen(s). The ultimate goal of SIT is to decrease

Table 13. Comparison of Features of SCIT and SLIT.

	SCIT	SLIT
Effectiveness for allergic rhinitis	Supported by systematic reviews of randomized controlled trials	Supported by systematic reviews of randomized controlled trials
Safety	Deaths: 1 per 2.5 million injections	No reported deaths
Rate of systemic reactions	0.06%-0.9%	0.056%
Dosing	Administered in physician's office	Administered at home SLIT aqueous dosing not standardized First dose of SLIT tablet should be administered in physician's office
FDA status	FDA approved	SLIT aqueous FDA "off-label" use SLIT tablets approved by FDA in April 2014; limited number of allergens available for treatment
Socioeconomic	*CPT* code exists for SCIT vial preparation and injections Covered by most insurance plans	No *CPT* code exists for SLIT aqueous preparation. SLIT aqueous not covered by most insurance plans. SLIT tablet insurance coverage to be determined by individual insurance carriers.

Abbreviations: *CPT, Current Procedural Terminology*; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

AR symptoms. SIT is the only proven treatment for AR that has the potential to change the natural history of the disease. There is a large role for patient preference in the decision to undertake immunotherapy, as the therapy carries potentially serious risks (such as anaphylaxis), has added costs (ie, frequent office visits for injections), and entails delayed onset of symptom control, and the duration of therapy is several years. In the United States, 2 forms of immunotherapy are in clinical use: subcutaneous immunotherapy (SCIT), and sublingual immunotherapy (SLIT) in aqueous and tablet form.[295] The FDA approved SLIT tablets for use in the United States in April 2014; however, there are no FDA-approved aqueous formulations, and therefore using any aqueous SLIT would be considered an off-label use. Currently there are no US practice guidelines specifically addressing the dosing of aqueous SLIT, which is not standardized. Typically, SCIT injections are performed at a physician's office at regular intervals, while SLIT is administered daily at home with the allergen held under the tongue for mucosal absorption for a short period of time. It must be emphasized that demonstration of IgE-mediated allergy based on history and confirmed by specific allergy testing (skin or in vitro) is a prerequisite for all forms of immunotherapy, both SLIT and SCIT. The typical duration of treatment for either form of immunotherapy is several years, typically 3 to 5 years.[296,297]

Both SCIT and SLIT have been shown to be efficacious in reducing the symptoms of AR in several large-scale systematic reviews. A 2013 systematic review of the efficacy of SCIT for AR included 61 RCTs and found high-grade evidence that SCIT reduces AR symptoms, with moderate evidence that SCIT decreases medication usage.[298] This confirms the findings of previous systematic reviews of SCIT, which found reductions in rhinitis symptom scores and medication use.[101,299,300] The efficacy of SLIT for AR has also been confirmed by several systematic reviews.[296,301,302] The most recent of these included 63 RCTs of SLIT, providing a moderate grade level of evidence that SLIT improves AR symptoms.[296] Both forms of SIT have been shown to improve the control of comorbid conditions, such as asthma,[102,298,303] conjunctivitis,[298,303,304] and disease-specific quality of life[298,303]; in addition, RCTs have shown that SIT may prevent the development of asthma[305-307] and new allergic sensitivities.[307,308] The positive effects of immunotherapy can continue after discontinuation of SIT, with studies documenting continued beneficial effects at 10 and 8 years after treatment cessation for SCIT[309] and SLIT, respectively.[310] Patients on SIT should be monitored on a regular basis for effectiveness based on clinical parameters such as symptoms and medication use; typically, positive benefits of immunotherapy on AR symptoms appear from several weeks to 1 year after initiation of therapy, but repetitive allergy testing is not recommended.[297]

While SIT has been shown to be beneficial in AR, the use of immunotherapy has potential adverse events. These reactions are classified as either local or systemic. In SCIT, local reactions include redness and induration at the site of injection; in SLIT, local reactions include oral itching and discomfort. The rates of local reactions have been reported to be in the range of 0.6% to 58% for SCIT and 0.2% to 97% for SLIT.[303] Systemic reactions can be provoked by either form of SIT and can include urticaria, gastrointestinal upset, wheezing, and anaphylaxis. For SCIT, the rate of systemic reactions has been reported to be 0.06% to 0.9%[311] and deaths have been reported at 1 per 2.5 million SCIT injections (3.4 deaths per year)[312]; for SLIT, systemic reactions are reported at 0.056%, with no reported deaths.[303,311] Due to the potential for serious reactions, current practice guidelines indicate that SCIT should not be used in patients with uncontrolled asthma, SCIT should be administered in a physician's office where serious reactions can be promptly recognized, and the patient should be observed for 30 minutes after injection.[297] However, a prospective observational study was conducted of 635,000 patients who received more than 1 million injections of

immunotherapy; the injections were either self-administered by patients at home or administered by medical staff in-office. No hospitalizations or deaths were reported, and the authors concluded that home immunotherapy was safe in selected patients when using appropriate precautions.[313] In addition, the use of β-blockers is a relative contraindication as this may complicate the treatment of anaphylaxis.[297] SLIT dosing is generally done at home because of the perceived improved safety profile. However, there have been reports of anaphylaxis with SLIT,[314] and in Europe there have been calls for the first dose of sublingual immunotherapy tablets to be given in a physician's office.[315] The recommendations regarding the SLIT tablets recently approved by the FDA also include the first administration of the tablet in a physician's office with a 30-minute observation period and prescription of an autoinjectable epinephrine device as a precaution for home administration of the tablet.[316-319] The SLIT tablet is contraindicated in patients with severe, unstable, or uncontrolled asthma. While the risks of serious systemic adverse events are very rare for either form of SIT, patients considering immunotherapy should be informed of this risk. The overall benefit-harm assessment of SIT demonstrates a preponderance of benefit, in consideration of this effective form of therapy with potential for disease modification and the very rare risk for serious reactions.

Both SCIT and SLIT have been shown to be efficacious for AR, but there is ongoing debate as to whether one form is superior; systematic reviews have addressed this subject.[320-322] The first of these[320] concluded that superiority of one mode over another could not be consistently demonstrated through indirect comparison. The second systematic review of 8 RCTs with head-to-head comparisons of SCIT versus SLIT[321] provided moderate-grade evidence for greater effectiveness of SCIT for nasal symptom reduction; however, the authors concluded that additional studies are required to strengthen this evidence base for clinical decision making. In addition, a pooled analysis of SCIT studies compared with SLIT studies for grass allergens showed a significantly higher effect size on seasonal AR symptoms and medications scores with SCIT compared with SLIT.[322] **Table 13** compares some additional features of SCIT and SLIT.

These guidelines apply to children and adults with AR, diagnosed by history and confirmed by specific allergy testing (see Key Action Statement 2 regarding allergy testing). SIT should be offered to patients with AR whose response to pharmacologic therapy is inadequate. However, immunotherapy may be beneficial for symptom control even if there is partial response to medical therapy, as SIT is currently the only form of treatment with the potential to alter the natural history of the disease. Other potential indications for pursuing immunotherapy may include patient preference, adherence to therapy, medication requirements, response to avoidance measures, adverse effects of medications, coexisting allergic asthma, and possible prevention of asthma in patients with AR. In addition, recent literature suggests there may be a long-term cost savings with immunotherapy. The economic considerations regarding immunotherapy were evaluated, and evidence supports the cost-effectiveness of immunotherapy (SCIT and SLIT) compared with pharmacotherapy for AR.[323] A recent systematic review found a need for further research to determine the relative cost-effectiveness in comparing SCIT with SLIT[324]; a 2012 US study found a wide variation of cost to the patient in regard to SCIT by insurance plan, and the cost of SLIT varied between practices 4-fold.[325] While there are significant benefits of immunotherapy in AR, the decision to pursue immunotherapy should be based on shared decision making between the physician and the patient.

STATEMENT 12. INFERIOR TURBINATE REDUCTION: Clinicians may offer, or refer to a surgeon who can offer, inferior turbinate reduction in patients with AR with nasal airway obstruction and enlarged inferior turbinates who have failed medical management. *Option based on observational studies, with a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Improved nasal breathing and quality of life
- Aggregate evidence quality: Grade C, based on observational studies
- Level of confidence in the evidence: Moderate
- Benefits: Improved symptoms, improved quality of life, improved medication delivery, reduced medication use, better sleep
- Risks, harms, costs: Unnecessary surgery, cost of surgery, risks of surgery, atrophic rhinitis
- Benefit-harm assessment: Balance of benefit and harm
- Value judgments: The panel felt that in spite of lack of head-to-head trials between medical and surgical therapy, surgery should be reserved for patients failing medical therapy due to the higher risk of any surgical management.
- Intentional vagueness: The panel elected to use the term "failure of medical therapy" as there are circumstances where inferior turbinate reduction may be beneficial for symptom control even if there is some response to medical therapy.
- Role of patient preferences: Large—Clinicians should use a shared decision-making process about the risks, benefits, and costs of undergoing surgery and associated use of anesthesia.
- Exclusions: Patients who are not surgical candidates
- Policy level: Option
- Differences of opinion: Minor difference of opinion whether AR is an independent risk factor for turbinate hypertrophy

Supporting Text

The purpose of this statement is to increase awareness of and allow for appropriate use of inferior turbinate reduction surgery as part of the management for AR patients with persistent nasal symptoms and turbinate hypertrophy despite medical treatment.

The inferior turbinates are tissues located on the lateral wall of the inside of the nose that consist of bone covered with tissue that can enlarge and swell in response to inflammation.

Nasal airway obstruction, secondary to hypertrophic inferior turbinates, is a common symptom of AR. Several surgical procedures are available for addressing inferior turbinate hypertrophy. These generally involve different methods for removing either (1) entire portions of the turbinate (turbinectomy) or (2) only the tissues between the mucosal covering and/or the bone of the turbinate (submucous resection); or shrinking the volume of the turbinate (tissue ablation). One prospective randomized study of 382 patients with inferior turbinate hypertrophy compared turbinectomy, laser cautery, electrocautery, cryotherapy, submucosal resection, and submucosal resection with inferior turbinate outfracture.[326] Of these methods, submucous resection with outfracture was the most effective surgical therapy with the fewest complications. These procedures have been described as being performed under local anesthetic, sedation, or a general anesthetic.

Currently, the 2 most common techniques for turbinate reduction are submucous resection and tissue ablation. One prospective randomized study of 60 patients assessed the long-term effect of tissue ablation and submucous resection.[327] Both techniques reduced subjective nasal obstruction at 3 and 6 months. However, the submucous resection group had greater nasal patency at 12 months post treatment compared with the group that underwent tissue ablation.[327]

A nonblinded randomized trial of 58 perennial AR patients who had failed oral antihistamines compared inferior turbinate reduction surgery to INS and assessed the outcome of nasal congestion.[328] After 1 year, both groups had reduction in nasal resistance by acoustic rhinometry. However, the surgical group had statistically significant improvement in nasal congestion symptoms, while the medical group showed a nonsignificant trend for improvement.

Several uncontrolled studies suggest that inferior turbinate procedures may also diminish the symptoms of rhinorrhea and sneezing in patients with AR.[329-331] Fukazawa et al[330] prospectively evaluated 95 patients who underwent inferior turbinate reduction for nasal congestion due to AR. The patients had reduced nasal congestion, rhinorrhea, and sneezing at 1, 3, 6, and 12 months after the procedure. Another uncontrolled prospective cohort of 60 patients undergoing submucous resection of the inferior turbinates showed a decreased nasal response to allergy provocation test at 2 and 12 months after the procedure.[329] A second report in this cohort with 3- and 5-year follow-up demonstrated sustained improvement of symptoms of nasal congestion, sneezing, and rhinorrhea.[331] However, patients with persistent symptoms after surgery may require ongoing medical treatment.

While generally considered to be safe, inferior turbinate reduction can be complicated by nasal bleeding, synechiae (scar) formation, or crusting. Rarely atrophic rhinitis ("empty nose syndrome") can be a complication from inferior turbinate reduction, in which patients have the sensation of nasal obstruction due to lack of sensations of airflow. Atrophic rhinitis is very rare when only submucous resection, rather than turbinectomy, is performed. Finally, turbinate reduction is a surgical procedure with the attendant cost of surgery and the general risks of anesthesia.

While primary medical management is favored as the initial treatment for AR due to its high efficacy, low risk, and relatively low cost, inferior turbinate reduction surgery is a reasonable option for those AR patients with inferior turbinate hypertrophy who have continued symptoms despite medical management or in those patients who cannot tolerate medical treatment.

STATEMENT 13. ACUPUNCTURE: Clinicians may offer acupuncture, or refer to a clinician who can offer acupuncture, for patients with AR who are interested in nonpharmacologic therapy. *Option based on RCTs with limitations, observational studies with consistent effects, and a preponderance of benefit over harm.*

Action Statement Profile

- Quality improvement opportunity: Increased awareness of acupuncture as a treatment option for AR
- Aggregate evidence quality: Grade B, based on randomized controlled trials with limitations, observational studies with consistent effects
- Level of confidence in evidence: Low; the randomized trials did not show comparison to traditional medical therapy for AR and had methodological flaws.
- Benefits: Effective alternative to medical therapies, reduction of symptoms, may more closely align with patient values, improved quality of life, avoidance of medication use and potential side effects
- Risks, harms, costs: Logistics of multiple treatments, need for multiple needle sticks, cost of treatment, rare infections
- Benefit-harm assessment: Equilibrium of benefit and harm
- Value judgments: Panel members varied in their preconceived bias for or against acupuncture.
- Intentional vagueness: None
- Role of patient preferences: Limited—Potential for shared decision making
- Exclusions: None
- Policy level: Option
- Differences of opinions: None

Supporting Text

The purpose of this statement is to enable patient access to potentially beneficial nontraditional treatment and increase awareness of the possible benefit of acupuncture in the treatment of patients with AR.

The NIH National Center for Complementary and Alternative Medicine (NCCAM) defines acupuncture as a family of procedures involving the stimulation of points on the body. The technique that has been most often studied involves penetrating the skin with thin, solid, metallic needles that are manipulated by hand or by electrical stimulation. There are no published estimates of the frequency of acupuncture for AR in the United States, but a nested case-control study of adults with allergic disease in Germany reported that lifetime acupuncture use was 17% for those with AR.[332] A 2006 systematic review of complementary and integrative medicine by the

Allergic Rhinitis and its Impact on Asthma (ARIA) group found that most of the studies up to then were uncontrolled, not randomized, and primarily descriptive.[333] Their evaluation of the RCTs available at the time suggested that results were inconsistent and found that there was no clear evidence supporting the use of acupuncture in AR.

The only pediatric study included in this review was a randomized controlled study of 72 children with perennial AR who were 6 years of age and older.[334] In this study, the children undergoing acupuncture had significant improvement in daily symptoms over 3 months and significantly more symptom-free days but no decrease in symptomatic medication use. The investigators also found that the improvements from acupuncture dissipated in the 10 weeks after completing acupuncture.

A subsequent review separated studies that involved seasonal AR versus perennial AR.[335] This review found that trials evaluating acupuncture for seasonal AR did not support specific effects of acupuncture.[336-339] However, for studies investigating the effect of acupuncture for patients with perennial AR, pooled meta-analysis (N = 152 patients) results suggested that acupuncture patients had a significant improvement in symptom score when compared with those treated with sham acupuncture.[334,335,340-342] Two RCTs included in this review compared acupuncture to cetirizine[343] or to saitezan[344] for perennial AR. Meta-analysis (N = 193) showed that the response rate to acupuncture was not significantly better than conventional medical therapy.[335]

Several large randomized trials have been conducted since the publication of the above reviews. One trial of acupuncture in adults with AR randomized 981 patients to acupuncture versus no treatment; perennial versus seasonal AR was not differentiated in this trial.[345] The standard deviation of number of acupuncture treatments averaged around 10, and patients had as few as 7 and as many as 13 treatments based on the randomized acupuncture numbers mentioned above. At 3 months, scores on the Rhinitis Quality of Life Questionnaire (RQLQ) improved by a mean of 1.48 in the acupuncture group and 0.5 in the control group ($P < .001$); changes of 0.5 are considered clinically relevant, and overall quality of life improvements were statistically greater in the acupuncture group. The RQLQ measures the influence of AR on quality of life and consists of 28 items in the 7 domains of sleep, non–nasal/eye symptoms, emotional function, practical problems, nasal symptoms, eye symptoms, and activities. The patients were asked to assess the impact of AR on these areas during the previous week. Another subsequent large (N = 422), randomized, controlled, multicenter trial of acupuncture in patients with seasonal AR compared acupuncture plus rescue medication (cetirizine) to sham acupuncture with rescue medication to rescue medication alone.[346] Patients undergoing acupuncture were reported to have better RQLQ and reduced rescue medication scores at 7 to 8 weeks than those patients with sham acupuncture and rescue medication ($P < .001$ for both) or rescue medication alone ($P < .001$ for both). Treatment response at 7 to 8 weeks was 71% for acupuncture, 56% for sham acupuncture, and 44% for rescue medication; however, the confidence intervals for improvement in RQLQ and rescue medication scores included values below levels considered to be clinically important. A second multicenter RCT of 191 adults with perennial AR reported a significant improvement in Total Nasal Symptom Score at the end of treatment ($P = .029$) and 4 weeks after treatment ($P = .04$), with 3.68 and 3.77 standard deviation, respectively, when compared with sham acupuncture, and a significant improvement in the Total Non-Nasal Symptom Score compared with the waitlist group ($P = .0002$).[347] Throughout the study, 4 nasal symptoms (nasal obstruction, sneezing, rhinorrhea, and nasal itch) were self-assessed daily and recorded in a diary by participants, using a 5-point scale (0 = no symptom; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe). Seven-day individual and Total Nasal Symptom Scores were determined from the daily symptom scores. No other outcomes were significantly different.[347]

The use of a placebo control in the medical and immunotherapy treatment trials for AR has shown that placebo effects are significant and can be greater than 50% for symptom improvement. For most of the clinical trials reviewed here, sham acupuncture was used. However, the location, depth, and manipulation of the sham needles varied widely, and while some trials report that sham therapy itself might have a therapeutic effect, several showed no placebo effect from sham acupuncture.[348]

The mechanism of action of acupuncture in the treatment of AR is unknown. Studies suggest that acupuncture inhibits cytokine synthesis, such as interleukin-10 in patients with AR and interleukin-6 and interleukin-10 in patients with asthma; however, it remains unclear whether these findings correlate with clinical effect.[349-352]

In summary, one systematic review and several subsequent large RCTs have found that acupuncture offers some symptom control and improved quality of life in patients with perennial AR. Although the systematic reviews of earlier trials did not find a benefit in seasonal AR, subsequent RCTs found benefit to acupuncture for symptom control in seasonal AR patients. Additionally we could find no evidence of significant harms associated with acupuncture. Accordingly, for patients with an interest in nonpharmacologic approaches to management of AR, acupuncture may be offered as an option.

STATEMENT 14. HERBAL THERAPY: No recommendation regarding the use of herbal therapy for patients with AR. *No recommendation based on limited knowledge of herbal medicines and concern about the quality of standardization and safety.*

Action Statement Profile

- Quality improvement opportunity: Not applicable
- Aggregate evidence quality: Uncertain
- Level of confidence in evidence: Low. Many of the studies were small and of questionable methodology. The meta-analyses were done in English but looked at articles from the Chinese literature that are not available for assessment by the panel.
- Benefits: Improved awareness of alternative treatments, improved education of side effects of herbal therapy
- Risks, harms, costs: Not applicable

- Benefit-harm assessment: Not applicable
- Value judgments: There are many herbal therapies, but there is only evidence for a few that have appropriate studies. There is limited knowledge about these products among most of the panel members, and accordingly there was a bias against their use. There is concern about the quality of standardization of herbal medicines and their safety,
- Intentional vagueness: None
- Role of patient preferences: None
- Exclusions: None
- Policy level: No recommendation
- Differences of opinion: None

Supporting Text

The guideline development panel was unable to make a recommendation on the use of herbal therapy for treating patients with AR due to the lack of English-language translation of the majority of the literature, the diversity of and lack of standardization of herbal therapies, and a poor understanding by the panel of the risks and harms of these therapies.

Traditional Chinese herbal medicine has been practiced for over 80 centuries and continues to evolve. The Chinese pharmacopeia has over 13,000 medicinals and more than 100,000 herbal combinations recorded in ancient literature.[353] Although the prevalence and use of traditional Chinese herbal formulations is on the rise globally,[354] there are limited high-quality, large-scale, multicenter trials validating their safety and effectiveness.[355] Studies of traditional Chinese medicine have demonstrated positive benefits in the treatment of AR; however, many of the studies are small in size, the studies investigate different medicines, and some of these studies have possible methodological issues. Therefore, based on the myriad differing herbal therapies, lack of knowledge regarding risks, and the shortcomings of the existing literature, no recommendation can be made regarding the use of traditional Chinese medicine in AR.

The ARIA 2006 guideline identified 3 studies of reasonable quality with an average number of 74 patients evaluating Butterbur, Biminne, and a Chinese herbal mixture. These all showed positive results on clinical symptoms and quality of life for AR, but the ARIA guideline concluded that "the studies were too few to make recommendations."[333]

Many Chinese herbal remedies are commonly prescribed for AR depending on the traditional Chinese medical diagnosis of the patients' signs and symptoms. Various small clinical trials have reported that those herbal decoctions possess antiallergic, anti-inflammatory, or immunomodulatory actions, such as inhibition of the release of mast cell mediation, reduction of histamine release, inhibition of inflammation induced by chemical agents, and modulation of serum IgE levels or of lymphocyte and/or macrophage activity.[356-360] Although progress is ongoing toward global regulation of Chinese herbal products and improved safety,[361,362] currently none of these herbal remedies are regulated by the FDA.

Safety of Chinese Herbal Medicine

While American clinicians may be skeptical of the safety and efficacy of herbal therapies for AR with which they are not familiar,[354,363,364] there have been no reported deaths due to Chinese herbal medicine in the United States in the past 40 years.

Implementation Considerations

The clinical practice guideline is published as a supplement to *Otolaryngology—Head and Neck Surgery*, which will facilitate reference and distribution. A full-text version of the guideline will be accessible, free of charge, at http://www.entnet.org. In addition, all AAO-HNSF guidelines are now available via the *Otolaryngology—Head and Neck Surgery* app for smartphones and tablets. The guideline will be presented to AAO-HNS members as a miniseminar at the 2014 AAO-HNSF Annual Meeting and OTO EXPO. Existing brochures and publication by the AAO-HNSF will be updated to reflect the guideline's recommendations.

As a supplement to clinicians, an algorithm of the guideline's action statements, **Figure 2**, and a table with common allergic rhinitis clinical scenarios, **Figure 3**, has been provided. The algorithm allows for a more rapid understanding of the guideline's logic and the sequence of the action statements. The Guideline Development Group hopes the algorithm can be adopted as a quick reference guide to support the implementation of the guideline's recommendations.

Research Needs

This guideline was based on the current body of evidence regarding treatment of AR. While many of the key action statements were supported by Grade A level evidence, review of the evidence profile for other statements revealed knowledge gaps and the need for further research. As determined by the Guideline Development Group's review of the literature, assessment of current clinical practices, and determination of evidence gaps, research needs were determined as follows:

1. Research is needed to determine the effect of environmental control strategies on AR. The aggregate evidence profile for environmental controls was a Grade B. Controlled trials to identify the efficacy of environmental controls on measurable AR endpoints are needed.
2. Research is needed to evaluate the safety and efficacy of SIT, specifically SLIT. There have been few US-based studies evaluating SLIT, which has been offered in the United States in an off-label, non-FDA-approved fashion. With FDA approval of Oralair, a mixed allergen extract consisting of several pollens (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass), Grastek (treatment for Timothy grass pollen) and Ragwitek (treatment for short ragweed pollen) in 2014, prospective RCTs are needed to properly evaluate the effect of

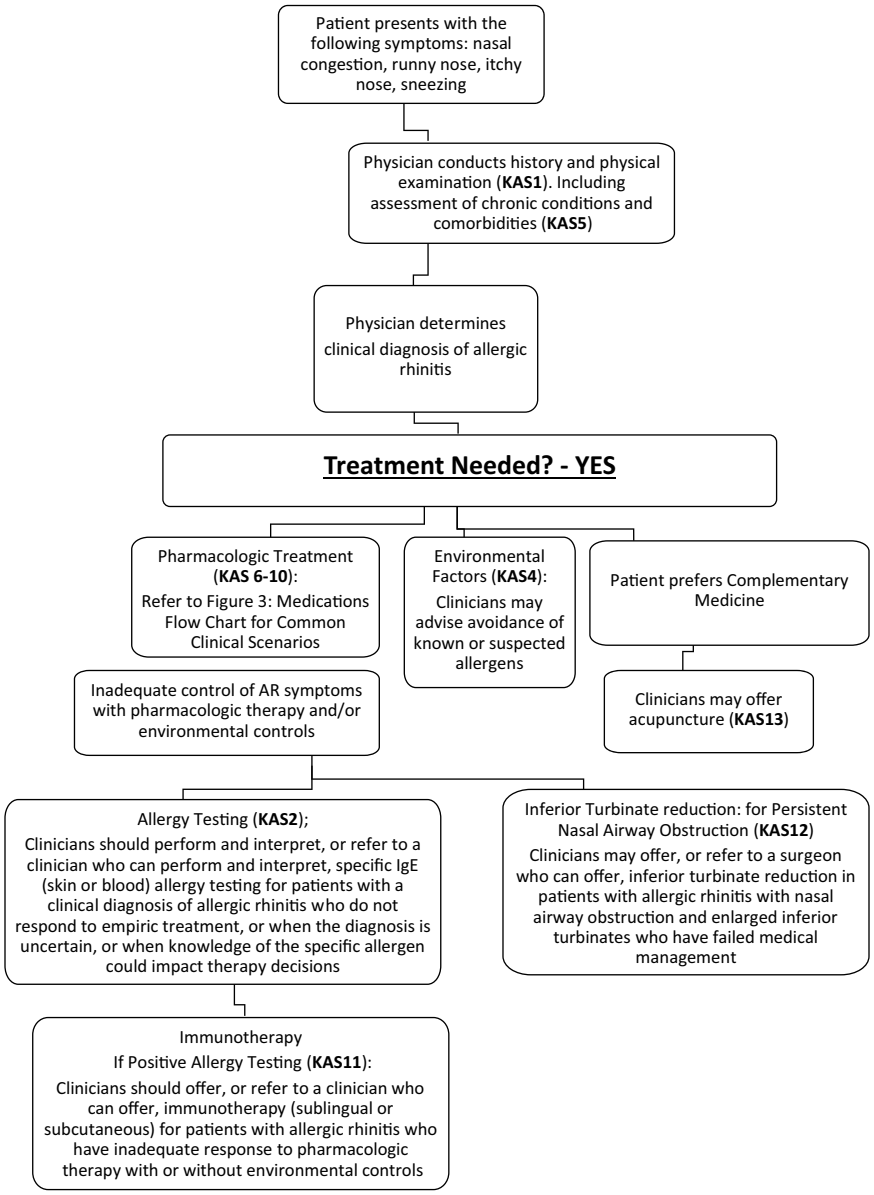

Figure 2. Allergic rhinitis (AR) diagnosis and treatment flow chart for evaluating and managing patients with AR based on this guideline's recommendations. KAS, key action statement.

the office-sold, physician-diluted, nonstandardized products and other SLIT preparations.

3. Cost-effectiveness research (including direct and indirect costs) of SCIT compared with SLIT is needed. Also needed are better comparisons of SLIT versus SCIT; such comparisons are very few and far between, and there are none in the United States.
4. Research is needed to determine the molecular effects of first-line therapies for AR target end-organ immune responses (ie, topical steroids and antihistamines for nasal symptoms). Basic mechanistic research in the fields of allergy and immunology addressing the underlying triggers for specific patients is needed, as well as other immune-modulating treatments that alter the pathophysiology of AR and its comorbid conditions.
5. Research is needed to determine the safety and efficacy of acupuncture for AR. There is a relative paucity of data in the English-language literature regarding the use of complementary and integrative medicine for AR. As such, specific recommendations for or against these treatments could not be made. Higher levels of evidence regarding these therapies need to be obtained through well-designed clinical trials and/or systematic reviews of existing data.
6. The studies on herbal therapies involve use of preparations that combine numerous herbal extracts in varying amounts; thus, research needs to be conducted on specific herbal extracts along with standardization of dosing to determine efficacy for AR.
7. Controlled trials are needed comparing surgical versus medical management of inferior turbinate hypertrophy

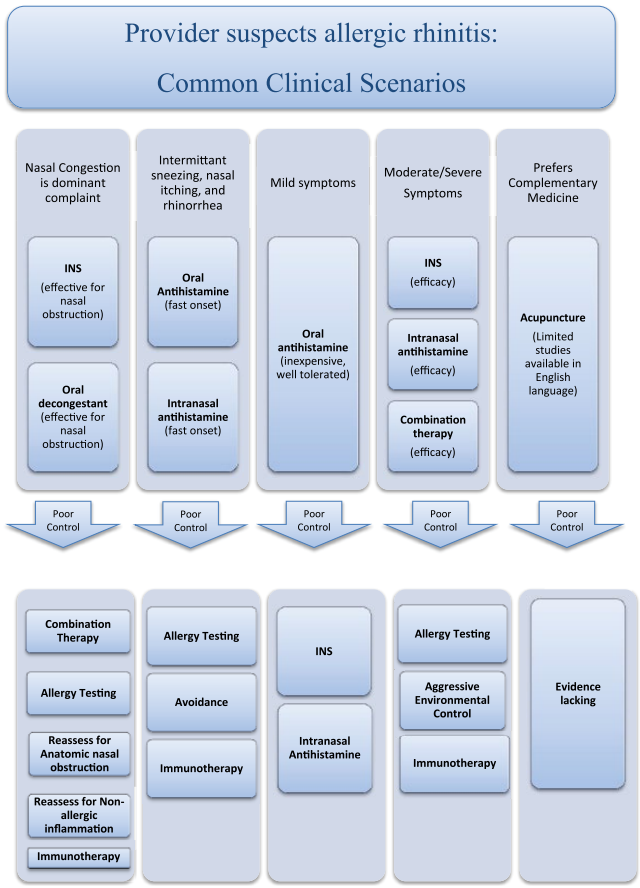

Figure 3. Common allergic rhinitis clinical scenarios. The guidelines task force could not agree on a simple algorithm for treating allergic rhinitis as variations in patient preferences, severity of symptoms, duration of symptoms, coexisting conditions, and allergen sensitizations all influenced reasonable recommendations. Instead, **Figure 3** provides guidance for practitioners using illustrative clinical scenarios that are consistent with available evidence and expert advice.

with nasal congestion in patients with AR. In addition, there is a need for further research regarding the role of septoplasty in the treatment of AR.

8. Research is needed to determine the relationship between AR and comorbid conditions such as otitis media and sinusitis. In addition, research is needed to determine the effect of AR treatment on comorbid conditions and the effect of treatment for comorbid conditions on AR.
9. Research is needed regarding the impact of patient adherence to different treatments, and treatment outcomes, which often is neglected in establishing the evidence base for AR or other treatments in trials. There is a need for increased diversity in trial subjects and the examination of other factors influencing treatment outcomes such as ease or utility of treatment administrations, as well as the impact of patient education aids on patient adherence and subsequent outcomes.
10. More research, including basic and/or translational trials, is needed to evaluate novel forms of immunotherapy such as peptide vaccines, DNA conjugated vaccines, intradermal injections, and intralymphatic injections. These are all strategies that are hypothesized to reduce the allergenicity of extracts while maintaining or enhancing the beneficial effects on the immune system.
11. Analysis is needed of the impact of immunomodulatory agents for the treatment of asthma on AR.
12. The relationship between AR and comorbid conditions such as otitis media and sinusitis should be determined. In addition, research is needed to determine the effect of AR on comorbid conditions.
13. It should be determined whether different forms of allergy testing can provide clinically meaningful information. It is still unclear whether one form of testing is superior to the other in identifying clinically relevant allergens.
14. Studies are needed to determine the effect of combined allergen formulations for AR that are standardized, tolerable, and effectively dosed.
15. Outcome measures are needed using SN-5 or other tools to measure and compare efficacy of medical and surgical treatments for nasal congestion/AR in both children and adults.

Disclaimer

The clinical practice guideline is not intended as the sole source of guidance in managing patients with AR. 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 all individuals with this condition and may not provide the only appropriate approach to diagnosing and managing this program of care. 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.

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