

Correspondence

Reply

To the Editor:

We thank Dr Chipps and his colleagues¹ for their comments pointing to the differences between the recommendations made in the Diagnosis and Management of Rhinitis Practice Parameter (DMRPP)² and the updated Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,³ particularly related to the use of intranasal H₁-antihistamines. A second letter by Dr Spector and colleagues,⁴ some of whom authored the former letter, raises, in our view, similar issues. Our responses address the points made in both letters.

We agree with Dr Chipps and his colleagues¹ that management strategies for allergic rhinitis should reflect carefully reviewed and graded evidence. This is why we used an approach to reviewing and grading evidence and recommendations in the updated evidence-based ARIA guidelines that has been adopted by over 50 major organizations worldwide (<http://www.gradeworkinggroup.org>).^{5,6} This approach, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach, transparently describes the necessary judgments about evidence and recommendations. GRADE includes the merits of the 100 existing systems while following new developments in the field of health research methodology. Thus, GRADE has largely replaced previous evidence assessment systems, including the system suggested by Shekelle et al⁷ that we believe was used in the DMRPP (we were unable to detect a reference to the original system or a detailed description of the applied methods). Earlier approaches to evidence grading, including the one probably used in DMRPP, relied almost exclusively on study design (eg, randomized trials vs observational studies). GRADE emphasizes that, as an example, randomized controlled trials do not automatically provide the highest quality evidence because a body of evidence from randomized controlled trials may have important limitations. Hence, GRADE provides additional explicit and comprehensive criteria for downgrading or upgrading the quality of a body of evidence (ie, the confidence that estimates of effects are correct) that go beyond simple assessments of study design. Although Dr Chipps and colleagues¹ imply that the use of GRADE requires more subjective assessments than earlier approaches, we believe they are misguided. All approaches to grading evidence (including the one presumably used by the DMRPP) require judgments, but GRADE makes these judgments explicit and transparent, as was done in the 2010 revision of ARIA with an extensive supplement showing the evidence for each recommendation.

Dr Chipps and colleagues¹ describe the US experience and the deviation of the ARIA recommendations from current US practice. As with any evidence-based guideline, the ARIA update does not focus on what current practice is (unless that practice provides the best evidence), but rather on what current practice should be. Those may or may not be the same.

Another source of the differences between the DMRPP and the ARIA guidelines may be in the formulation of recommendations. The DMRPP authors formulated their recommendations as statements about the available evidence (eg, intranasal antihistamines have been associated with a clinically significant effect on nasal congestion) but did not explicitly specify what action should follow. We followed the GRADE approach and recommendations

by others⁸ and phrased recommendations as actionable items (eg, we suggest new-generation oral H₁-antihistamines rather than intranasal H₁-antihistamines in adults with seasonal allergic rhinitis).

GRADE also separates quality of evidence from strength of recommendations (ie, the extent to which one can be confident that the desirable effects of an intervention outweigh the undesirable effects across the range of patients for whom the recommendation is intended). This is because the quality of a body of evidence is just 1 of several factors influencing the strength of recommendations. The direction and the strength of recommendations are determined by the balance of desirable and undesirable patient outcomes. Evaluating this balance requires assessing the magnitude of effects of treatment options on all outcomes of interest (including possible harms), the quality of the body of supporting evidence, and values and preferences of those for whom the recommendation is made and the consumption of resources.

We agree with Dr Chipps and his colleagues¹ that patient values and preferences and resource use may be difficult to evaluate. We disagree, however, that patient preferences and cost are secondary and subjective.^{9,10} They can be assessed in similarly rigorous ways as efficacy of health outcomes, but unfortunately this is rarely done. Nevertheless, it seems far more beneficial for users of guidelines if those making recommendations are explicit about what values and preferences they assumed or how they considered resource use (cost) rather than asking users of recommendations to guess the implicit assumptions of the guideline developers. These assumptions were transparently laid out in the statements accompanying the ARIA recommendations. Because the recommendations about using intranasal versus oral H₁-antihistamines in adults with seasonal allergic rhinitis were conditional and based on moderate-quality evidence because of serious imprecision of the estimated effects for most critical outcomes (the recommendations for adults with persistent allergic rhinitis and children were based on very low-quality evidence because of the serious imprecision and the very serious indirectness of the estimated results), the recommendation explicitly states that “in many patients with different values and preferences [*than assumed here*] or those who experience adverse effects of new generation oral H₁-antihistamines an alternative choice may be equally reasonable.”³ All of these judgments were transparently presented and explained in the accompanying evidence tables. Such summaries were not available for DMRPP recommendations. Furthermore, the ARIA guidelines provide clear and explicit suggestions about the implications of strong and conditional recommendations for patients, clinicians, and policy makers.

A systematic approach to developing clinical recommendations requires the evaluation of the whole body of evidence supporting a recommendation in a well done and up-to-date systematic review rather than relying on single studies. When relying on existing systematic reviews, it is important to assess whether they addressed the clinical question of interest, their methodologic rigor, and the precision and consistency of the results. The ARIA guideline panel did not rely on one of the reviews cited by Dr Chipps and colleagues¹ about the use of oral versus intranasal antihistamines because of its methodologic

limitations. That review by Lee and Pickard¹¹ included studies using terfenadine, which was withdrawn from the market (ie, not approved anymore by the US Food and Drug Administration) and combined the results of studies in patients with allergic and vasomotor rhinitis by using absolute effects of the various studies rather than relative effects. This practice is generally discouraged and finds application only under rare conditions because of statistical considerations that limit its use.^{12,13} We also did not use the other review cited by Dr Chipps and colleagues¹ because it was not a systematic review¹⁴ but a narrative review with its inherent limitations.^{15,16} However, the ARIA panel systematically evaluated the results of *all* studies that fulfilled *a priori* inclusion criteria in accompanying evidence tables. Therefore, we will not highlight *single* studies that favor one or the other hypothesis. Moreover, the work of the ARIA panel involved detailed discussions among all reviewers of the ARIA panel concerning these studies, including requests for evidence that we might have missed.

Dr Chipps and colleagues “believe that these patients require careful individualization of treatment, and recommendations cannot be generalized at this time.”¹ We are puzzled by this statement because the DMRPP made this recommendation implicitly, stating that “intranasal antihistamines may be considered for use as first-line treatment for allergic and non-allergic rhinitis,”² whereas it did not state the same about oral antihistamines. The ARIA panel, however, made a recommendation that includes more than a general statement, with a description of the possible value structure to facilitate individualized decision-making. Describing the underlying values and the other factors influencing the recommendation also allows implementation of the guidelines on a global level and with individual patients. To be able to balance the desirable and undesirable consequences of using one treatment relative to another requires that guideline developers consider all patient-important outcomes (eg, symptoms, quality of life, adverse effects), not just one (eg, only symptoms). Although in the case of oral versus intranasal antihistamines this balance is uncertain, we labeled the rationale for recommending one over the other.

In the second letter, Dr Spector and colleagues⁴ remarked that ARIA was a product of largely European authors. That statement is incorrect. The ARIA panel is an international group with members and reviewers from 40 countries in the world, including 10 scientists from the United States and 8 from Canada, reflecting the fact that the evidence base for making recommendations is not restricted to one part of the world. The ARIA guidelines are meant for a global audience, which requires consideration of all available management options, not only those available or approved in particular countries. Dr Spector and colleagues⁴ stressed that the DMRPP underwent a thorough review process, not mentioning the review process of the ARIA guidelines. We described the ARIA review process in the full version of the guidelines (Online Repository) and believe it was at least as rigorous as that of the DMRPP, including the review by the Journal before publication. Dr Spector and colleagues⁴ further mention the consideration of cost. The ARIA panel describes why the consideration of resource use and cost is critical for health care decision-making and is in line with most organizations that specialize in guideline development. This is particularly important for guidelines that have an international audience. Laying out resource assumptions transparently, as in the ARIA guidelines, ensures that local adaptation of the recommendations can be

accomplished. Finally, on the basis of the arguments raised, we likely disagree that DMRPP “provide[s] a more relevant approach to the management of patients with this condition in the United States,”⁴ but we are unsure about the meaning of *relevant* in this context.

In summary, we welcome the opportunity to clarify reasons for the differences between the ARIA and USRPP. In our opinion, clinical experts make the right decisions most of the time, and their clinical experience is invaluable. However, history teaches us about the danger of overreliance on clinical experts without systematically and transparently considering the best available evidence.¹⁵ The science of evidence-based guideline development demands collaboration of various stakeholders—clinical content experts, clinical researchers, methodologists, other health care professionals, and patients. We believe that it would be beneficial for society if groups developing clinical practice guidelines considered unifying their efforts.¹⁷ On the other hand, we maintain our evidence-based recommendation on intranasal H₁-antihistamines.

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Disclosure of potential conflict of interest: J. Bousquet receives honoraria from Allmiral, AstraZeneca, Centocor, Chiesi, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Nycomed-Altana, Pfizer, Roche, Sanofi-Aventis, Stallergenes, Schering-Plough, UCB, and Uriach. S. Bonini receives honoraria from A. Menarini, AstraZeneca, MSD, Novartis, Nycomed, Phadia, Schering-Plough, Sigma Tau, and Stallergenes. G. W. Canonica receives honoraria and consulting fees from A. Menarini, Alcon, ALK-Abelló, Almirall, Altana, Anallergo, AstraZeneca, Aventis Pharma, Bayer, Biofutura Pharma, Boehringer Ingelheim, Chiesi, Chiron, Essex, Fujisawa, Genentech, Gentili, GlaxoSmithKline, Lofarma, Merck Sharp & Dohme, Novartis, Pfizer, Pharmacia & Upjohn, Schering-Plough, Sigma Tau, Stallergenes, Yamanuchi, UCB Pharma, and Valcas. T. B. Casale has consultant arrangements with Ono Pharma, Hoffman LaRoche, Capnia, and Stallergenes; receives research support from Novartis, Merck, Pfizer, Schering-Plough, Genentech, Capnia, Stallergenes, and Roche; and is executive vice-president of the AAAAI. R. Gerth van Wijk has consultant arrangements with HAL, Crucell, Gilde, and Merck and receives speakers' fees from Allergopharma. T. Zuberbier has consultant arrangements with Ansell, Bayer Schering, DST, Fujisawa, HAL, Henkel, Kryolan, Leti, MSD, Novartis, Procter and Gamble, Sanofi-Aventis, Schering-Plough, Stallergenes, and UCB; is on the Scientific Advisory Board of the German Society for Allergy and Clinical Immunology and the Expert Commission “Novel Food” of the German Federal Ministry of Consumer Protection; is chairman of the European Academy of Allergology and Clinical Immunology Dermatology Section; is head of the European Centre for Allergy Research Foundation; is a committee member of the WHO Initiative on Allergic Rhinitis and

its Impact on Asthma; is a member of the World Allergy Organisation Communications Council; and is secretary general of the Global Allergy and Asthma European Network. The rest of the authors have declared that they have no conflict of interest.

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doi:10.1016/j.jaci.2011.01.069