

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision

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Background: Allergic rhinitis represents a global health problem affecting 10% to 20% of the population. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines have been widely used to treat the approximately 500 million affected patients globally.

Objective: To develop explicit, unambiguous, and transparent clinical recommendations systematically for treatment of allergic rhinitis on the basis of current best evidence.

Methods: The authors updated ARIA clinical recommendations in collaboration with Global Allergy and Asthma European Network following the approach suggested by the Grading of Recommendations Assessment, Development and Evaluation working group.

Results: This article presents recommendations about the prevention of allergic diseases, the use of oral and topical medications, allergen specific immunotherapy, and complementary treatments in patients with allergic rhinitis as well as patients with both allergic rhinitis and asthma. The guideline panel developed evidence profiles for each recommendation and considered health benefits and harms, burden, patient preferences, and resource use, when appropriate, to formulate recommendations for patients, clinicians, and other health care professionals.

Conclusion: These are the most recent and currently the most systematically and transparently developed recommendations about the treatment of allergic rhinitis in adults and children. Patients, clinicians, and policy makers are encouraged to use these recommendations in their daily practice and to support their decisions. (*J Allergy Clin Immunol* 2010;126:466-76.)

Key words: AR, practice guideline

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Abbreviations used

AR: Allergic rhinitis

ARIA: Allergic Rhinitis and its Impact on Asthma

GRADE: Grading of Recommendations Assessment, Development and Evaluation

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TABLE I. Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

*Guideline panels applying GRADE use the term “conditional” and “weak” synonymously.

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Allergic rhinitis (AR) is an important health problem because of its prevalence and its impact on patients' social life, school performance, and work productivity.¹ Epidemiologic studies have consistently shown that asthma and rhinitis often coexist in the same patients.^{1,2} It is therefore important to advise clinicians and patients about the best evidence-based management of AR in patients with and without concomitant asthma.

Clinical practice guidelines for the management of AR had been developed over the past 15 years and were found to improve care.³ The first of those guidelines that were evidence-based were the Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations.⁴ More recently, other guidelines have been published: the International Primary Care Respiratory Group guidelines,⁵ the British Society of Allergy and Clinical Immunology guidelines,⁶ the American Academy of Allergy, Asthma & Immunology and American College of Allergy Asthma and Immunology Practice Parameters for the diagnosis and management of rhinitis,⁷ and the ARIA 2008 Update.¹ These guidelines used

evidence-based approaches to various degrees, but none used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.^{8,9}

In this 2010 revision of ARIA, we present recommendations for the prevention and treatment of AR and asthma coexisting with AR. The ARIA guideline panel revised its clinical recommendations to improve their usefulness following the transparent and systematic approach developed by the GRADE working group.^{8,9} For strong recommendations, we used the words “we recommend” and for conditional recommendations, “we suggest,” and we offer the suggested interpretations of “strong” and “conditional (also known as “weak”)” recommendations in Table I. Understanding the interpretation of these 2 grades—either strong or conditional—of the strength of recommendations is essential for sagacious clinical decision-making.

OBJECTIVE

Our objective was to develop explicit, unambiguous, and transparent clinical and practical recommendations systematically for the treatment of AR on the basis of current best evidence following the GRADE approach. This article summarizes the ARIA recommendations, and the complete rationale and explanation of all recommendations are provided in the unabridged text of the ARIA guidelines in this article's [Online Repository 1](#) at www.jacionline.org.

METHODS

We previously described the methods of the ARIA 2010 Revision,⁹ and the detailed methods are also provided in the unabridged text of the guidelines in [Online Repository 1](#). We followed the principles for developing transparent, evidence-based guidelines suggested by the World Health Organization.⁹⁻¹¹

We used the previous version of the ARIA guidelines as a starting point for the identification of clinical questions.¹ We followed the systematic approach suggested by the GRADE working group and other groups.¹²⁻¹⁶ For each recommendation, we provide its strength and the quality of the supporting evidence. As described, for strong recommendations, we used the words “we recommend” and for conditional (also known as “weak”) recommendations, “we suggest” (see Table I for interpretation aids). According to GRADE, we classified the quality of evidence into 4 categories: high, moderate, low, and very low.^{8,15} The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.¹⁵ Assessments of the quality of evidence for each

TABLE II. A summary of the GRADE approach to grading the quality of evidence for each outcome (see [Online Repository 1](#) for details)

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency	1. Large effect 2. Dose-response	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕○)
Observational studies	Low	3. Indirectness 4. Imprecision 5. Publication bias	3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	Low (⊕⊕○○) Very low (⊕○○○)

important outcome took into account the study design, the risk of bias, the consistency of the evidence across studies, the directness of the evidence, and the precision of the estimate of the effect (Table II; [Online Repository 1](#)).

RESULTS

In this article, we present 10 recommendations about the primary, secondary, and tertiary prevention of allergy, AR, and asthma; 31 recommendations about the management of AR; and 7 recommendations about the management of AR and asthma in the same patient. In-depth explanations, search strategies, evidence syntheses, and rationales are presented in [Online Repository 1](#) and this article's [Online Repository 2](#) at www.jacionline.org.

Statements about the underlying values and preferences as well as the remarks are integral parts of the recommendations and serve to facilitate accurate interpretation. They should not be omitted when citing or translating recommendations in the ARIA guidelines.

I. Prevention of allergy

1. Should exclusive breast-feeding be used in infants to prevent allergy?. Recommendation. We suggest exclusive breast-feeding for at least the first 3 months for all infants irrespective of their family history of atopy (conditional recommendation | low-quality evidence).

Values and preferences. This recommendation places a relatively high value on the prevention of allergy and asthma and a relatively low value on challenges or burden of breast-feeding in certain situations.

Remarks. The evidence that exclusive breast-feeding for at least the first 3 months reduces the risk of allergy or asthma is not convincing, and the recommendation to breast-feed exclusively is conditional. This recommendation applies to situations in which other reasons do not suggest harm from breast-feeding (eg, classic galactosemia, active untreated tuberculosis or HIV infection in the mother, antimetabolites, chemotherapeutic agents or radioactive isotopes used in the mother until they clear from the milk, and bacterial or viral infection of a breast).

2. Should antigen avoidance diet be used in pregnant or breast-feeding women to prevent development of allergy in children?. Recommendation. For pregnant or breast-feeding women, we suggest no antigen avoidance diet to prevent development of allergy in children (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on adequate nourishment of mothers and children and a relatively low value on very uncertain effects on the prevention of allergy and asthma in this setting.

3. Should children and pregnant women avoid environmental tobacco smoke (ie, passive smoking) to reduce the risk of developing allergy, wheezing, or asthma in children?. Recommendation. In children and pregnant women, we recommend total avoidance of environmental tobacco smoke (ie, passive smoking) (strong recommendation | very low-quality evidence).

Remarks. Smoking and exposure to secondhand smoke are common health problems around the world, causing a substantial burden of disease for children and adults. Although it is very rare to make a strong recommendation based on low-quality or very low-quality evidence, the ARIA guideline panel felt that in the absence of important adverse effects associated with smoking cessation or reducing the exposure to secondhand smoke, the balance between the desirable and undesirable effects is clear.

4. Should infants and preschool children avoid exposure to house dust mite to reduce the risk of developing dust mite allergy and asthma?. Recommendation. In infants and preschool children, we suggest multifaceted interventions to reduce early life exposure to house dust mite (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively low value on the burden and cost of using multiple preventive measures (eg, encasings to parental and child's bed, washing bedding and soft toys at temperature exceeding 55°C [131°F], use of acaricide, smooth flooring without carpets, and so forth) and relatively high value on an uncertain small reduction of the risk of developing wheeze or asthma. For some children at lower risk of developing asthma and in certain circumstances, an alternative choice will be equally reasonable.

Remarks. Children at high risk of developing asthma are those with at least 1 parent or sibling with asthma or other allergic disease.

5. Should infants and preschool children avoid exposure to pets at home to reduce the risk of developing allergy or asthma?. Recommendation. In infants and preschool children, we suggest no special avoidance of exposure to pets at home (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on possible psychosocial downsides of not having a pet and relatively low value on potential reduction in the uncertain risk of developing allergy and/or asthma.

Remarks. Clinicians and patients may reasonably choose an alternative action considering circumstances that include other sensitized family members.

6. Should specific measures reducing occupational agent exposure be used to decrease the risk of sensitization and subsequent development of occupational rhinitis and asthma?. Recommendation. For individuals exposed to occupational agents, we recommend specific prevention measures eliminating or reducing occupational allergen exposure (strong recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on reducing the risk of sensitization to occupational allergens and developing occupational rhinitis and/or asthma with the subsequent adverse consequences, and a relatively low value on the feasibility and cost of specific strategies aimed at reducing occupational allergen exposure.

Remarks. Total allergen avoidance, if possible, seems to be the most effective primary prevention measure.

II. Treatment of AR—reducing allergen exposure

7. Should methods aimed at reducing exposure to house dust mite be used in patients with allergy to dust mite allergens?. Recommendation. In patients with AR and/or asthma sensitive to house dust mite allergens, we recommend that clinicians do **not** administer and patients do **not** use currently available single chemical or physical preventive methods aimed at reducing exposure to house dust mites (strong recommendation | low-quality evidence) or their combination (conditional recommendation | very low-quality evidence), unless this is done in the context of formal clinical research.

We suggest multifaceted environmental control programs be used in inner-city homes to improve symptoms of asthma in children (conditional recommendation | very low-quality evidence).

Underlying values and preferences. The recommendation to use multifaceted environmental control programs in inner-city homes places a relatively high value on possible reduction in the symptoms of asthma in children and a relatively low value on the cost of such programs.

8. Should patients with allergy to indoor molds avoid exposure to these allergens at home?. Recommendation. In patients with allergy to indoor molds, we suggest avoiding exposure to these allergens at home (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on possible reduction in the symptoms of rhinitis and asthma and a relatively low value on the burden and cost of interventions aimed at reducing exposure to household molds.

9. Should patients with allergy to animal dander avoid exposure to these allergens at home?. Recommendation. In patients with AR caused by animal dander, we recommend avoiding exposure to these allergens at home (strong recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on potential reduction of symptoms of AR and a relatively low value on psychosocial downsides of not having a pet or the inconvenience and cost of environmental control measures.

Remarks. On the basis of a biological rationale, there is little doubt that total avoidance of animal allergens at home, and probably also marked reduction in their concentration, can

improve symptoms, despite the paucity of published data to substantiate this statement.

10. Should immediate and total cessation of exposure to an occupational agent or exposure control be used in patients with occupational rhinitis and asthma?. Recommendation. In patients with occupational asthma, we recommend immediate and total cessation of exposure to occupational allergen (strong recommendation | very low-quality evidence). When total cessation of exposure is not possible, we suggest specific strategies aimed at minimizing occupational allergen exposure (conditional recommendation | very low-quality evidence).

Underlying values and preferences. The recommendation to cease the exposure to occupational allergen immediately and totally places a relatively high value on reducing the symptoms of asthma and deterioration of lung function and a relatively low value on the potential socioeconomic downsides (eg, unemployment).

III. Pharmacologic treatment of AR

11. Should oral H₁-antihistamines be used for the treatment of AR?. Recommendation. In patients with AR, we recommend new-generation oral H₁-antihistamines that do not cause sedation and do not interact with cytochrome P450 (strong recommendation | low-quality evidence). In patients with AR, we suggest new-generation oral H₁-antihistamines that cause some sedation and/or interact with cytochrome P450 (conditional recommendation | low-quality evidence).

Underlying values and preferences. The recommendation to use new generation oral H₁-antihistamines that cause some sedation and/or interact with cytochrome P450 places a relatively high value on a reduction of symptoms of AR and a relatively low value on side effects of these medications.

Remarks. Astemizole and terfenadine were removed from the market because of cardiotoxic side effects.

12. Should new-generation oral H₁-antihistamines versus old-generation oral H₁-antihistamines be used for the treatment of AR?. Recommendation. In patients with AR, we recommend new-generation over old-generation oral H₁-antihistamines (strong recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on the reduction of adverse effects and a relatively low value on an uncertain comparative efficacy of new-generation versus old-generation oral H₁-antihistamines.

13. Should oral H₁-antihistamines be used in preschool children with other allergic diseases for the prevention of wheezing or asthma?. Recommendation. In infants with atopic dermatitis and/or family history of allergy or asthma (at high risk of developing asthma), we suggest clinicians do **not** administer and parents do **not** use oral H₁-antihistamines for the prevention of wheezing or asthma (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding side effects of oral H₁-antihistamines in infants and a lower value on the very uncertain reduction in the risk of developing asthma or wheezing.

Remarks. The recommendation not to use oral H₁-antihistamines in these infants refers only to prevention of asthma or wheezing. The guideline panel did not consider other conditions in which these medications may be commonly used (eg, urticaria).

14. Should intranasal H₁-antihistamines be used for treatment of AR?. Recommendation. We suggest intranasal H₁-antihistamines in adults with seasonal AR (conditional recommendation | low-quality evidence) and in children with seasonal AR (conditional recommendation | very low-quality evidence). In adults and children with persistent AR, we suggest that clinicians do **not** administer and patients do **not** use intranasal H₁-antihistamines until more data on their relative efficacy and safety are available (conditional recommendation | very low-quality evidence).

Underlying values and preferences. The recommendation to use intranasal H₁-antihistamines in patients with seasonal AR places a relatively high value on reduction of symptoms and a relatively low value on the risk of rare or mild side effects. The recommendation not to use intranasal H₁-antihistamines in patients with persistent AR places a relatively high value on their uncertain efficacy and possible side effects and a relatively low value on a possible small reduction in symptoms.

15. Should newer oral H₁-antihistamines versus intranasal H₁-antihistamines be used for treatment of AR?. Recommendation. We suggest new-generation oral H₁-antihistamines rather than intranasal H₁-antihistamines in adults with seasonal AR (conditional recommendation | moderate-quality evidence) and in adults with persistent AR (conditional recommendation | very low-quality evidence). In children with intermittent or persistent AR, we also suggest new-generation oral H₁-antihistamines rather than intranasal H₁-antihistamines (conditional recommendation | very low-quality evidence).

Underlying values and preferences. These recommendations place a relatively high value on probable higher patient preference for an oral versus intranasal route of administration as well as avoiding the bitter taste of some intranasal H₁-antihistamines, and a relatively low value on increased somnolence with some new-generation oral H₁-antihistamines. In many patients with different values and preferences or those who experience adverse effects of new-generation oral H₁-antihistamines, an alternative choice may be equally reasonable.

16. Should oral leukotriene receptor antagonists be used for treatment of AR?. Recommendation. We suggest oral leukotriene receptor antagonists in adults and children with seasonal AR (conditional recommendation | high-quality evidence) and in preschool children with persistent AR (conditional recommendation | low-quality evidence). In adults with persistent AR, we suggest that clinicians do **not** administer and patients do **not** use oral leukotriene receptor antagonists (conditional recommendation | high-quality evidence).

Underlying values and preferences. The recommendation to use oral leukotriene receptor antagonists in adults and children with seasonal AR and in preschool children with persistent AR places a relatively high value on their safety and tolerability and a relatively low value on their limited efficacy and high cost.

The recommendation not to use oral leukotriene receptor antagonists in adults with persistent AR places a relatively high value on their very limited efficacy and high cost and a relatively low value on a potential small benefit in few patients.

Remarks. Evidence is available only for montelukast. This recommendation refers to the treatment of rhinitis, not to the treatment of asthma in patients with concomitant AR (see recommendation 45).

17. Should oral leukotriene receptor antagonists versus oral H₁-antihistamines be used for treatment of AR?. Recommendation. We suggest oral H₁-antihistamines over oral leukotriene receptor antagonists in patients with seasonal AR (conditional recommendation | moderate-quality evidence) and in preschool children with persistent AR (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding resource expenditure.

18. Should intranasal glucocorticosteroids be used for treatment of AR?. Recommendation. We recommend intranasal glucocorticosteroids for treatment of AR in adults (strong recommendation | high-quality evidence) and suggest intranasal glucocorticosteroids in children with AR (conditional recommendation | moderate-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on the efficacy of intranasal glucocorticosteroids and a relatively low value on avoiding their possible adverse effects.

19. Should intranasal glucocorticosteroids versus oral H₁-antihistamines be used in patients with AR?. Recommendation. In patients with seasonal AR, we suggest intranasal glucocorticosteroids over oral H₁-antihistamines in adults (conditional recommendation | low-quality evidence) and in children (conditional recommendation | very low-quality evidence). In patients with persistent AR, we suggest intranasal glucocorticosteroids over oral H₁-antihistamines in adults (conditional recommendation | moderate-quality evidence) and in children (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on the likely higher efficacy of intranasal glucocorticosteroids. In many patients with strong preference for the oral versus intranasal route of administration, an alternative choice may be reasonable.

20. Should intranasal glucocorticosteroids versus intranasal H₁-antihistamines be used in patients with AR?. Recommendation. In patients with AR, we recommend intranasal glucocorticosteroids rather than intranasal H₁-antihistamines (strong recommendation | high-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on efficacy of intranasal glucocorticosteroids and a relatively low value on their rare adverse effects.

21. Should intranasal glucocorticosteroids versus oral leukotriene receptor antagonists be used for treatment of AR?. Recommendation. In patients with seasonal AR, we recommend intranasal glucocorticosteroids over oral leukotriene receptor antagonists (strong recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a high value on the efficacy of intranasal glucocorticosteroids.

Remarks. Evidence is available for montelukast only.

22. Should oral glucocorticosteroids be used for treatment of AR in patients not responding to other therapy?. Recommendation. In patients with AR and moderate to severe nasal and/or ocular symptoms that are not controlled with other treatments, we suggest a short course of oral glucocorticosteroids (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on possible relief of severe symptoms and a relatively low value on avoiding possible side effects of a short course of oral glucocorticosteroids.

Remarks. Systemic glucocorticosteroids should not be considered as a first line of treatment for AR. They can be used for few days as a last resort of treatment when combinations of other medications are ineffective. Oral glucocorticosteroids should be avoided in children, pregnant women, and patients with known contraindications.

23. Should intramuscular glucocorticosteroids be used for treatment of AR? Recommendation. In patients with AR, we recommend that clinicians do **not** administer intramuscular glucocorticosteroids (strong recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding possible side effects of a single or multiple injections of intramuscular glucocorticosteroids and relatively low value on their efficacy and convenience of use.

Remarks. Possible side effects of intramuscular glucocorticosteroids may be far more serious than the condition they are supposed to treat (ie, AR).

24. Should intranasal chromones be used for treatment of AR? Recommendation. In patients with AR, we suggest intranasal chromones (conditional recommendation | moderate-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on excellent safety and tolerability of intranasal chromones and a relatively low value on their limited efficacy and on limiting resource expenditure.

Remarks. The need for administration 4 times daily is likely to reduce patient adherence and reduce efficacy.

25. Should intranasal H₁-antihistamines versus intranasal chromones be used for treatment of AR? Recommendation. In patients with AR, we suggest intranasal H₁-antihistamines over intranasal chromones (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on possibly higher efficacy of intranasal H₁-antihistamines and a relatively low value on safety and tolerability of intranasal chromones.

Remarks. Chromones require administration 4 times daily that may limit patient adherence to treatment and reduce efficacy.

26. Should intranasal ipratropium bromide be used for treatment of AR? Recommendation. In patients with persistent AR, we suggest intranasal ipratropium bromide for treatment of rhinorrhea (conditional recommendation | moderate-quality evidence).

Remarks. Intranasal ipratropium bromide is effective for rhinorrhea. It is unlikely to be beneficial for other symptoms of AR.

27. Should intranasal decongestant be used for treatment of AR? Recommendation. In adults with AR and severe nasal obstruction, we suggest a very short course (not longer than 5 days and preferably shorter) of intranasal decongestant while coadministering other drugs (conditional recommendation | very low-quality evidence). We suggest that clinicians do **not** administer and parents do **not** use intranasal decongestants in preschool children (conditional recommendation | very low-quality evidence).

Underlying values and preferences. The recommendation for use of a very short course of an intranasal decongestant in adults with AR places a relatively high value on the prompt relief of nasal obstruction and a relatively low value on avoiding the risk of adverse effects with a prolonged use of intranasal decongestant.

The recommendation against the use of an intranasal decongestant in children and against long-term use in adults places a relatively high value on avoiding the risk of serious adverse effects and a relatively low value on a possible benefit from a reduced nasal blockage.

28. Should oral decongestant be used for treatment of AR? Recommendation. In patients with AR, we suggest that clinicians do **not** administer and patients do **not** use oral decongestants regularly (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding adverse effects of oral decongestants and a relatively low value on a possible small reduction in symptoms of rhinitis.

Remarks. Oral decongestants may be of benefit for some patients as a rescue or as-needed medication.

29. Should a combination of oral decongestant and H₁-antihistamine versus oral H₁-antihistamine alone be used for treatment of AR? Recommendation. In patients with AR, we suggest clinicians do **not** administer and patients do **not** use regularly a combination of oral H₁-antihistamine and an oral decongestant compared with oral H₁-antihistamine alone (conditional recommendation | moderate-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding adverse effects of oral decongestant and a relatively low value on a small additional reduction in symptoms of rhinitis.

Remarks. In adults with symptoms not controlled with oral H₁-antihistamine alone who are less averse to side effects of oral decongestants, an alternative choice may be equally reasonable. Administration of a combined treatment as a rescue medication may also be beneficial to some patients.

30. Should intraocular H₁-antihistamines be used for the treatment of ocular symptoms in patients with AR? Recommendation. In patients with AR and symptoms of conjunctivitis, we suggest intraocular H₁-antihistamines (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on consistent effectiveness of intraocular H₁-antihistamines and a relatively low value on their side effects and uncertain effectiveness in patients already using other medications for AR.

Remarks. Only 1 study was done in children.

31. Should intraocular chromones be used for treatment of ocular symptoms in patients with AR? Recommendation. In patients with AR and symptoms of conjunctivitis, we suggest intraocular chromones (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on excellent safety and tolerability of intraocular chromones and a relatively low value on their limited effectiveness.

Remarks. In adults and children with limited ocular symptoms, chromones may be tried first because of their excellent safety and tolerability. Chromones require administration 4 times

daily, which may limit patient compliance with treatment and reduce efficacy.

IV. Allergen-specific immunotherapy of AR

32. Should subcutaneous specific immunotherapy be used for treatment of AR in adults without concomitant asthma?. Recommendation. We suggest subcutaneous allergen specific immunotherapy in adults with seasonal (conditional recommendation | moderate-quality evidence) and persistent AR caused by house dust mites (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on relieving the symptoms of AR and a relatively low value on avoiding adverse effects and on resource expenditure.

33. Should subcutaneous specific immunotherapy be used for treatment of AR in children without concomitant asthma?. Recommendation. In children with AR, we suggest subcutaneous specific immunotherapy (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on probable reduction in symptoms of AR and the potential prevention of the development of asthma and a relatively low value on avoiding adverse effects in children and resource expenditure.

34. Should sublingual specific immunotherapy be used for treatment of AR in adults without concomitant asthma?. Recommendation. We suggest sublingual allergen specific immunotherapy in adults with rhinitis caused by pollen (conditional recommendation | moderate-quality evidence) or house dust mites (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on alleviating the symptoms of rhinitis and a relatively low value on avoiding adverse effects and resource expenditure.

Remarks. Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable if patients' values or preferences differ from those described.

35. Should sublingual specific immunotherapy be used for treatment of AR in children without concomitant asthma?. Recommendation. In children with AR caused by pollens, we suggest sublingual allergen-specific immunotherapy (conditional recommendation | moderate-quality evidence). In children with AR caused by house dust mites, we suggest that clinicians do **not** administer sublingual immunotherapy outside rigorously designed clinical trials (conditional recommendation | very low-quality evidence).

Underlying values and preferences. The recommendation to use sublingual immunotherapy in children with seasonal AR places a relatively high value on small reduction in nasal symptoms and a relatively low value on avoiding adverse effects in children and resource expenditure. The recommendation to use sublingual immunotherapy in children with persistent AR only in the context of clinical research places a relatively high value on avoiding adverse effects and resource expenditure and a relatively low value on possible small reduction in nasal symptoms.

Remark. Local adverse effects are relatively frequent (~35%). An alternative choice may be equally reasonable if patients' values or preferences differ from those described.

36. Should local nasal specific immunotherapy be used for treatment of AR?. Recommendation. We suggest intranasal allergen specific immunotherapy in adults (conditional recommendation | low-quality evidence) and in children with AR caused by pollens (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on the reduction of symptoms of AR during pollen season and a relatively low value on avoiding local side effects and cost. An alternative choice may be equally reasonable.

V. Complementary and alternative treatments of AR

37. Should homeopathy be used for treatment of AR?. Recommendation. In patients with AR, we suggest that clinicians do **not** administer and patients do **not** use homeopathy (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding possible adverse effects and resource expenditure and a relatively low value on any possible, but unproven, benefit of these treatments in AR.

38. Should acupuncture be used for treatment of AR?. Recommendation. In patients with AR, we suggest clinicians do **not** administer and patients do **not** use acupuncture (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding the potential complications of acupuncture and a relatively low value on uncertain reduction in symptoms of rhinitis.

Remarks. In patients who choose to be treated with acupuncture, only disposable needles should be used.

39. Should butterbur be used for treatment of AR?. Recommendation. In patients with AR, we suggest clinicians do **not** administer and patients do **not** use butterbur (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding the uncertain adverse effects of butterbur and a relatively low value on an equally uncertain reduction in symptoms of rhinitis.

Remarks. In patients who are less risk-averse, an alternative may be equally reasonable. However, if one chooses to use butterbur, one should consider only commercial preparations in which butterbur extract does not contain toxic pyrrolizidine alkaloids.

40. Should herbal medicines other than butterbur be used for treatment of AR?. Recommendation. In patients with AR, we suggest clinicians do **not** administer and patients do **not** use herbal medicines (conditional recommendation | very low-quality evidence).

Underlying values and preferences. The recommendation places a relatively high value on avoiding possible serious adverse events and drug interactions and a relatively low value on possible reduction in symptoms of rhinitis.

41. Should physical techniques and other alternative therapies be used for treatment of AR?. Recommendation. In patients with AR, we suggest that clinicians do **not** administer and patients do **not** use phototherapy or other physical techniques (conditional recommendation | very low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding potential adverse

effects of these therapies and a relatively low value on their very uncertain effect on symptoms of rhinitis.

VI. Treatment of AR and asthma in the same patient

42. Should oral H₁-antihistamines be used for treatment of asthma in patients with AR and asthma?.

Recommendation. In patients (both children and adults) with AR and asthma, we suggest clinicians do not administer and patients do not use oral H₁-antihistamines for the treatment of asthma (conditional recommendation | very low-quality evidence).

Underlying values and preferences. The recommendation not to use oral H₁-antihistamines in adults with AR and asthma for the treatment of asthma places a relatively high value on avoiding their adverse effects and a relatively low value on their very uncertain effect on symptoms of asthma.

The recommendation not to use oral H₁-antihistamines in children with AR for the treatment of asthma or wheeze, despite the evidence of efficacy of ketotifen when used alone in children with mild to moderate asthma, places a relatively high value on avoiding its side effects and a relatively low value on its unknown efficacy in children already using inhaled corticosteroids, because inhaled corticosteroids are currently considered medications of first choice in treatment of chronic asthma.

Remarks. This recommendation suggests that oral H₁-antihistamines should not be used to treat symptoms of asthma, but they may still be used in patients with asthma and rhinitis for treatment of rhinitis (recommendations 11 and 12).

43. Should combination of oral H₁-antihistamine and oral decongestant be used for treatment of asthma in patients with AR and asthma?.

Recommendation. In patients with AR and asthma, we suggest clinicians do not administer and patients do not use a combination of oral H₁-antihistamine and oral decongestant for treatment of asthma (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding adverse effects of combination of oral H₁-antihistamine and oral decongestant and a relatively low value on possible small reduction in asthma symptoms of uncertain clinical significance.

44. Should intranasal glucocorticosteroids be used for treatment of asthma in patients with AR and asthma?.

Recommendation. In patients with AR and asthma, we suggest that clinicians do not administer and patients do not use intranasal glucocorticosteroids for treatment of asthma (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on avoiding adverse effects, albeit a minor burden, and the cost of intranasal glucocorticosteroids, and a relatively low value on a small clinical benefit.

Remarks. This recommendation suggests that intranasal glucocorticosteroids are not used to treat symptoms of asthma, but they may still be used in patients with asthma and rhinitis for treatment of rhinitis (recommendations 18-21).

45. Should leukotriene receptor antagonists be used for treatment of asthma in patients with AR and asthma?.

Recommendation. In patients with AR and asthma, we recommend inhaled glucocorticosteroids over oral leukotriene receptor antagonists as a single controlling medication for asthma (strong recommendation | moderate-quality evidence).

In patients with AR and asthma who prefer not to use or cannot use inhaled glucocorticosteroids or in children whose parents do not agree to use inhaled glucocorticosteroids, we suggest oral leukotriene receptor antagonists for treatment of asthma (conditional recommendation | moderate-quality evidence).

Underlying values and preferences. These recommendations place a relatively high value on a limited efficacy of leukotriene receptor antagonists and additional cost of treatment. The suggestion to use oral leukotriene receptor antagonists in patients who do not use inhaled glucocorticosteroids places relatively high value on small reduction in symptoms of asthma and improvement in quality of life and a relatively low value on limiting the cost of treatment.

Remarks. These recommendations do not apply to the treatment of rhinitis (recommendations 16, 17, and 21).

46. Should subcutaneous allergen-specific immunotherapy be used in patients with AR and asthma?.

Recommendation. In patients with AR and asthma, we suggest subcutaneous specific immunotherapy for treatment of asthma (conditional recommendation | moderate-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on reducing the symptoms of asthma and a relatively low value on avoiding adverse effects and limiting the cost of subcutaneous specific immunotherapy. In patients who are more averse to the side effects of subcutaneous specific immunotherapy, an alternative choice may be equally reasonable.

Remarks. Subcutaneous specific immunotherapy may also be used in patients with asthma and concomitant AR for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation.

47. Should sublingual allergen-specific immunotherapy be used in patients with AR and asthma?.

Recommendation. In patients with AR and asthma, we suggest sublingual specific immunotherapy for treatment of asthma (conditional recommendation | low-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on possible reduction of asthma symptoms and a relatively low value on avoiding adverse effects and limiting the cost of sublingual specific immunotherapy.

Remarks. Sublingual specific immunotherapy may also be used in patients with asthma and concomitant AR for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation.

48. Should a mAb against IgE be used for treatment of asthma in patients with AR and asthma?.

Recommendation. In patients with AR and asthma with a clear IgE-dependent allergic component, uncontrolled despite optimal pharmacologic treatment and appropriate allergen avoidance, we suggest mAb against IgE for treatment of asthma (conditional recommendation | moderate-quality evidence).

Underlying values and preferences. This recommendation places a relatively high value on reduction of symptoms of asthma and exacerbations in patients with severe asthma and a relatively low value on avoiding the burden of subcutaneous injections, cost of treatment, small risk of anaphylaxis, and some uncertainty about the risk of malignancy.

DISCUSSION

The updated recommendations of the ARIA guidelines were developed by an international panel following the systematic and

transparent GRADE approach.^{16,17} The target audience of these guidelines is all physicians treating patients with AR, other health care professionals, health care policy makers,^{1,13,18} and patients.¹⁹ Our review of the literature identified many areas where there are few studies or only studies with a high risk of bias are available. We also identified many areas that require more rigorous systematic reviews or where existing systematic reviews require updating. Nonetheless, the ARIA guideline panel believes that these recommendations reflect the current best treatment of patients with AR.

The strengths of these guidelines are the transparent, evidence-based approach to the development of recommendations and the consideration and explicit description of the values and preferences that influenced the recommendations. Other strengths include wide consultation with over 80 world experts in treatment and research of AR and asthma, review by patient representatives, and the availability of full evidence profiles that summarize research evidence supporting the recommendations (Online Repository 2). The main limitations include the paucity of high-quality evidence and lack of systematic reviews for many of the questions.

The ARIA guideline panel developed these recommendations with the aim of facilitating their implementation. The most important barrier to implementation results from the scarcity of high-quality evidence supporting decisions about the treatment of AR. As a result, many clinicians and patients base their decisions on unsystematic observations, advertisement, and poorly supported claims made by manufacturers of various medical products or proponents of certain techniques (both conventional and alternative). Systematic summaries of evidence will help these clinicians, despite the lack of high-quality evidence in many areas. Other important barriers include the unavailability of certain medications (eg, new-generation H₁-antihistamines²⁰) in many countries or jurisdictions and the relatively high cost of some management options, particularly multifaceted environmental interventions.

It is crucial that these recommendations should never be seen as dictates. No recommendation can take into account all of the often compelling unique features of individual clinical circumstances. Thus, nobody charged with evaluating clinicians' actions should attempt to apply these recommendations by rote or in a blanket fashion.

The ARIA guideline panel raised additional issues regarding current clinical research in AR. The process highlighted relatively limited knowledge of the mechanisms of the development of allergy. There is also very little direct research evidence about the effectiveness of many management options, particularly in the primary and secondary prevention of AR and in treatment of asthma in patients with coexisting AR.

Despite the rationale for distinguishing intermittent and persistent AR, most research is still classifying AR according to the causative allergen as either seasonal or perennial. These studies rarely, if ever, specify whether the symptoms were intermittent or persistent, although it has been found that the 2 classifications are independent.⁴

There is also uncertainty about relative effects of treatments customarily belonging to certain classes because of their mechanism of action (eg, H₁-antihistamines, intranasal glucocorticosteroids, allergen extracts for immunotherapy, and so forth). For instance, H₁-antihistamines exert other actions in addition to antagonizing the effect of histamine that may contribute to the

difference in their effectiveness or safety.²¹ There are many classifications of H₁-antihistamines according to their chemical structure, the time when they reached the market, or their adverse effects.²⁰ All potential adverse effects and interactions are not dichotomous but rather a continuum, with any threshold arbitrary. As a result, there is no consensus which H₁-antihistamine belongs to which group, and this causes confusion for clinicians and patients. In the absence of a rigorous comparative systematic review of the effects of various medications within the class, their magnitude cannot be reliably estimated, and any relative benefits or downsides should be interpreted with care. Interestingly, we were not able to identify any systematic review of H₁-antihistamines and intranasal glucocorticosteroids in the treatment of AR in adults despite many agents being available in each group, their ubiquitous use, and large numbers of randomized trials available. Last, there seems to be room for improvement in the methodologic quality of primary and secondary clinical research in AR.

The ARIA guideline panel raised additional issues regarding the current clinical research in AR and asthma. The process highlighted a limited availability of high-quality, direct research evidence about patient-important outcomes of the treatment of asthma in patients with AR. There also seems to be room for improvement in the methodologic quality of primary and secondary clinical research in AR.

A revision of the ARIA guidelines will be required on the basis of new systematic reviews of the best evidence. The ARIA guideline panel will continue efforts to fill these gaps by supporting conducting additional reviews. ARIA will register and prioritize additional questions that have been identified as potentially important in treatment of AR and its impact on asthma to be included in subsequent revisions.

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Clinical implications: Patients, clinicians, and policy makers can use these systematically developed and transparent recommendations to inform their judgments about the choice of the most appropriate treatment for patients with AR.

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