International consensus statement on allergy and rhinology: allergic rhinitis—executive summary

Sarah K. Wise, MD, MSCR[1], Sandra Y. Lin, MD[2] and Elina Toskala, MD, PhD, MBA[3]

Background: **The available allergic rhinitis (AR) literature continues to grow. Critical evaluation and understanding of this literature is important to appropriately utilize this knowledge in the care of AR patients. The International Consensus statement on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR) has been produced as a multidisciplinary international effort. This Executive Summary highlights and summarizes the findings of the comprehensive ICAR:AR document.**

Methods: **The ICAR:AR document was produced using previously described methodology. Specific topics were developed relating to AR. Each topic was assigned a literature review, evidence-based review (EBR), or evidence-based review with recommendations (EBRR) format as dictated by available evidence and purpose within the ICAR:AR document. Following iterative reviews of each topic, the ICAR:AR document was synthesized and reviewed by all authors for consensus.**

Results: **Over 100 individual topics related to AR diagnosis, pathophysiology, epidemiology, disease burden, risk factors, allergy testing modalities, treatment, and other conditions/comorbidities associated with AR were addressed in the comprehensive ICAR:AR document. Herein, the Executive Summary provides a synopsis of these findings.**

Conclusion: **In the ICAR:AR critical review of the literature, several strengths were identified. In addition, significant knowledge gaps exist in the AR literature where current practice is not based on the best quality evidence; these should be seen as opportunities for additional research. The ICAR:AR document evaluates the strengths and weaknesses of the AR literature. This Executive Summary condenses these findings into a short summary. The reader is also encouraged to consult the comprehensive ICAR:AR document for a thorough description of this work.** © 2018 ARS-AAOA, LLC.

Key Words:
allergic rhinitis; allergy immunotherapy; evidence-based medicine; immunotherapy; rhinitis

***How to Cite this Article*:**
Wise SK, Lin SY, Toskala E. International consensus statement on allergy and rhinology: allergic rhinitis—executive summary. *Int Forum Allergy Rhinol.* 2018;8: 85–107.

I. Introduction

The literature on allergic rhinitis (AR) continues to grow, yet there is substantial variation in the type and quality of AR publications. As the allergy practitioner, researcher, or academician evaluates the literature, it is critical to understand the strength and quality of the evidence to allow for appropriate translation to daily clinical care in AR. The International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR)[1] was developed to summarize and critically review the best external evidence in the realm of AR. This includes broad categories of epidemiology, risk factors, diagnosis, management, and associated conditions/comorbidities related to AR. Over 100 individual AR topics were developed through a process of primary authorship, iterative reviews by additional authors, and close editorial evaluation. ICAR:AR follows previously developed methodology that has produced

[1]*Department of Otolaryngology–Head and Neck Surgery, Emory University, Atlanta, GA;* [2]*Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University, Baltimore, MD;* [3]*Department of Otolaryngology–Head and Neck Surgery, Temple University, Philadelphia, PA*

Correspondence to: Sarah K. Wise, MD, MSCR, Department of Otolaryngology–Head and Neck Surgery, Emory University, 550 Peachtree Street, MOT 11th Floor, Atlanta, GA 30308; e-mail: skmille@emory.edu

Funding source for the study: The American Academy of Otolaryngic Allergy Foundation provided funding for administrative support in preparation of this document but exercised no control over its content. Potential conflicts of interest: S.K.W.: Medtronic, consultant; Elron, consultant; OptiNose, advisory board. S.Y.L.: Agency for Healthcare Research and Quality, research funding. E.T.: Medtronic, research funding.

Received: 22 October 2017; Revised: 13 November 2017; Accepted: 25 November 2017
DOI: 10.1002/alr.22070
View this article online at wileyonlinelibrary.com.

numerous evidence-based reviews with recommendations in the *International Forum of Allergy and Rhinology*, as well as the 2016 ICAR: Rhinosinusitis document.[2] Using this established methodology, ICAR:AR provides a strong and critical review of the existing AR literature. Recommendations for AR diagnosis and treatment modalities contained in the ICAR:AR document rely directly on the best external evidence, while also considering benefit, harm, and cost considerations for determination of each recommendation level.

ICAR:AR is not a standard literature review or an expert panel report. Systematic literature searches, structured grading of evidence, initial anonymous review of each section followed by achievement of consensus, and close critique of the manuscript by a panel of editors during the ICAR:AR process minimizes reliance on expert opinion and other potential biases. ICAR:AR, however, is not a manual or flowchart for the treatment of AR patients. ICAR:AR summarizes the best available AR evidence and, when appropriate, develops recommendations from this evidence. This is similar to the systematic literature review performed for a clinical practice guideline. However, it should also be noted that ICAR:AR is not a clinical practice guideline, because certain steps of clinical practice guideline development (ie, medical specialty society and patient advocate review) were not utilized in the ICAR:AR process.

Although some topics in the ICAR:AR document have very strong evidence, the evidence in other topic areas is weak. Some of our routine practices in the evaluation and management of the AR patient are based on weak external evidence. Through the process of developing the ICAR:AR document, we have identified several knowledge gaps in the understanding of epidemiology, risk factors, diagnosis, and treatment of AR. We anticipate that the summary of the evidence in AR will help to direct additional research efforts as we strive to improve patient outcomes.

This Executive Summary is a synopsis of the full ICAR:AR document. The summaries of the evidence grades and recommendation levels are provided in this Executive Summary, but the description of the literature that supports these evidence grades and recommendation levels is found in the full ICAR:AR document. The reader is directed to the full ICAR:AR document for detailed information.

II. Methods

Each of 103 AR topics was assigned to 1 of 72 content experts worldwide. Some of the topics, such as those providing background or definitions, were assigned as literature reviews without evidence grades. Topics that were not appropriate for clinical recommendations were assigned as evidence-based reviews without recommendations (EBRs). Topics that had sufficient evidence to inform clinical recommendations were assigned as evidence-based reviews with recommendations (EBRRs). The methodology for EBR and EBRR topic development was based on the work of Rudmik and Smith.[3]

Briefly, for each topic, specific instructions were given to perform a systematic review for the topic literature using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standardized guidelines.[4] Ovid MEDLINE® (1947 to September 2016), EMBASE (1974 to September 2016), and Cochrane Review databases were included. Published systematic reviews, meta-analyses, and randomized, controlled trials (RCTs) were highlighted during the search as providing the highest levels of evidence. Included studies in EBR and EBRR topic sections are presented in a standardized table format, with the level of evidence delineated. At the completion of the systematic review and research quality evaluation for each clinical topic, an aggregate grade of evidence was produced for the topic based on the guidelines from the American Academy of Pediatrics Steering Committee on Quality Improvement and Management (AAP SCQIM).[5] For EBRR sections, an evidence-based recommendation was produced. This recommendation considered the aggregate grade of evidence, as well as the balance of benefit, harm, and costs. Please refer to the full ICAR:AR document Methods section and Table II.A-2 for the specifics of recommendation level determination.

Following initial topic development, each section then underwent a 2-stage online iterative review process using 2 independent reviewers. This iterative review process evaluated the completeness of the included literature and assessed the appropriateness of EBRR recommendations. Following topic development and 2 iterative reviews, the principal editor (S.K.W.) compiled all topics into 1 ICAR:AR statement. A panel of 6 to 8 authors further reviewed each large ICAR:AR portion (ie, Evaluation and Diagnosis, Pharmacotherapy, Immunotherapy, etc) for consistency and understanding. Finally, the draft ICAR:AR was circulated to all authors for consensus.

Although the ICAR:AR document aims to be systematic and thorough in its methods, there are some limitations. First, each topic author individually performed the literature search for his/her assigned topic, which introduces some variability despite detailed literature search instructions. Second, this document does not present every study published on every topic. For certain topics, the literature is extensive and only high-quality studies or systematic reviews are listed. If the aggregate evidence on a topic reached a high evidence grade with only high-level studies, an exhaustive list of lower level studies (or all studies ever performed) is not provided.

III. Results

The ICAR:AR document addresses several significant areas, including:

1. Definitions, classification, and differential diagnosis of AR.
2. A synopsis of the pathophysiology and mechanisms of AR.

TABLE III.A. Definition and differential diagnosis of AR

Definition	AR is an IgE-mediated inflammatory nasal condition resulting from allergen introduction in a sensitized individual[6]
Differential diagnosis[a]	• Drug-induced rhinitis • Rhinitis medicamentosa • Occupational rhinitis • Chemical rhinitis • Smoke-induced rhinitis • Infectious rhinitis • Rhinitis of pregnancy and hormonally induced rhinitis • Food- and alcohol-induced rhinitis • NARES • Vasomotor rhinitis (nonallergic rhinopathy) • Age-related rhinitis (ie, elderly) • Empty nose syndrome • Atrophic rhinitis • Autoimmune, granulomatous, and vasculitic rhinitis • Rhinosinusitis

[a]This table is specific to various etiologies of rhinitis. Structural sinonasal conditions, tumors, and cerebrospinal fluid leak are not listed here.
AR = allergic rhinitis IgE = immunoglobulin E; NARES = nonallergic rhinitis with eosinophilia syndrome.

3. Epidemiology of AR, risk factors for AR, and disease burden.
4. Assessment of diagnostic modalities and management options for AR, including evidence-based recommendations where appropriate literature exists.
5. Consideration of conditions and comorbidities associated with AR.

III.A. Results—definitions, classification, and differential diagnosis of allergic rhinitis

In the ICAR:AR document, AR is defined as an immunoglobulin E (IgE)–mediated inflammatory nasal condition resulting from allergen introduction in a sensitized individual, which is based on the Allergic Rhinitis and its Impact on Asthma (ARIA) document.[6] Classification of AR typically includes seasonal vs perennial and intermittent vs persistent. Sensitization to an allergen is indicated by a positive reaction on allergy skin test or antigen-specific IgE test, whereas clinical allergy is evidenced by active symptoms upon allergen exposure in a sensitized individual. Not all sensitized individuals exhibit clinical allergy. The differential diagnosis of AR is rather extensive and includes numerous inflammatory conditions of the sinonasal region. Of note, the section on AR differential diagnosis is specific to various etiologies of rhinitis. Other entities that may enter into the differential diagnosis of AR, such as structural sinonasal conditions (ie, deviated septum), tumors, and cerebrospinal fluid leak, are not discussed (Table III.A).

III.B. Results—pathophysiology and mechanisms of allergic rhinitis

Although we do not fully comprehend the pathophysiology of AR, prior studies have demonstrated AR to be an IgE-mediated condition, often with notable systemic effects. Some of these systemic effects include skin reactivity and associated lower airway inflammation, as demonstrated by the unified airway concept. In certain situations, systemic allergy testing is negative, and a phenomenon known as local allergic rhinitis may occur, with IgE produced locally in the sinonasal tissues. Although IgE-mediated inflammation is the primary inciting event in AR, multiple other inflammatory mechanisms contribute as well. These include non–IgE-mediated inflammation, cellular inflammatory infiltrates, contributions from epithelial cells and epithelial barrier changes, as well as a coordinated network of cytokines and soluble mediators. Finally, recent literature has demonstrated a potential contribution to AR pathophysiology from alterations in the systemic microbiome. Each aspect of AR pathophysiology is discussed in the ICAR:AR document (IV. Pathophysiology and Mechanisms).

III.C. Results—epidemiology of allergic rhinitis

The epidemiology of AR has been quantified by various means in adults and children. Our current understanding of the prevalence of AR primarily results from large epidemiologic survey studies. However, it should be noted that surveys differ in terms of disease definitions, geography, and seasonality of the area surveyed. These issues can introduce variability into prevalence estimates drawn from survey data. A discussion of the prevalence of AR in adults, incidence and prevalence of AR in children, and geographic variation of AR is provided in the ICAR:AR document.

III.D. Results—risk factors for allergic rhinitis

The authors of ICAR:AR reviewed several potential risk factors for the development of AR, as well as some proposed protective factors against the development of AR. The summary of these findings is shown in Tables III.D.1. and III.D.2. The ICAR:AR document reviews each of these factors in detail.

III.E. Results—disease burden

The ICAR:AR authors reviewed the disease burden of AR regarding its effect on quality of life (QoL) and sleep at the level of the individual. The summary of these findings is shown in Table III.E. The societal impact of AR was also considered.

- *QoL:* Based on systematic reviews, it has been concluded that AR patients suffer from significantly decreased general and disease-specific QoL due to the impact of physical and mental health. Treatment of AR leads to QoL improvements.

TABLE III.D.1. Proposed risk factors for the development of AR

Risk factor or exposure	Number of listed studies	Aggregate grade of evidence	Interpretation
Genetics	5 (GWAS)	C	Some genes have been associated with development of AR and other atopic diseases.
In utero or early exposure (mites)	6	C	Data inconclusive.
In utero or early exposure (pollen)	2	C	Data inconclusive.
In utero or early exposure (animal dander)	39	C	Data inconclusive.
In utero or early exposure (fungal allergens)	13	C	Data inconclusive.
Restricted diet (in utero and early childhood)	5	A	Maternal diet restriction while child is in utero is not a contributing factor to the development of AR. Food allergy during childhood is a risk factor for AR.
Pollution	14	C	Data inconclusive.
Tobacco smoke	9	A	Most studies found no association between active or passive tobacco smoke and AR. Specific patient populations and temporal variations (ie, length of exposure) should be further evaluated.
SES	10	C	Most studies show an association between high SES and AR, but this is not a consistent finding across all studies.

AR = allergic rhinitis; GWAS = genome-wide association studies; SES = socioeconomic status.

TABLE III.D.2. Proposed protective factors against the development of AR

Protective factor or exposure	Number of listed studies	Aggregate grade of evidence	Recommendation level	Interpretation
Breastfeeding	2 (SRs)	C	Option	Option for breastfeeding for the specific purpose of AR prevention. In general, breastfeeding has been strongly recommended due to its multiple beneficial effects.
Pet exposure	6	C	—	No evidence that pet avoidance in childhood prevents AR later in life. Early pet exposure, especially dog exposure in nonallergic families early in childhood, may be protective.
Microbial diversity ("hygiene hypothesis")	15	B	—	Microbial diversity of the skin, airways, and gut is important for the prevention of sensitization and allergic disease in populations.

AR = allergic rhinitis; SR = systematic review.

TABLE III.E. Effect of AR on the individual: QoL and sleep

Burden of AR	Number of listed studies	Aggregate grade of evidence	Recommendation level	Interpretation
Effect on QoL	33	B	Recommendation	AR has significant effects on general and disease-specific QoL. Treatment of AR is recommended to improve QoL.
Effect on sleep	46	B	Recommendation	AR has significant negative effects on sleep. Treatment of AR is recommended to decrease sleep disturbance.

AR = allergic rhinitis; QoL = quality of life.

- Aggregate Grade of Evidence: B (Level 1b: 11 studies; Level 2a: 2 studies; Level 2b: 16 studies; Level 2c: 1 study; Level 3b: 3 studies).
- Benefit: Successful management of AR leads to improved overall and disease-specific QoL.
- Harm: Management strategies for AR are associated with variable levels of harm and are further specified in the Management section of the ICAR:AR document.
- Cost: Management strategies for AR are associated with variable levels of cost and are further specified in the Management section of the ICAR:AR document.
- Benefits-Harm Assessment: The benefits of treating patients with AR to improve QoL may outweigh risks of treatment.
- Value Judgments: Successful control of AR symptoms leads to important improvements in generic and disease-specific QoL.
- Policy Level: Recommend treatment of AR to improve QoL.
- Intervention: AR patients may be offered various management strategies to improve general and disease-specific QoL.

- *Sleep:* AR negatively impacts sleep QoL, and the successful treatment of AR reduces sleep disturbance. The overall quality of the data is higher for adults than for children.

  - Aggregate Grade of Evidence: B (Level 1b: 5 studies; Level 2b: 10 studies; Level 2c: 3 studies; Level 3a: 1 study; Level 3b: 21 studies; Level 4: 6 studies).
  - Benefit: Successful management of AR leads to decreased sleep disturbance.
  - Harm: Management strategies for AR are associated with variable levels of harm and are further specified in the Management section of the ICAR:AR document.
  - Cost: Management strategies for AR are associated with variable levels of cost and are further specified in the Management section of the ICAR:AR document.
  - Benefits-Harm Assessment: The benefits of treating patients with AR for symptoms of sleep disturbance may outweigh risks of treatment.
  - Value Judgments: Successful control of AR symptoms leads to improvements in sleep.
  - Policy Level: Recommend treatment of AR to decrease sleep disturbance.
  - Intervention: AR patients may be offered various management strategies to improve sleep.

- *Societal burden:* The societal burden of AR can be quantified in direct costs, indirect costs, lost work/school days, and other measures. By any account, as one of the most common chronic diseases in adults and children, AR has a substantial impact on society. These issues are discussed in further detail in the ICAR:AR document.

III.F. Results— evaluation and diagnosis

During patient evaluation, the suspicion of AR is based on clinical history and often supported by physical examination. Various methods of objective testing may also be used in the diagnosis of AR. The ICAR:AR authors reviewed numerous modalities for the diagnosis of AR. The summary of these findings is shown in Table III.F.

This section summarizes the recommendations for each method of evaluation and diagnosis of AR that was reviewed in the ICAR:AR document.

- *Clinical examination (history and physical):*

  - Aggregate Grade of Evidence: D (Level 3b: 1 study; Level 4: 3 studies; Level 5: 4 guidelines).
  - Benefit: Improve accuracy of diagnosis, and avoid unnecessary referrals, testing, or treatment; possible improved diagnosis of AR with physical examination findings, evaluation/exclusion of alternative diagnoses.
  - Harm: Possible patient discomfort from routine examination, not inclusive of endoscopy; potential misdiagnosis, inappropriate treatment.
  - Cost: Minimal.
  - Benefits-Harm Assessment: Preponderance of benefit over harm, potential misdiagnosis and inappropriate treatment if physical exam used in isolation.
  - Value Judgments: Making a presumptive diagnosis of AR on history (ideally combined with physical examination) is reasonable and would not delay treatment initiation. Confirmation with diagnostic testing is required for progression to allergen immunotherapy (AIT), or desirable with inadequate response to initial treatment.
  - Policy Level: Recommendation.
  - Intervention: History-taking is essential in the diagnosis of AR. Physical examination is recommended in the diagnosis of AR, and, when combined with patient history, increases diagnostic accuracy and excludes alternative causes.

- *Nasal endoscopy:*

  - Aggregate Grade of Evidence: D (Level 3b: 2 studies; Level 4: 3 studies).
  - Benefit: Possible improved diagnosis with visualization of turbinate contact or isolated central compartment edema.
  - Harm: Possible patient discomfort.
  - Cost: Moderate equipment and processing costs, as well as procedural charges.
  - Benefits-Harm Assessment: Equal.
  - Value Judgments: None.
  - Policy Level: Option.

TABLE III.F. Techniques for evaluation and diagnosis of AR

Method of evaluation	Number of listed studies	Aggregate grade of evidence	Recommendation level	Interpretation
Clinical examination (history and physical)	4	D	Recommendation	Despite the lack of studies to address clinical examination in the diagnosis of AR, history-taking is essential and physical examination is recommended. Multiple prior guideline documents support this recommendation.
Nasal endoscopy	5	D	Option	Evidence does not support the routine use of nasal endoscopy for diagnosing AR. However, it may be helpful in ruling out other causes of symptoms.
Radiologic imaging	0	N/A	Recommend against	Radiologic imaging is not recommended for the diagnosis of AR.
Use of validated survey instruments	10	A	Strong recommendation	Validated survey instruments can be used to screen for AR, follow treatment outcomes, and as an outcome measure for clinical trials.
SPT	8	B	Recommendation	SPT is recommended for evaluation of allergen sensitivities in appropriately selected patients. The practitioner may decide whether skin or in vitro sIgE testing is best in an individual patient.
Skin intradermal testing	17	B	Option	Intradermal testing may be used to determine specific airborne allergen sensitization for individuals suspected of having AR.
Blended skin testing techniques	5	D	Option	MQT is a skin testing technique that may be used to determine a safe starting dose for AIT.
Serum tIgE	15	C	Option	Serum tIgE is an option to assess atopic status.
Serum sIgE	7	B	Recommendation	Serum sIgE testing is recommended for evaluation of allergen sensitivities in appropriately selected patients. The practitioner may decide whether skin or in vitro sIgE testing is best in an individual patient.
Correlation between skin and in vitro testing	19	B	—	Studies differ regarding the concordance of various allergy testing methods.
Nasal sIgE	24	C	Option	Nasal sIgE is an option in patients with suspected or known LAR to aid in diagnosis or guide therapy.
Basophil activation test	12	B	Option	BAT may be used for diagnosis when first-line tests are discordant, and for monitoring response to AIT.
Nasal provocation testing	4	C	—	NPT has been employed for diagnosis of occupational rhinitis and LAR.
Nasal cytology	4	C	—	Nasal cytology is an investigational tool, rather than diagnostic.
Nasal histology	11	B	—	Nasal histology is used for research on the pathophysiology of AR, but is not routinely used in clinical practice for the diagnosis of AR.

AIT = allergen immunotherapy; AR = allergic rhinitis; BAT = basophil activation test; LAR = local allergic rhinitis; MQT = Modified Quantitative Testing; NPT = nasal provocation testing; sIgE = antigen-specific immunoglobulin E; SPT = skin-prick test; tIgE = total immunoglobulin E.

- Intervention: Nasal endoscopy may increase diagnostic sensitivity among children and adults with AR and may aid in ruling out other causes for nasal symptoms.

- *Radiology:*
  - Aggregate Grade of Evidence: Not applicable.
  - Benefit: None appreciated.
  - Harm: Unnecessary radiation exposure with concern for tumor development.
  - Cost: High equipment and processing costs.
  - Benefits-Harm Assessment: Preponderance of harm over benefit.
  - Value Judgments: Long-term risks of unnecessary ionizing radiation exposure outweigh potential benefit.
  - Policy Level: Recommend against.

- Intervention: Routine imaging is not recommended in the evaluation of suspected AR, but may be considered to rule-in/out other sinonasal conditions.

- *Use of validated survey instruments:*
  - Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 4 studies; Level 2b: 4 studies). Note: multiple additional studies reviewed, but Grade A evidence was reached with these 10 studies, so an extensive listing of all studies employing validated survey instruments is not provided in the ICAR:AR document.
  - Benefit: Validated surveys offer a simple point-of-care option for screening and tracking symptoms, QoL, and control of allergic disease.
  - Harm: Minimal to none.
  - Costs: No financial burden to patients; some fees associated with validated tests used for clinical research.
  - Benefits-Harm Assessment: Preponderance of benefit over harm. Low risk of misdiagnoses leading to unnecessary additional testing. Likewise, there is low risk that false-negative responses will lead to delay in testing and further management.
  - Value Judgments: Level 1 evidence to use validated surveys as a screening tool and primary or secondary outcome measure.
  - Policy Level: Strong recommendation.
  - Intervention: Validated surveys may be used to screen for AR, follow treatment outcomes, and as a primary outcome measure for clinical trials. Specific tests are optimized for various clinicopathologic scenarios and should be tailored to the patient and clinical setting.

- *Skin-prick testing (SPT):*
  - Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 3b: 7 studies).
  - Benefit: Supports diagnosis and directs pharmacologic therapy while possibly avoiding unnecessary/ineffective treatment, guides avoidance, and directs AIT.
  - Harm: Adverse events from testing include discomfort, pruritus, erythema, worsening of asthma symptoms and anaphylaxis, inaccurate test results, and misinterpreted test results.
  - Cost: Low.
  - Benefits-Harm Assessment: Preponderance of benefit over harm.
  - Value Judgments: Patients can benefit from identification of their specific sensitivities. SPT is a quick and relatively comfortable way to test several antigens with accuracy similar to other available methods of testing.
  - Policy Level: Recommendation.
  - Intervention: SPT is recommended for evaluation of allergen sensitivities in appropriately selected patients. Regular use of the same SPT device will allow clinicians to familiarize themselves with it and interpretation of results may therefore be more consistent. The use of standardized allergen extracts can further improve consistency of interpretation.

- *Skin intradermal testing:*
  - Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 2b: 11 studies; Level 3b: 4 studies; Level 4: 1 study).
  - Benefit: Generally well tolerated, easy to perform, and with a favorable level of sensitivity and specificity when used as a stand-alone diagnostic test.
  - Harm: Very low risk of severe adverse reactions.
  - Cost: Low.
  - Benefits-Harm Assessment: Benefit over harm when used as a stand-alone diagnostic test. Balance of benefit and harm when used to confirm the results of SPT, as a quantitative diagnostic test or as a vial safety test.
  - Value Judgments: It is important to determine the presence of IgE-mediated sensitivity for individuals with suspected AR. If SPT is negative, there is limited clinical benefit in performing intradermal testing for confirmation.
  - Policy Level: Option for using intradermal testing as a stand-alone diagnostic test for individuals with suspected AR. Option for using intradermal testing as a confirmatory test following negative SPT for nonstandardized allergens. The evidence for quantitative IDT is sparse and prevents a recommendation for this specific testing technique.
  - Intervention: Intradermal testing may be used to determine specific airborne allergen sensitization for individuals suspected of having AR.

- *Blended skin testing techniques:*
  - Aggregate Grade of Evidence: D (Level 3b: 1 study; Level 4: 4 studies).
  - Benefit: Ability to establish an endpoint in less time than IDT.
  - Harm: The additional risks, including systemic or anaphylactic reactions, of intradermal tests; additional time and discomfort.
  - Cost: Similar to intradermal testing.
  - Benefits-Harm Assessment: Benefit outweighs harm.
  - Value Judgments: AIT can be initiated from SPT results alone; however, endpoint-based AIT may decrease time to reaching therapeutic dose.
  - Policy Level: Option.
  - Intervention: Modified quantitative testing (MQT) is a skin testing technique that may be used to determine a starting point for AIT.

- *Issues that may affect the performance or interpretation of skin tests—medications:*
    - H_1 antihistamines: Aggregate Grade of Evidence: A (Level 1b: 2 studies; Level 2b: 3 studies). Should be discontinued 2–7 days prior to testing.
    - H_2 antihistamines: Aggregate Grade of Evidence: B (Level 1b: 2 studies). Ranitidine suppresses skin whealing response and may result in false negatives.
    - Topical antihistamines (nasal, ocular): Aggregate Grade of Evidence: Unable to determine from 1 Level 1b study. Should be discontinued 2 days prior to testing.
    - Anti-IgE (omalizumab): Aggregate Grade of Evidence: A (Level 1b: 2 studies). Results in negative allergy skin test results.
    - Leukotriene receptor antagonists (LTRAs): Aggregate Grade of Evidence: A (Level 1b: 2 studies; Level 2b: 1 study). May be continued during testing.
    - Tricyclic antidepressants: Aggregate Grade of Evidence: Unable to determine from 1 Level 2b study. Agents with antihistaminic properties suppress allergy skin test responses.
    - Topical (cutaneous) corticosteroids: Aggregate Grade of Evidence: A (Level 1b: 2 studies; Level 2b: 1 study). Skin tests should not be placed at sites of chronic topical steroid treatment.
    - Systemic corticosteroids: Aggregate Grade of Evidence: C (no effect—Level 1b: 1 study; Level 2b: 1 study; suppression—Level 3b: 1 study; Level 4: 1 study). Systemic corticosteroid treatment does not significantly impair skin test responses.
    - Selective serotonin reuptake inhibitors (SSRIs): Aggregate Grade of Evidence: B (Level 2b: 1 study, Level 4: 1 study). Does not suppress allergy skin test response.
    - Benzodiazepines: Aggregate Grade of Evidence: C (Level 4: 1 study, Level 5: 1 case report). May suppress skin test responses.
    - Topical calcineurin inhibitors (ie, tacrolimus, picrolimus): Aggregate Grade of Evidence: D (Level 1b: 1 study, Level 2b: 1 study—results conflicting). Conflicting results regarding skin test suppression.
- *Issues that may affect the performance or interpretation of skin tests—skin conditions:* Common sense dictates that allergy skin testing should not be performed at sites of active dermatitis, but clinical studies investigating this phenomenon are lacking. Due to the lack of published studies on this topic, an Aggregate Grade of Evidence and evidence-based recommendation cannot be provided.
- *Serum total IgE (tIgE):*
    - Aggregate Grade of Evidence: C (Level 2b: 5 studies; Level 3b: 10 studies).
    - Benefit: Possibility to suspect allergy in a wide screening.
    - Harm: Low level does not exclude allergy.
    - Cost: Modest cost of test.
    - Benefits-Harm Assessment: Slight preponderance of benefit over harm. In addition, the ratio of tIgE:sIgE (antigen-specific IgE) may be useful.
    - Value Judgments: The evidence does not support routine use.
    - Policy Level: Option.
    - Intervention: tIgE assessment is an option to assess atopic status.
- *Serum antigen-specific IgE (sIgE):*
    - Aggregate Grade of Evidence: B (Level 3b: 7 studies).
    - Benefit: Confirms sensitization in support of an AR diagnosis and directs appropriate therapy while possibly avoiding unnecessary/ineffective treatment, guides avoidance measures, and directs AIT.
    - Harm: Adverse events from testing including discomfort from blood draw, inaccurate test results, false-positive test results, and misinterpreted test results.
    - Cost: Moderate cost of testing.
    - Benefits-Harm Assessment: Preponderance of benefit over harm.
    - Value Judgments: Patients can benefit from identification of their specific sensitivities. Further, in some patients who cannot undergo skin testing, sIgE testing is a safe and effective alternative.
    - Policy Level: Recommendation.
    - Intervention: Serum sIgE testing may be used in the evaluation of AR. Using standardized allergens and rigorous proficiency testing on the part of laboratories may improve accuracy.
- *Nasal-specific IgE:*
    - Aggregate Grade of Evidence: C (Level 2b: 13 studies; Level 3b: 3 studies; Level 4: 8 studies).
    - Benefit: Identifying patients with local allergic rhinitis (LAR) allows for the opportunity to treat a subset of patients who may respond to avoidance or AIT. Identification of nasal sIgE allows for diagnosis and AIT.
    - Harm: Measurement of nasal sIgE is minimally invasive, and no adverse effects have been reported.
    - Cost: Associated costs consist of the direct costs of testing, and indirect cost of increased time and effort for performing nasal sIgE diagnostic test.
    - Benefits-Harm Assessment: The benefits of identifying patients with an allergic component to their rhinitis may outweigh any associated risks.
    - Value Judgments: In patients with rhinitic symptoms and negative systemic testing, identifying nasal sIgE may assist with appropriate treatment. Standards for abnormal levels of nasal sIgE have

not been established nor correlated with clinical outcomes.
  - Policy Level: Option.
  - Intervention: Nasal sIgE assessment is an option in patients with suspected or known LAR to aid in diagnosis or guide allergen-specific therapy.

- *Basophil activation test (BAT):*
  - Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 2 studies; Level 3b: 8 studies; Level 4: 3 studies).
  - Benefit: Ex vivo test, patient discomfort minimal, less time consuming than nasal provocation and SPT for patient, reliable correlation between clinical symptoms and basophil sensitivity when measuring response to therapy, and no risk of anaphylaxis compared with provocation testing.
  - Harm: None known.
  - Cost: Requires proximity of laboratory trained in basophil testing; cost of testing.
  - Benefits-Harm Assessment: Balance of benefit over harm.
  - Value Judgments: Basophil sensitivity may be a useful marker for following response to immunotherapy. Differences in BAT methodology for diagnosis of AR and rare need for laboratory tests to diagnose AR make it likely to be implemented for diagnosis in tertiary care centers only.
  - Policy Level: Option.
  - Intervention: BAT is an option for AR diagnosis when first-line tests are inconclusive or for measuring response to AIT. Many small-scale studies have been completed. There is scope for meta-analysis and for larger trials to be completed.

- *Local allergen challenge testing—nasal provocation test (NPT):*
  - Aggregate Grade of Evidence: C (Level 2b: 4 studies). Due to the variation in NPT technique and outcome measures, a reliable evidence grade for NPT is difficult to determine.

- *Nasal cytology:*
  - Aggregate Grade of Evidence: C (Level 3b: 3 studies; Level 4: 1 study). Nasal cytology is largely an investigational tool.

- *Nasal histology:*
  - Aggregate Grade of Evidence: B (Level 1b: 8 studies; Level 3b: 3 studies). Nasal histology is used for research on the pathophysiology of AR, but is not used routinely in clinical practice for the diagnosis of AR.

III.G. Results—management

Various management options for the treatment of AR were reviewed by the ICAR:AR authors. These are broken down into 4 broad topic areas—avoidance measures, pharmacotherapy, surgical treatment, and AIT.

III.G.1. Results— management: avoidance measures

Avoidance measures and environmental controls may include physical and chemical means to reduce allergen load. These methods have been advocated for the reduction of allergy symptoms, based on the principle that decreased allergen exposure may result in decreased symptomatology. Avoidance measures and environmental control methods were reviewed for house dust mite (HDM), cockroach, pet, and pollen/occupational allergens. The summary of these findings is shown in Table III.G.1.

- *House dust mite:* Physical techniques (eg, heating, ventilation, freezing, barrier methods, air filtration, vacuuming, and ionizers) have been evaluated for the treatment of AR. Several studies have demonstrated decreased concentrations of environmental HDM antigens, but reduction in clinical symptoms has not been reliably demonstrated. A systematic review demonstrated acaricide chemical treatment to be the most effective as a single measure, or in combination with other measures, to decrease mite levels and improve symptoms. Recommendations are as follows:
  - Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 1b: 3 studies; Level 2a: 1 study; Level 2b: 7 studies).
  - Benefit: Reduced concentration of environmental HDM antigens with potential improvement in symptom scores and QoL.
  - Harm: None.
  - Cost: Low to moderate, but cost-effectiveness was not evaluated.
  - Benefits-Harm Assessment: Benefit outweighs harm.
  - Value Judgments: The use of acaricides and/or bedroom-based control programs in reducing HDM concentration is promising, but further, high-quality studies are needed to evaluate clinical outcomes.
  - Policy Level: Option.
  - Intervention: Concomitant use of acaricides and environmental control measures, such as personalized air-filtration techniques, are options for the treatment of AR.

- *Cockroach:* In a substantial number of RCTs that evaluated the efficacy of specific environmental control measures to eliminate the number of cockroaches and reduce cockroach allergen level, respiratory health outcomes were rarely measured. Most studies did not include

TABLE III.G.1. Allergen avoidance and environmental control measures

Allergen avoided	Number of listed studies	Aggregate grade of evidence	Recommendation level	Interpretation
House dust mite	12	B	Option	Concomitant use of acaricides and EC measures is an option for the treatment of AR.
Cockroach	11	B	Option	Combination of physical measures (bait traps, housecleaning) and education is an option for AR management related to cockroach exposure.
Pets	3	B	Option	Pet avoidances and EC strategies are an option for AR related to pets.
Pollen and occupational allergens	3	B	Option	Pollen and occupational allergen avoidance by EC strategies are an option for the treatment of AR.

AR = allergic rhinitis; EC = environmental controls.

clinical endpoints. No studies included any assessment of symptoms associated with AR or its treatment. Recommendations are as follows:

- Aggregate Grade of Evidence: B (Level 1a: 1 study; Level 1b: 8 studies; Level 2b: 1 study; Level 3b: 1 study).
- Benefit: Reduction in cockroach count, but allergen levels (Bla g 1 and Bla g 2) were often above acceptable levels for clinical benefits. No studies included clinical endpoints related to AR.
- Harm: None reported.
- Cost: Moderate. Multiple treatments applications required as well as a multi-interventional approach.
- Benefits-Harm Assessment: Balance of benefit and harm, given lack of clear clinical benefit.
- Value Judgments: Control of cockroach populations especially in densely populated, multifamily dwellings is important for controlling allergen levels.
- Policy Level: Option.
- Intervention: Combination of physical measures (such as insecticide bait traps, house cleaning) and educational-based methods are options in the management of AR related to cockroach exposure.

- *Pets:* Pet removal is a commonly cited strategy without high-quality outcomes evaluation. Therefore, pet avoidance and environmental controls represent options for the treatment of AR. Recommendations are as follows:
  - Aggregate Grade of Evidence: B (Level 1b: 1 study; Level 2b: 2 studies).
  - Benefit: Decreased environmental antigen exposure with possible reduction in nasal symptoms and secondary prevention of asthma.
  - Harm: Emotional distress caused by removal of household pets, and financial and time costs of potentially ineffective intervention.
  - Cost: Low to moderate.
  - Benefits-Harm Assessment: Equivocal.
  - Value Judgments: Although several studies have demonstrated an association between environmental controls and reductions in environmental antigens, only a single, multimodality RCT has demonstrated clinical improvement in nasal symptoms among patients with Fel d 1 sensitivity. The secondary prevention and treatment of asthma in sensitized individuals must also be considered.
  - Policy Level: Option.
  - Intervention: Pet avoidance and environmental control strategies, particularly multimodality environmental control among patients with diagnosed Fel d 1 sensitivity, are an option for the treatment of AR related to pets.

- *Pollen and occupational allergens:* Limited data exist on pollen and occupational allergen avoidance. Additional studies are needed. This represents an option in the treatment of AR. Recommendations are as follows:
  - Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 1 study).
  - Benefit: Decreased allergen exposure with possible reduction in symptoms and need for allergy medication, along with improved QoL.
  - Harm: Financial and time costs of potentially ineffective intervention.
  - Cost: Low, but dependent on the environmental control strategy (ie, for occupational allergy ventilation measures and other "engineering controls" may be high).
  - Benefits-Harm Assessment: Equivocal.
  - Value Judgments: A limited number of studies show clinical effects of investigated environmental control measures. General environmental control recommendations are mainly based on expert opinions rather than evidence.
  - Policy Level: Option.

- Intervention: Pollen and occupational allergen avoidance by environmental control strategies are an option for the treatment of AR; however, clinical efficacy has not been definitively demonstrated. More RCTs with larger samples are warranted to prospectively evaluate clinical efficacy.

III.G.2. Results—management: pharmacotherapy

Medications are often used to control allergic symptoms. The ICAR:AR authors reviewed numerous medication options for their use in the treatment of AR. The summary of these findings is shown in Table III.G.2.

This section summarizes the recommendations for each pharmacotherapy option that was reviewed in the ICAR:AR document.

- *Oral H_1 antihistamines:*
  - Aggregate Grade of Evidence: A (Level 1a: 21 studies). There is a preponderance of high-grade investigations that have examined oral H_1 antihistamines. Only Level 1a studies were included in the ICAR:AR review.
  - Benefit: Reduced nasal itching, sneezing, rhinorrhea, and nasal obstruction.
  - Harm: Mild drowsiness, fatigue, headache, nausea, and dry mouth.
  - Cost: Direct costs low (average $2 per daily dose). Indirect costs for newer-generation (nonsedating) agents lower than first-generation agents.
  - Benefits-Harm Assessment: Benefits outweigh harm for use of newer-generation oral H_1 antihistamines.
  - Value Judgments: Due to the central nervous system side effects of the first-generation oral H_1 antihistamines, their use is not recommended for typical AR.
  - Policy Level: Strong recommendation for use of newer-generation oral antihistamines to treat AR.
  - Intervention: Prescribing newer-generation oral H_1 antihistamines for patients with AR should be considered early in treatment.
- *Oral H_2 antihistamines:*
  - Aggregate Grade of Evidence: B (Level 1b: 6 studies).
  - Benefit: Decreased objective nasal resistance, and improved symptom control in 1 study when used in combination with H_1 antagonists.
  - Harm: Drug-drug interaction (P450 inhibition, inhibited gastric secretion and absorption),
  - Cost: Increased cost associated with H_2 antagonist.
  - Benefits-Harm Assessment: Unclear benefit and possible harm.
  - Value Judgments: No studies evaluating efficacy of H_2 antihistamines in the context of topical nasal corticosteroids.
  - Policy Level: No recommendation. The data available do not adequately address the question as to the benefit of H_2 antihistamines in clinical AR as part of modern treatment protocols.
  - Intervention: Addition of an oral H_2 antagonist to an oral H_1 antagonist may improve symptom control in AR, but the evidence to support this is not strong.
- *Intranasal antihistamines:*
  - Aggregate Grade of Evidence: A (Level 1b: 43 studies; Level 2b: 1 study). Due to the large number of studies with a high level of evidence, studies of lower evidence levels were not considered in the ICAR:AR review.
  - Benefit: Intranasal antihistamines have a rapid onset, are more effective for nasal congestion than oral antihistamines, are more effective for ocular symptoms than intranasal corticosteroids (INCSs), and show consistent reduction in symptoms and improvement in QoL in RCTs compared with placebo.
  - Harm: Concerns for patient tolerance, especially with regard to taste. Intranasal antihistamines are less effective for congestion than INCSs.
  - Costs: Low-to-moderate financial burden; available as prescription only.
  - Benefits-Harm Assessment: Preponderance of benefit over harm. Intranasal antihistamine as monotherapy is consistently more effective than placebo. Most studies showed intranasal antihistamines are superior to INCSs for sneezing, itching, rhinorrhea, and ocular symptoms. Adverse effects are minor and infrequent.
  - Value Judgments: Extensive Level 1 evidence comparing intranasal antihistamine monotherapy to active and placebo controls demonstrates overall effectiveness and safety.
  - Policy Level: Recommendation.
  - Intervention: Intranasal antihistamines may be used as first- or second-line therapy in the treatment of AR.
- Oral corticosteroids:
  - Aggregate Grade of Evidence: B (Level 1b: 5 studies; Level 2b: 1 study; Level 4: 3 studies).
  - Benefit: Oral corticosteroids can attenuate symptoms of AR.
  - Harm: Oral corticosteroids have known undesirable adverse effects; these include effects on the hypothalamic-pituitary axis, growth and musculoskeletal system, gastrointestinal system, hypertension, glycemic control, mental/emotional state, and others.

TABLE III.G.2. Pharmacotherapy options for the treatment of AR

Medication	Number of listed studies	Aggregate grade of evidence	Recommendation level	Interpretation
Oral H_1 antihistamines	21	A	Strong recommendation	Newer-generation (nonsedating) oral H1 antihistamines are strongly recommended for the treatment of AR.
Oral H_2 antihistamines	6	B	No recommendation	Available data does not adequately address the question of benefit in the treatment of AR.
Intranasal antihistamines	44	A	Recommendation	Intranasal antihistamines many be used as first-line or second-line therapy for the treatment of AR.
Oral corticosteroids	9	B	Recommend against	Due to the risks of oral steroid use, along with the availability of other pharmacotherapy options, this therapy is not recommended for routine AR management.
Injectable corticosteroids	13	B	Recommend against	Due to the risks of injectable steroid use, along with the availability of other pharmacotherapy options, systemic or intraturbinate injection of corticosteroids is not recommended for the routine treatment of AR.
INCS	53	A	Strong recommendation	INCS should be used as first-line therapy in the treatment of AR.
Oral decongestants	9	B	Option	Option for pseudoephedrine for short-term treatment of AR symptoms.
			Recommend against	Recommend against phenylephrine, as it has not been shown to be superior to placebo.
Topical decongestants	4	B	Option	Option for topical IND use in the short-term for nasal decongestion. Chronic use carries a risk of RM.
LTRAs	31	A	Recommend against	LTRAs should not be used as monotherapy in the treatment of AR.
Cromolyn (DSCG)	22	A	Option	DSCG may be considered in the treatment of AR, particularly for patients with known triggers who cannot tolerate INCS.
Intranasal anticholinergic (IPB)	14	B	Option	IPB nasal spray may be considered as an adjunct to INCS in PAR patients with uncontrolled rhinorrhea.
Omalizumab	6	A	No indication	Omalizumab is not approved by the U.S. FDA for the treatment of AR alone.
Nasal saline	12	A	Strong recommendation	Nasal saline is strongly recommended as part of the treatment strategy for AR.
Probiotics	28	A	Option	Probiotics may be considered in the treatment of AR.
Combination: oral antihistamine and oral decongestant	21	A	Option	Option, particularly for acute exacerbations with a primary symptom of nasal congestion.
Combination: oral antihistamine and INCS	5	B	Option	Combination equivocal over either drug alone.
Combination: oral antihistamine and LTRA	13	A	Option	Combination is an option for AR management, particularly in patients with comorbid asthma who do not tolerate INCS and are not well-controlled on oral antihistamine monotherapy.
Combination: INCS and intranasal antihistamine	12	A	Strong recommendation	Strong recommendation for combination therapy when monotherapy fails to control AR symptoms.
Acupuncture	15	B	Option	In patients who wish to avoid medications, acupuncture many be suggested as a possible therapeutic adjunct.
Honey	3	B	No recommendation	Studies are inconclusive and heterogeneous.
Herbal therapies	—	—	No recommendation	Multiple different herbs studied, with few studies for each specific therapy. Results are inconclusive.

AR = allergic rhinitis; DSCG = disodium cromoglycate; FDA = Food and Drug Administration; INCS = intranasal corticosteroids; IND = intranasal decongestants; IPB = ipratropium bromide; LTRA = leukotriene receptor antagonist; PAR = perennial allergic rhinitis; RM = rhinitis medicamentosa.

- Cost: Low.
- Benefits-Harm Assessment: The risks of using oral corticosteroids outweigh the benefits when compared with similar symptom improvement with the use of INCSs.
- Value Judgments: In the presence of effective symptom control using INCS, the risk of adverse effects from using oral corticosteroids for AR appears to outweigh the potential benefits.
- Policy Level: Recommendation against the routine use of oral corticosteroids for AR.
- Intervention: Although not recommended for routine use in AR, certain clinical scenarios warrant the use of short courses of systemic corticosteroids after a discussion of the risks and benefits with the patient. This may include patients with significant nasal obstruction that would preclude penetration of intranasal agents (INCSs or antihistamines). In these cases, a short course of systemic oral corticosteroids could improve congestion and facilitate access and efficacy of the topical agents.

- *Injectable corticosteroids:*
  - Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2b: 3 studies; Level 4: 7 studies).
  - Benefit: Injectable corticosteroids improve symptoms of AR in clinical studies.
  - Harm: Injectable corticosteroids have known adverse effects on the hypothalamic-pituitary axis, growth suppression, osteoporosis, hyperglycemia, and other systemic adverse effects. Intraturbinate corticosteroids have a small, but potentially serious, risk of ocular side effects, including decline or loss of vision.
  - Cost: Low.
  - Benefits-Harm Assessment: In routine management of AR, the risk of serious adverse effects outweighs the demonstrated clinical benefit.
  - Value Judgments: Injectable corticosteroids are effective for the treatment of AR. However, given the risk of significant systemic adverse effects, the risk of serious ocular side effects, and the availability of effective alternatives (ie, topical INCS therapy), injectable corticosteroids are not recommended for the routine treatment of AR.
  - Policy Level: Recommendation against.
  - Intervention: None.

- *Intranasal corticosteroids:*
  - Aggregate Grade of Evidence: A (Level 1a: 15 studies; Level 1b: 33 studies; Level 2a: 3 studies; Level 2b: 1 study; Level 5: 1 study).
  - Benefit: INCSs are effective in reducing nasal and ocular symptoms of AR. They have superior efficacy compared with oral antihistamines and LTRAs.
  - Harm: INCS have known undesirable local adverse effects, such as epistaxis with some increased frequency compared with placebo in prolonged administration studies. There are no apparent negative effects on the hypothalamic-pituitary axis. There may be some negative effects on short-term growth in children, but it is unclear whether these effects translate into long-term growth suppression.
  - Cost: Low.
  - Benefits-Harm Assessment: The benefits of using INCS outweigh the risks when used to treat seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).
  - Value Judgments: None.
  - Policy Level: Strong recommendation for the use of INCS to treat AR.
  - Intervention: The well-proven efficacy of INCS, as well as their superiority over other agents, make them first-line therapy in the treatment of AR.

- *Oral decongestants:*
  - Aggregate Grade of Evidence: B (Level 1a: 2 studies; Level 1b: 3 studies; Level 3b: 2 studies; Level 4: 2 studies).
  - Benefit: Reduction of nasal congestion with pseudoephedrine. No benefit with phenylephrine.
  - Harm: Side effects include insomnia, loss of appetite, irritability, palpitations, and increased blood pressure. Risk of toxicity in young children.
  - Cost: Low.
  - Benefits-Harm Assessment: Balance of benefit and harm for pseudoephedrine. Harm likely outweighs benefit for phenylephrine.
  - Value Judgments: Patient's other comorbidities and age should be considered before use.
  - Policy Level: Option for pseudoephedrine. Recommendation against use of phenylephrine.
  - Intervention: Pseudoephedrine as an oral decongestant can be effective in reducing symptom of nasal congestion in patients with AR and for short-term symptom relief. Side effects, comorbidities, and age of patient should be considered before use.

- *Intranasal decongestants:*
  - Aggregate Grade of Evidence: B (Level 1b: 3 studies; Level 2b: 1 study).
  - Benefit: Reduction of nasal congestion with topical decongestants.
  - Harm: Side effects include nasal burning, stinging, dryness, and mucosal ulceration. Potential for rebound congestion when used long term.
  - Cost: Low.
  - Benefits-Harm Assessment: Harm likely outweighs benefit if used for more than 3 days.
  - Value Judgments: Topical decongestants can be helpful for short-term relief of nasal congestion.

- Policy Level: Option.
- Intervention: Topical decongestants can provide effective short-term nasal decongestion in patients with AR, but long-term use is not recommended due to risk for rhinitis medicamentosa.

- *Leukotriene receptor antagonists:*
  - Aggregate Grade of Evidence: A (Level 1a: 6 studies; Level 1b: 17 studies; Level 2a: 2 studies; Level 2b: 3 studies; Level 4: 3 studies).
  - Benefit: Consistent reduction in symptoms and improvement in QoL compared with placebo, as demonstrated in RCTs and systematic review of RCTs.
  - Harm: Consistently inferior when compared with INCSs for symptom reduction and improvement in QoL, based on RCTs and systematic reviews of RCTs. Equivalent-to-inferior effect compared with oral antihistamines in symptom reduction and improvement of QoL.
  - Cost: Annual incurred drug and medical costs estimated to be $631 for generic montelukast.
  - Benefits-Harm Assessment: Preponderance of benefit over harm. LTRAs are effective as monotherapy compared with placebo. However, there is a consistently inferior or equivalent effect compared with other, less expensive agents used as monotherapy.
  - Value Judgments: LTRAs are equivalent to oral antihistamine alone and more effective than placebo at controlling both asthma and AR symptoms in patients with both conditions. Control of AR symptoms with LTRAs, however, is less effective than with INCSs, and inferior or equivalent to oral antihistamines. Therefore, evidence is lacking for recommending LTRAs as first- or second-line monotherapy in the management of AR alone or in combination with asthma.
  - Policy Level: Recommendation against use of LTRAs as first-line therapy for AR.
  - Intervention: LTRAs should not be used as monotherapy in the treatment of AR, but can be considered as second-line therapy, such as when INCSs are contraindicated.

- *Cromolyn:*
  - Aggregate Grade of Evidence: A (Level 1b: 13 studies; Level 2b: 9 studies).
  - Benefit: Disodium cromoglycate (DSCG) is effective in reducing sneezing, rhinorrhea, and nasal congestion.
  - Harm: Rare local side effects include nasopharyngeal irritation, sneezing, rhinorrhea, and headache.
  - Cost: Low.
  - Benefits-Harm Assessment: Preponderance of benefit over harm. Benefit is considered mild to moderate. Use of DSCG is less effective than INCSs.
  - Value Judgments: Useful for preventive short-term use in patients with known exposure risks.
  - Policy Level: Option.
  - Intervention: DSCG may be considered for the treatment of AR, particularly in patients known triggers and who cannot tolerate INCSs.

- *Intranasal anticholinergics:*
  - Aggregate Grade of Evidence: B (Level 1b: 9 studies; Level 2b: 5 studies).
  - Benefit: Reduction of rhinorrhea with topical anticholinergics.
  - Harm: Local side effects include nasopharyngeal irritation, burning, headache, pharyngitis, epistaxis, nasal dryness, nasal congestion, and dry mouth. Care should be taken to avoid overdose leading to systemic side effects.
  - Cost: Low to moderate.
  - Benefits-Harm Assessment: Preponderance of benefit over harm in PAR patients with rhinorrhea.
  - Value Judgments: No significant benefits in controlling symptoms other than rhinorrhea. Evidence for combined use with INCSs is limited but encouraging for patients with persistent rhinorrhea.
  - Policy Level: Option.
  - Intervention: Ipratropium bromide nasal spray may be considered as an adjunct medication to INCSs in PAR patients with uncontrolled rhinorrhea.

- *Biologics (omalizumab):*
  - Aggregate Grade of Evidence: A (Level 1a: 1 study; Level 1b: 5 studies).
  - Benefit: Consistent reduction in symptoms and rescue medication as well as improvement in QoL in RCTs and systematic review of RCTs when compared with placebo.
  - Harm: Injection-site reactions; possibility of anaphylactic reaction.
  - Costs: High. Annual incurred drug costs estimated to be above $18,000 per year in the United States.
  - Benefits-Harm Assessment: No therapy option as omalizumab is not registered for treatment of AR alone. This review was limited to evaluation of AR only; comorbid asthma was not evaluated.
  - Value Judgments: Omalizumab monotherapy is superior to placebo, but treatment effects are small over pharmacotherapy. Its use may be evaluated in exceptional cases of highly sensitive, polysensitized individuals in combination with AIT.
  - Policy Level: No indication for the treatment of AR alone.
  - Intervention: Omalizumab should not be used as monotherapy in the treatment of AR but may be considered in combination with AIT for highly sensitive poly-allergic rhinitis patients with increased risk of anaphylaxis. As omalizumab is not currently

approved by the FDA for AR treatment, in the US this treatment approach would likely not be performed in routine clinical practice presently.

- *Nasal saline:*
  - Aggregate Grade of Evidence: A (Level 1a: 1 study; Level 1b: 11 studies). Lower-level studies were not considered in the ICAR:AR review.
  - Benefit: Reduced nasal symptom scores, improved QoL, improved mucociliary clearance, and well tolerated, with an excellent safety profile.
  - Harm: Intranasal irritation, headaches, and ear pain.
  - Cost: Minimal.
  - Benefits-Harm Assessment: Preponderance of benefit over harm.
  - Value Judgments: Nasal saline should be used as an adjunct to other pharmacologic treatments for AR. Isotonic solutions may be more beneficial in adults, whereas hypertonic solutions may be more effective in children.
  - Policy Level: Strong recommendation.
  - Intervention: Nasal saline is strongly recommended as part of the treatment strategy for AR.
- *Probiotics:*
  - Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 26 studies).
  - Benefit: Improved nasal/ocular symptoms or QoL in most studies; possible improvement in immunologic parameters (T helper 1 [Th1]:Th2 ratio).
  - Harm: Low.
  - Benefits-Harm Assessment: Balance of benefit and harm.
  - Value Judgments: Minimal harm associated with probiotics, but heterogeneity across studies makes magnitude of benefit difficult to quantify. Variation in organism and dosing across trials prevents specific recommendation for treatment.
  - Policy Level: Option.
  - Intervention: Consider adjuvant use of probiotics for patients with symptomatic seasonal and perennial AR.
- *Combination oral antihistamine and oral decongestant:*
  - Aggregate Grade of Evidence: A (Level 1b: 21 studies).
  - Benefit: Improved control of nasal congestion with combination of oral antihistamines and oral decongestants.
  - Harm: Oral decongestants can cause significant adverse effects, particularly in patients with hypertension, cardiovascular disease, or benign prostatic hypertrophy. In addition, these medications should not be used in children under 4 years of age or in pregnant patients. This should be weighed against the potential benefits prior to prescribing.
  - Cost: Low.
  - Benefits-Harm Assessment: Harm likely outweighs benefit when used on a routine basis.
  - Value Judgments: Combination therapy of oral antihistamines and oral decongestants can be helpful for relief of an acute exacerbation of AR, especially nasal symptoms, when exposed to triggers. Caution should be exercised regarding long-term use, given the possibility of significant adverse effects.
  - Policy Level: Option, particularly for acute exacerbations of nasal congestion.
  - Intervention: Combination therapy with oral antihistamine and oral decongestant can provide effective reduction of nasal congestion symptoms in patients with AR; however, there is recommendation against long-term use given the significant side-effect profile of oral decongestants.
- *Combination oral antihistamine and intranasal corticosteroid:*
  - Aggregate Grade of Evidence: B (Level 1b: 5 studies).
  - Benefit: Reduction of nasal congestion with combination of oral antihistamines and INCSs compared with oral antihistamines alone.
  - Harm: Side effects include sedative properties of antihistamines, although significantly decreased with the newer second-generation agents. Side effects of topical INCSs include nasal dryness and epistaxis, burning in the nose, and, with prolonged use, possible growth suppression in the pediatric population.
  - Cost: Low.
  - Benefits-Harm Assessment: Harm likely outweighs benefit of adding the oral antihistamine unless treating symptoms other than nasal symptoms.
  - Value Judgments: Combination therapy of oral antihistamine and INCS can be helpful when managing the symptoms of nasal congestion.
  - Policy Level: Option.
  - Intervention: Combination therapy of INCSs and oral antihistamine does not improve symptoms of nasal congestion over INCSs use alone, and does risk have the adverse effects of systemic antihistamine use.
- *Combination oral antihistamine and leukotriene receptor antagonist:*
  - Aggregate Grade of Evidence: A (Level 1a: 1 study; Level 1b: 11 studies; Level 2b: 1 study).
  - Benefit: Inconsistent evidence that combination LTRA and oral antihistamine were superior in symptom reduction and QoL improvement than either agent as monotherapy. Combination therapy is

inferior in symptom reduction compared with INCS alone.
- Harm: No significant safety-related adverse events from combination therapy.
- Costs: Generic montelukast was more expensive than either generic loratadine or cetirizine on a per-dose basis, according to weekly data provided by the Centers for Medicare and Medicaid Services.
- Benefits-Harm Assessment: Balance of benefit and harm.
- Value Judgments: Combination therapy with LTRA and oral antihistamine does not result in consistently improved AR symptoms compared with either agent alone. There are few reported safety-related adverse events from combination therapy. The addition of an LTRA may have a role in management of comorbid asthma.
- Policy Level: Option.
- Intervention: Combination therapy with LTRA and oral antihistamine is an option for management of AR, particularly in patients with comorbid asthma or those who do not tolerate INCSs and symptoms are not well-controlled on oral antihistamine monotherapy.

- *Combination intranasal corticosteroid and intranasal antihistamine:*
  - Aggregate Grade of Evidence: A (Level 1b: 9 studies; Level 2b: 1 study; Level 2c: 2 studies).
  - Benefit: Rapid onset, more effective for relief of multiple symptoms than either INCS or intranasal antihistamine alone.
  - Harm: Patient intolerance, especially due to taste.
  - Costs: Moderate financial burden; average wholesale price of $202 USD per 23-gram bottle (1-month supply when used as labeled).
  - Benefits-Harm Assessment: Preponderance of benefit over harm. Combination therapy with intranasal antihistamine and INCS is consistently more effective than placebo; there is low risk of nonserious adverse effects.
  - Value Judgments: Despite Level 1 evidence demonstrating that combination spray therapy (INCS plus intranasal antihistamine) is more effective than monotherapy and placebo, the increased financial cost and need for prescription limit the value of combination therapy as a routine first-line treatment for AR.
  - Policy Level: Strong recommendation for the treatment of AR when monotherapy fails to control symptoms.
  - Intervention: Combination therapy with INCS and intranasal antihistamine may be used as second-line therapy in the treatment of AR when initial monotherapy with either an INCS or antihistamine does not provide adequate control.

- *Acupuncture:*
  - Aggregate Grade of Evidence: B (Level 1a: 2 studies; Level 2b: 13 studies).
  - Benefit: Unclear, as 1 meta-analysis showed no overall effects of acupuncture on AR symptoms or need for rescue medications, and a second meta-analysis showed an effect of acupuncture on symptoms, QoL, and need for rescue medications.
  - Harm: Needle sticks associated with minor adverse events, including skin irritation, pruritis, erythema, subcutaneous hemorrhage, infection, and headache. Need for multiple treatments and possible ongoing treatment to maintain any benefit gained.
  - Cost: Cost of acupuncture treatment with multiple treatments required.
  - Benefits-Harm Assessment: Balance of benefit and harm.
  - Value Judgments: The authors determined that the evidence was inconclusive but that acupuncture could be appropriate for some patients to consider as an adjunct therapy.
  - Policy Level: Option.
  - Intervention: In patients who wish to avoid medications, acupuncture may be suggested as a possible therapeutic adjunct.

- *Honey:*
  - Aggregate Grade of Evidence: B (Level 1b: 2 studies; Level 2b: 1 study).
  - Benefit: Unclear, as studies have shown differing results. Honey may be able to modulate symptoms and decrease need for antihistamines.
  - Harm: Some patients stopped treatment because they could not tolerate the level of sweetness. Some patients could have an allergic reaction to honey intake, and, in rare instances, anaphylaxis. Use of this therapy in prediabetics and diabetics would likely need to be avoided out of concern for elevated blood glucose levels.
  - Cost: Cost of honey is low.
  - Benefits-Harm Assessment: Balance of benefit and harm.
  - Value Judgments: Studies are inconclusive and heterogeneous.
  - Policy Level: No recommendation.
  - Intervention: None.

- *Herbal therapies:*
  - Aggregate Grade of Evidence: Uncertain.
  - Benefit: Unclear, but some herbs may be able to provide symptomatic relief.

- Harm: Some herbs are associated with mild side effects. Also, the safety and quality of standardization of herbal medications is unclear.
- Cost: Cost of herbal supplements is variable.
- Benefits-Harm Assessment: Unknown.
- Value Judgments: The authors determined that there is a lack of sufficient evidence to recommend the use of herbal supplements in AR.
- Policy Level: No recommendation.
- Intervention: None.

III.G.3. Results—management: surgical therapy

- *Surgical therapy:* Whereas AR is typically considered a medical disease, surgical therapies are sometimes offered. Surgical treatment of the septum, inferior and/or middle turbinates, and possibly vidian/posterior nasal neurectomy, may be considered in both allergic and nonallergic patients. Outcomes of these various techniques are variable in patients with AR. Recommendations are as follows:

  - Aggregate Grade of Evidence: C (Level 1a: 1 study; Level 1b: 1 study; Level 2b: 1 study; Level 3b: 4 studies; Level 4: 5 studies).
  - Benefit: Improved postoperative symptoms and nasal airway status.
  - Harm: Possible septal perforation, empty nose syndrome, nasal dryness, mucosal damage, and epistaxis.
  - Cost: Office-associated vs operating room–associated procedural costs.
  - Benefits-Harm Assessment: Preponderance of benefit over harm.
  - Value Judgments: Properly selected patients can experience an improved nasal airway with judicious surgical intervention.
  - Policy Level: Option.
  - Intervention: Turbinate reduction with or without septoplasty may be considered in AR patients who had have failed medical management, and have anatomic features that explain symptoms of nasal obstruction.

III.G.4. Results—management: allergen immunotherapy

AIT is one of the management options for AR. Through scheduled administration of allergen extracts at effective doses, AIT aims to effect a sustained immunologic change, resulting in control of allergy symptoms and reduction in allergy medication use.

A description of allergen extract units, potency, and standardized vs nonstandardized allergen extracts is found in the ICAR:AR document. This information is necessary in developing a meaningful understanding of AIT. In additional to traditional allergen extracts, which are created by collecting raw material from a plant, mold, or animal and then using a solution to extract proteins from the source, modified allergen extracts have also been developed and studied in AIT. These modified allergen extracts aim to decrease adverse events associated with AIT, limit extract production costs, or increase consistency between batches. The laboratory production of allergens allows for modification of extracts and epitope structures that aim to enhance immunogenicity while decreasing the risk of adverse reactions. Modified allergen extracts include recombinant allergens, peptide constructs, allergoids and polymerized allergens, and adjuvant constructs, each of which is discussed in the ICAR:AR document.

Various AIT methods and their efficacy in AR were reviewed. The summary of these findings is shown in Table III.G.4.

- *Subcutaneous immunotherapy (SCIT):* High-level evidence demonstrates that SCIT is effective for the treatment of AR. There are many nuances to providing SCIT for the treatment of AR, including patient selection, knowledge of contraindications, selection of allergen extracts, dosing, monosensitized vs polysensitized patients, and use of single vs multiple allergen immunotherapy, along with various mixing and administration options and other considerations. The ICAR:AR document should be consulted for a more thorough discussion of these issues. Recommendations are as follows:

  - Aggregate Grade of Evidence: A (Level 1a: 3 recent studies listed; Level 1b: 5 recent studies listed). Of note, due to the large body of literature supporting SCIT as a treatment for AR, only recent systematic reviews and select double-blind, placebo-controlled RCTs were reviewed.
  - Benefit: Improvement in symptoms and decreased need for rescue medication. There is a decreased likelihood of progression from AR to bronchial asthma. Persistent benefit for years after completion of 3 to 5 years of SCIT.
  - Harm: Inconvenience of multiple visits to a medical facility to receive injections. Potential for systemic reactions, including anaphylaxis.
  - Cost: Cost for preparation of allergen extract for treatment, as well as costs associated with visits to medical facilities to receive injections.
  - Benefits-Harm Assessment: Benefit greater than harm for patients who cannot obtain adequate relief with symptomatic treatment and whose symptoms extend more than a few weeks each year.
  - Value Judgments: Patients who can obtain adequate relief of symptoms with medication must decide if the short-term increased cost and inconvenience of SCIT is compensated for by the long-term, persisting clinical benefit and relief from need to take medication. Pharmacoeconomic studies suggest that, in the long term, SCIT is cost-effective compared with symptomatic therapy.

TABLE III.G.4. AIT methods

Immunotherapy method	Number of listed studies	Aggregate grade of evidence	Recommendation level	Interpretation
SCIT	8	A	Strong recommendation	Strong recommendation for SCIT in patients unable to obtain adequate relief from pharmacotherapy and those who would benefit from secondary disease-modifying effects.
SLIT	25	A	Strong recommendation	Strong recommendation for SLIT in patients unable to obtain adequate relief from pharmacotherapy. Specific recommendations for various SLIT preparations and treatment effects given in section IX.D.4 of the full ICAR:AR document.
Trans/epicutaneous immunotherapy	4	B	Recommend against	Limited studies show variable effectiveness, along with adverse reactions. Trans/epicutaneous immunotherapy is not recommended for AR treatment.
ILIT	7	B	Option	Pending additional studies, ILIT may be a viable option for AR treatment in the clinical population.

AIT = allergen immunotherapy; AR = allergic rhinitis; ILIT = intralymphatic immunotherapy; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

  - Policy Level: Strong recommendation for SCIT in patients unable to obtain adequate relief with symptomatic therapy.
  - Intervention: SCIT should be recommended to AR patients who cannot obtain adequate relief from symptomatic medication for significant periods of time each year and to those who would benefit from its secondary disease-modifying effects (prevention of bronchial asthma and new sensitization), particularly children and adolescents.

- *Sublingual immunotherapy (SLIT):* The literature on SLIT for AR is strong, with several good meta-analyses and systematic reviews published over the past decade. Like SCIT, there are several aspects of treatment that need to be considered. These include, but are not limited to, treatment of adults vs children, efficacy and safety of SLIT vs SCIT, cost-effectiveness, specific choice of allergen, and SLIT treatment method (ie, aqueous drops vs tablets). The ICAR:AR document should be consulted for a more thorough discussion of these issues. Recommendations are as follows:

  - Aggregate Grade of Evidence: A (Level 1a: 10 studies; Level 1b: 3 studies; Level 2a: 11 studies; Level 3a: 1 study).
  - Benefit: SLIT improved patient symptom scores, even as add-on treatment on top of rescue medication. SLIT reduced medication use. The effect of SLIT lasted for at least 2 years after a 3-year course of high-dose therapy. Benefit is generally higher than with single-drug pharmacotherapy, but possibly somewhat less than with SCIT.
  - Harm: Minimal harm with very frequent, but mild, local adverse events. Systemic adverse events are very rare. SLIT seems to be safer than SCIT.
  - Cost: Intermediate, SLIT becomes cost-effective compared with pharmacotherapy after several years of administration. Data on cost of SLIT compared with SCIT is variable.
  - Benefits-Harm Assessment: Benefit of treatment over placebo is small, but tangible. SLIT benefit is demonstrated beyond the improvement seen with rescue medications. There is a lasting effect at least 2 years off treatment. Minimal harm with SLIT, with a greater risk for SCIT.
  - Value Judgments: SLIT improved patient symptoms with low risk for adverse events.
  - Policy Level:
    - Use of SLIT: grass pollen tablet, ragweed tablet, HDM tablet, tree pollen aqueous solution—Strong recommendation.
    - Alternaria SLIT—Recommendation.
    - Epithelia SLIT—Option.
    - Dual SLIT in biallergic patients—Recommendation.
  - Intervention: We recommend high-dose tablet or aqueous SLIT should be administered in patients (adults and children) with seasonal and/or perennial AR who wish to reduce their symptoms and their medication use. SLIT can be continued safely in pregnant patients.

- *Transcutaneous/epicutaneous immunotherapy:* Studies are limited and show variable outcomes. Recommendations are as follows:

  - Aggregate Grade of Evidence: B (Level 1b: 4 studies).
  - Benefit: Transcutaneous immunotherapy resulted in limited and variable improvement in symptoms, medication use, and allergen provocation tests in patients with AR or conjunctivitis.
  - Harm: Transcutaneous immunotherapy resulted in systemic and local reactions. Systemic reactions occurred in up to 14.6% of patients receiving grass transcutaneous immunotherapy.

- Cost: Unknown.
- Benefits-Harm Assessment: There are limited and inconsistent data on benefit of the treatment, but there is a concerning rate of adverse effects. Three of 4 studies on this topic were published by the same investigators from 2009 to 2015.
- Value Judgments: Transcutaneous immunotherapy could offer a potential alternative to SCIT and SLIT, but further research is needed.
- Policy Level: Recommend against.
- Intervention: Although transcutaneous immunotherapy may potentially have a future clinical application in the treatment of AR, at this juncture there are limited studies that show variable and limited effectiveness, and a significant rate of adverse reactions. Given the above and the availability of alternative treatments, transcutaneous immunotherapy is not currently recommended.

- *Intralymphatic immunotherapy (ILIT):* Given the reduction in treatment duration, allergen dose, financial burden relative to SCIT, and the low risk of adverse effects, ILIT is a promising new therapy for AR. Before ILIT is integrated into clinical practice, a well-designed pharmacoeconomic evaluation of ILIT vs SCIT and larger RCTs are needed, as well as further studies investigating the impact of treatment protocol on outcomes. Recommendations are as follows:

  - Aggregate Grade of Evidence: B (Level 1b: 5 studies; Level 2b: 1 study; Level 4: 1 study).
  - Benefit: Reduced treatment period, reduced number of injections, reduced dose of allergen injected, and decreased risk of adverse events.
  - Harm: Risk of anaphylaxis.
  - Cost: ILIT might be associated with reduced costs relative to SCIT (reduced time, reduced financial burden for patients and health-care provider). Application requires training.
  - Benefits-Harm Assessment: Balance of benefit over harm for ILIT relative to SCIT.
  - Value Judgments: ILIT appears to be effective in the treatment of AR. Preliminary data indicate that, relative to SCIT, the burdens of treatment on the patient and on the health-care system are lower.
  - Policy Level: Option, pending additional studies.
  - Intervention: Although the research is promising, further studies are needed before ILIT can be translated into routine clinical practice.

- *Alternative forms of AIT:* Oral/gastrointestinal, nasal, and inhaled (intrabronchial) AIT represent alternate options for the treatment of AR, with primarily historic significance. Oral/gastrointestinal immunotherapy has not shown significant benefit for treatment of aeroallergen sensitivity. Local nasal immunotherapy demonstrates efficacy, but local adverse reactions limit patient compliance. High-quality studies of inhaled/intrabronchial immunotherapy for the treatment of AR have not been performed. Oral mucosal immunotherapy is a new, alternative form of AIT different from SLIT and oral/gastrointestinal strategies, in which a glycerin-based toothpaste vehicle introduces antigen to high-density antigen-processing oral Langerhans cells in the oral vestibular and buccal mucosa. Additional study is needed to define the role of oral mucosal immunotherapy in the treatment of AR.

- *Combination omalizumab and subcutaneous immunotherapy:* Potential benefits of combination therapy include decreased incidence of AIT-associated systemic allergic reactions and improved control of AR symptoms. Four RCTs have evaluated this combination, and 2 additional iterative analyses of a parent RCTs have been performed. Recommendations are as follows:

  - Aggregate Grade of Evidence: B (Level 1b: 4 studies, plus 2 additional iterative analyses of a parent study).
  - Benefit: Improved safety of accelerated cluster and rush AIT protocols, with decreased symptom and rescue medication scores among a carefully selected population.
  - Harm: Financial cost and risk of anaphylactic reactions.
  - Cost: Moderate to high.
  - Benefits-Harm Assessment: Preponderance of benefit over harm.
  - Value Judgments: Combination therapy increases the safety of AIT, with decreased systemic reactions following cluster and rush protocols. Associated treatment costs and likelihood of systemic reactions must be considered, with greater consideration for omalizumab pretreatment prior to higher-risk AIT protocols. Although 2 high-quality RCTs have demonstrated improved symptom control with combination therapy over AIT or omalizumab alone, not all patients will require this approach. Rather, an individualized approach to patient management must be considered, with evaluation of alternative causes for persistent symptoms, such as unidentified allergen sensitivity. The current evidence does not support the utilization of combination therapy for all patients failing to benefit from AIT alone.
  - Policy Level: Option, based on current evidence. However, it is important to note that omalizumab is not currently approved by the FDA for the treatment of AR.
  - Intervention: Omalizumab may be offered as a premedication before induction of cluster or rush AIT protocols. Combination therapy is an option for carefully selected patients with persistent symptomatic AR following AIT. An individualized

approach to patient management must be considered. In addition, as omalizumab is not currently approved by the FDA for AR treatment, in the United States this treatment approach would likely not be performed in routine clinical practice.

III.H. Results—associated conditions

Several medical conditions were reviewed for their potential association with AR. The summary of these findings is shown in Table III.H.

- *Asthma:*
  - *Asthma association with AR and nonallergic rhinitis*: Most patients with asthma also have rhinitis, and 10%-40% of rhinitis patients have asthma. IgE-mediated inflammation may involve both the upper and lower airways, supporting the unified airway concept. Aggregate Grade of Evidence: C (Level 3b: 7 studies).
  - *Rhinitis as a risk factor for asthma*: Rhinitis, both allergic and nonallergic, is a risk factor for developing asthma. Asthma and AR also share common risk factors, such as allergen sensitization. Aggregate Grade of Evidence: C (Level 2a: 2 studies; Level 3b: 11 studies).
  - *Treatment of AR and its effect on asthma*:
    - *Allergen avoidance*: Strong evidence for benefit with chemical or physical methods of allergen elimination is lacking. However, there is theoretical benefit of reducing allergen exposure, and allergen avoidance may be considered as part of a multifactorial approach in the management of AR-associated asthma.
    - *Pharmacotherapy*: Oral H_1 antihistamines, oral corticosteroids, INCSs, and LTRAs were reviewed in the treatment of AR with coexisting asthma. Recommendations are as follows:
      - Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 23 studies). Antihistamines (Level 1b: 6 studies), INCSs (Level 1a: 2 studies; Level 1b: 12 studies), and LTRAs (Level 1b: 5 studies).
      - Benefit: Pharmacotherapy improves subjective and objective severity of asthma in patients with coexistent AR. Patient education and training on medication use improves compliance and benefits for INCSs, and likely all patient-administered pharmacotherapy.
      - Harm: Pharmacotherapy other than systemic steroids—minimal harm with rare mild adverse events such as drowsiness. No serious adverse events were reported in the studies reviewed. Systemic corticosteroids have significant side effects.
      - Cost: Generally low cost for pharmacotherapy.
      - Benefits-Harm Assessment: There is a benefit over placebo for asthma treatment, although no significant benefit is seen over standard asthma pharmacotherapy. Risks of routine use of systemic corticosteroids generally outweighs the benefits, but short courses for acute indications (eg, asthma exacerbation) have a favorable likelihood of benefit relative to harm.
      - Value Judgments: Pharmacotherapy for AR may also benefit asthma symptoms and objective parameters of pulmonary function in patients with coexisting asthma and AR; however, the benefit for asthma should be considered a positive side effect rather than an indication for use as there appears to be limited benefit compared with standard asthma therapy.
      - Policy Level: Use of pharmacotherapy other than systemic steroids: Recommended use for optimal control of AR, with potential additional benefit for coexistent asthma, although not recommended for primary intent of asthma treatment. Use of systemic corticosteroid is not recommended for routine use in AR with comorbid asthma due to an unfavorable risk-benefit profile, although certain situations may indicate a short course (eg, acute asthma exacerbation).
    - *Biologics*: Omalizumab was reviewed in the treatment of AR with coexisting asthma. Recommendations are as follows:
      - Aggregate Grade of Evidence: B (Level 1b: 2 studies). Grade A evidence with multiple Level 1b RCTs and Level 1a reviews exist for asthma and AR individually, but there is only 1 double-blind RCT specifically evaluating omalizumab vs placebo in patients with concurrent conditions.
      - Benefit: Decreased asthma exacerbations, decreased symptom scores, and improvement in disease-specific QoL in patients with coexisting asthma and AR.
      - Harm: There is evidence for acceptable safety for use up to 52 weeks. Potential longer-term harm unknown. Minor events, such as mild injection-site reactions, are reported. There is a possibility of anaphylaxis.
      - Cost: Substantially higher cost than conventional therapy for asthma and AR.
      - Benefits-Harm Assessment: Benefits appear to outweigh potential harm for the treatment of more severe/persistent coexistent AR and asthma.
      - Value Judgments: Added benefit of omalizumab as therapy for patients with AR and

TABLE III.H. AR-associated conditions

Diagnosis	Number of listed studies	Aggregate grade of evidence	Interpretation
Asthma: association with rhinitis	7	C	Asthma is associated with AR and NAR.
Asthma: rhinitis as a risk factor	13	C	AR and NAR are risk factors for developing asthma.
Asthma: benefit of AR treatment	—	—	See Section X.A.4. of the full ICAR:AR document for specific recommendations.
ARS	5	C	AR is thought to be a disease-modifying factor for ARS.
Recurrent acute rhinosinusitis	2	D	Data inconclusive.
Chronic rhinosinusitis without nasal polyps	10	D	Conflicting evidence for/against an association.
Chronic rhinosinusitis with nasal polyps	21	D	Conflicting evidence for/against an association.
Conjunctivitis	7	C	AC is a frequently occurring comorbidity of AR.
AD	20	C	There is evidence for an association between AR and AD.
Food allergy and PFAS	12	B	There is evidence for a link between pollen allergy and PFAS.
Adenoid hypertrophy	11	C	Data inconclusive.
Otologic conditions: ETD	7	C	There is a causal role for AR in some cases of ETD.
Otologic conditions: otitis media	16	C	Relationship between AR and OTE is unclear.
Otologic conditions: Meniere's disease	8	C	Evidence for an association is of low grade, with substantial defects in study design.
Cough	9	C	Low level evidence for an association between AR and cough.
Laryngeal disease	18	C	There is some evidence for an association between AR and laryngeal disease.
EoE	13	C	Limited observational data suggests a potential association between aeroallergens and EoE pathogenesis.
Sleep disturbance and OSA	20	B	Sleep disturbance is associated with AR.

AC = allergic conjunctivitis; AD = atopic dermatitis; AR = allergic rhinitis; ARS = acute rhinosinusitis; EoE = eosinophilic esophagitis; ETD = Eustachian tube dysfunction; NAR = nonallergic rhinitis; OSA = obstructive sleep apnea; OTE = otitis media with effusion; PFAS = pollen-food allergy syndrome.

asthma that is uncontrolled despite maximal conventional interventions. However, given the significantly increased cost associated with omalizumab, the value of this therapy is likely greatest for patients with severe asthma and symptoms that persist despite usual therapies.

- Policy Level: Omalizumab is recommended for those patients with clear IgE-mediated allergic asthma with coexistent AR who fail conventional therapy. The significant additional cost of this therapy should be considered in its evaluation.

- *AIT*: Evidence for SCIT and SLIT for asthma in the context of comorbid AR was reviewed. Recommendations are as follows:
  - Aggregate Grade of Evidence: A (Level 1a: 2 studies; Level 1b: 4 studies; Level 2b: 1 study).
  - Benefit: AIT (both SCIT and SLIT) has demonstrated benefit in concomitant AR and asthma, with decreased symptoms, rescue medication use, and bronchial hyperresponsiveness, as well as reduced development of asthma in patients with AR only.
  - Harm: Local-site reactions are common and there is potential for anaphylactic events with any form of AIT.
  - Cost: Increased cost compared with standard therapy for AR and asthma, although the potential to treat the underlying disease process and prevent progression of disease could reduce long-term costs.
  - Benefits-Harm Assessment: Significant evidence to support the use of AIT for patients with AR and asthma, as well as the potential utility of AIT for preventing progression of allergic disease from AR to the development of allergic asthma. Harm events are generally limited to minor local reactions, but there is

a potential risk of anaphylaxis. Benefits appear to outweigh potential harm, given that anaphylaxis is rare.
    - Value Judgments: There appears to be unique value in AIT, as this therapy treats the underlying pathology of AR and asthma, with the potential to halt progression of allergic disease. The unique benefits of this therapy are of value, despite some uncertainty regarding their true magnitude.
    - Policy Level: AIT (SCIT and SLIT) is recommended for treatment of AR with asthma in patients following an appropriate trial of medical therapy, and may also be considered for the benefit of preventing progression of AR to asthma in patients with AR only, and for whom AIT is otherwise indicated.

- *Rhinosinusitis:* AR is regarded as a disease-modifying factor for rhinosinusitis; however, the overall association between AR and rhinosinusitis is not strong.
    - *Acute rhinosinusitis (ARS):* Although the evidence is relatively weak, there is evidence to support an increased risk of ARS when AR is present. Aggregate Grade of Evidence: C (Level 2a: 2 studies; Level 2b: 1 study; Level 3a: 1 study; Level 3b: 1 study).
    - *Recurrent acute rhinosinusitis (RARS):* Two studies exist, with conflicting data. The relationship between AR and RARS is unclear. Aggregate Grade of Evidence: D (Level 2b: 2 studies; conflicting evidence).
    - *Chronic rhinosinusitis without nasal polyps (CRSsNP):* Ten studies exist, with conflicting data. The relationship between AR and CRSsNP is unclear. Aggregate Grade of Evidence: D (Level 1b: 1 study; Level 3a: 1 study; Level 3b: 8 studies; conflicting evidence).
    - *Chronic rhinosinusitis with nasal polyps (CRSwNP):* Twenty-one studies exist, with conflicting data. The relationship between AR and CRSwNP is unclear. Aggregate Grade of Evidence: D (Level 2b: 1 study; Level 3a: 1 study; Level 3b: 15 studies; Level 4: 4 studies; conflicting evidence).

- *Allergic conjunctivitis:* Allergic conjunctivitis is a frequently occurring comorbidity of AR, particularly in children. AR is associated with a 35%-74% prevalence of allergic conjunctivitis, and, among patients with allergic conjunctivitis, the prevalence of AR may be as high as 97%. Ocular allergy symptoms also contribute significantly to QoL impairment associated with AR. Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3a: 2 studies; Level 3b: 3 studies).
- *Atopic dermatitis:* The extent of the association between AR and atopic dermatitis remains poorly defined due to methodological differences and limitations of the studies examining this association. The phenotypic diversity of AR and atopic dermatitis, along with poor characterization of the phenotypes of their study populations, limits the conclusions that can be drawn about the association of these 2 conditions. Aggregate Grade of Evidence: C (Level 2b: 4 studies; Level 3b: 15 studies; Level 4: 1 study).
- *Food allergy and pollen-food allergy syndrome:* There is a known association between pollen sensitivity and certain food epitopes, with the prevalence of pollen-food allergy syndrome depending on the specific pollen allergen sensitivity. The effect of targeted AIT for pollen allergy in reducing pollen-food allergy syndrome symptoms has been studied, showing mixed results. Aggregate Grade of Evidence: B (Level 2b: 8 studies; Level 4: 1 study).
- *Adenoid hypertrophy:* At present, the data are inconclusive. When allergic vs nonallergic children are assessed for adenoid hypertrophy, there is a trend for allergic children to show increased prevalence of adenoid hypertrophy. However, when children with upper airway obstruction are assessed for inhalant allergy sensitivity, a consistently increased prevalence of allergic sensitivity is not found. This may potentially be explained by different age peaks for adenoid hypertrophy vs pediatric AR. Aggregate Grade of Evidence: C (Level 4: 11 studies).
- *Otologic conditions:*
    - *Eustachian tube dysfunction:* Current evidence demonstrates an association between Eustachian tube dysfunction and AR, including the potential for a direct causal link, as demonstrated by nasal challenge with histamine or aeroallergens resulting in transient Eustachian tube obstruction. Aggregate Grade of Evidence: C (Level 1b: 3 studies; Level 2b: 1 study; Level 3b: 1 study; Level 4: 2 studies).
    - *Otitis media:* Based on current evidence, the association between AR and otitis media with effusion remains unclear. Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3b: 3 studies; Level 4: 11 studies).
    - *Meniere's disease:* Evidence supporting a connection between type 1 IgE-mediated hypersensitivity and Meniere's disease is of low grade, with substantial defects in study design. Aggregate Grade of Evidence: C (Level 3b: 4 studies; Level 4: 4 studies).

- *Cough:* Aside from the demonstrated association of asthma (which may have cough as a symptom) with AR, there is low-level evidence for cough alone as an associated comorbidity of AR. Aggregate Grade of Evidence: C (Level 2b: 2 studies; Level 3b: 2 studies; Level 4: 4 studies; Level 5: 1 study).
- *Laryngeal disease:* There is some evidence suggesting a relationship between AR and laryngeal dysfunction. Thick endolaryngeal mucus has been associated with allergy. AR may be considered in the differential diagnosis of patients with vocal complaints. Aggregate Grade of

Evidence: C (Level 2b: 8 studies; Level 3a: 1 study; Level 3b: 4 studies; Level 4: 5 studies).

- *Eosinophilic esophagitis (EoE):* Studies examining the prevalence of clinician-diagnosed AR and aeroallergen sensitization in patients with EoE support an association between these entities. There are limited observational data, however, suggesting a potential association between aeroallergens and EoE pathogenesis. Aggregate Grade of Evidence: C (Level 3a: 1 study; Level 4: 12 studies).
- *Sleep disturbance and obstructive sleep apnea:* Nasal obstruction due to AR may substantially affect sleep, and sleep disturbance in AR patients is shown to affect QoL, work performance, and productivity. A correlation between AR severity and sleep disturbance has been demonstrated. Aggregate Grade of Evidence: B (Level 1b: 5 studies; Level 2b: 1 study; Level 2c: 5 studies; Level 3b: 7 studies; Level 4: 2 studies).

IV. Discussion

This Executive Summary has reviewed several key findings of the ICAR:AR document. Although certain areas demonstrate strong evidence to support AR diagnosis and treatment decisions, other areas show substantially weaker evidence and would benefit from additional study. For example, large RCTs, systematic reviews, and meta-analyses have demonstrated the benefit of INCSs and nonsedating second-generation antihistamines in the treatment of AR (Aggregate Grade of Evidence A). In contrast, evidence for the association of most studied risk factors (ie, genetics, in-utero allergen exposure, pollution, socioeconomic status) in the development of AR is weaker, with an Aggregate Grade of Evidence C.

Even within specific topic areas, the evidence may be varied. For example, the overall evidence for the use of SLIT in the treatment of AR is quite strong, with numerous systematic reviews and meta-analyses of RCTs. However, when evaluating the evidence for SLIT in AR in specific subgroups or more directed questions (ie, cost-effectiveness, long-term effectiveness, epithelial antigens, fungal antigens), the evidence is weaker.

Like the 2016 ICAR: Rhinosinusitis document, several areas were identified through the ICAR:AR process where relatively low levels of evidence guide our everyday clinical care of the AR patient. One example is the use of blended skin testing techniques, consisting of SPT followed by selected intradermal tests, often based on a predetermined algorithm. Although the Aggregate Grades of Evidence for SPT alone is B and skin intradermal testing alone is also B, studies to support the benefit of blended skin prick and intradermal techniques are rare, with an Aggregate Grade of Evidence of D. As many clinicians use this technique in practice, additional study is warranted. Another example is provided by the evidence supporting/refuting the association between AR and rhinosinusitis. Many practitioners commonly associate AR with ARS, RARS, or CRS, yet the evidence for this association is poor, as demonstrated by Aggregate Grades of Evidence C or D. The studies for ARS and RARS association with AR are few, but they have demonstrated a potential association between AR and ARS (Grade C evidence). The studies for RARS and CRS are highly conflicting and do not currently support an association (Grade D evidence). One consideration in analyzing this evidence, especially for the patients with CRSwNP, is the classic phenotypic definition of CRS (ie, with and without nasal polyposis). As our understanding of CRS advances, and we lean more toward endotype classifications of this disease, in addition to separating nasal polyp groups (ie, aspirin-exacerbated, allergic fungal rhinosinusitis, cystic fibrosis), we will likely find that AR has a greater association with certain types of CRS than the much broader categories of CRSsNP and CRSwNP.

The examples above highlight some of the benefits of the ICAR:AR document, as it has demonstrated the areas where our AR evidence is solid while also identifying knowledge gaps. As we acknowledge these gaps, we encourage further research and improvement of our understanding of AR from a pathophysiologic, diagnostic, and treatment perspective.

Acknowledgment

This Executive Summary is compiled by the editors of the ICAR:AR document (S.K.W., S.Y.L., E.T.). The data and recommendations contained in this report are the collective work of the 107 authors of the ICAR:AR document. This document would not have been possible without their contributions.

References

1. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. 2018;8:108–352.
2. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(Suppl 1):S22–S209.
3. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol*. 2011;1:431–437.
4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
5. American Academy of Pediatrics Steering Committee on Quality, Improvement, Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114:874–877.
6. Bousquet J, Van Cauwenberge P, Khaltaev N, ARIA Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(Suppl):S147–S334.