

## MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis

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**The selection of pharmacotherapy for patients with allergic rhinitis (AR) depends on several factors, including age, prominent symptoms, symptom severity, control of AR, patient preferences, and cost. Allergen exposure and the resulting symptoms vary, and treatment adjustment is required. Clinical**

**decision support systems (CDSSs) might be beneficial for the assessment of disease control. CDSSs should be based on the best evidence and algorithms to aid patients and health care professionals to jointly determine treatment and its step-up or step-down strategy depending on AR control. Contre les**

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**Maladies Chroniques pour un Vieillessement Actif en Languedoc-Roussillon (MACVIA-LR [fighting chronic diseases for active and healthy ageing]), one of the reference sites of the European Innovation Partnership on Active and Healthy Ageing, has initiated an allergy sentinel network (the MACVIA-ARIA Sentinel Network). A CDSS is currently being developed to optimize AR control. An algorithm developed by consensus is presented in this article. This algorithm should be confirmed by appropriate trials. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)**

**Key words:** Allergic rhinitis, conjunctivitis, Allergic Rhinitis and its Impact on Asthma, MACVIA-LR, information and communication technology, clinical decision support system

The selection of pharmacotherapy for patients with allergic rhinitis (AR) depends on several factors, such as age, prominent symptoms, symptom severity, control of AR, patient preferences, availability of treatment, and cost.<sup>1</sup> With allergen exposure and the resulting symptoms varying daily, patients with AR would

#### Abbreviations used

AR:	Allergic rhinitis
CDSS:	Clinical decision support system
MACVIA-LR:	Contre les MALadies Chroniques pour un Vieillessement Actif en Languedoc-Roussillon
MASK:	MACVIA-ARIA Sentinel Network
MCID:	Minimal clinically important difference
QOL:	Quality of life
RQLQ:	Rhinoconjunctivitis Quality of Life Questionnaire
VAS:	Visual analog scale

benefit from regular monitoring of their symptoms to facilitate treatment adjustment. Clinical decision support systems (CDSSs) might be beneficial for the accomplishment of this task by assessing disease control, such as in response to treatment.<sup>2</sup> A CDSS is a health information technology system designed to assist health care professionals and patients with clinical decision-making

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tasks. Knowledge-based CDSSs consist of 3 parts: the knowledge base, an inference engine, and a mechanism to communicate.<sup>3,4</sup> The knowledge base contains the rules and associations of compiled data. The inference engine combines the rules from the knowledge base with the patient's data. The communication mechanism allows the system to show the results to the user, as well as have input into the system. CDSSs should be based on the best evidence and algorithms to aid patients and health care professionals to jointly determine the treatment and its step-up or step-down strategy depending on AR control.<sup>1</sup> Thus CDSSs should help optimize treatment.

Contre les MALadies Chroniques pour un Vieillessement Actif en Languedoc-Roussillon (MACVIA-LR [fighting chronic diseases for active and healthy ageing], <http://macvia.cr-langue-docroussillon.fr>) is one of the reference sites of the European Innovation Partnership on Active and Healthy Ageing.<sup>5</sup> It initiated the project Integrated Care Pathways for Airway diseases

(AIRWAYS ICPs)<sup>6</sup> and the allergy sentinel network MACVIA-ARIA Sentinel Network (MASK).<sup>2</sup> A knowledge-based CDSS is currently being developed to optimize AR control. The communication mechanism of MASK uses interconnected tablets and cell phones.<sup>7,8</sup> The proposed algorithm of the MACVIA-CDSS is presented in this article.

## CONTROL OF AR AND RHINOCONJUNCTIVITIS

In asthmatic patients, the treatment strategy is based on disease control and current treatment.<sup>9-11</sup> The variability in symptom control is challenging and necessitates careful monitoring, as well as the step up/step down of individualized therapeutic regimens over time. Both long- and short-term maintenance and reliever approaches have been proposed,<sup>12</sup> including the combination of an inhaled corticosteroid and fast-onset long-acting  $\beta$ -agonist inhaler as maintenance and reliever therapy.<sup>13</sup>

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**Box 1.** Summary of recommendations for the treatment of AR and conjunctivitis used in the algorithm

- Oral or intranasal H<sub>1</sub>-antihistamines are less effective than intranasal corticosteroids for the control of all rhinitis symptoms.<sup>28-33</sup>
- Leukotriene receptor antagonists are usually considered less effective than oral H<sub>1</sub>-antihistamines.<sup>30,34,35</sup>
- Comparisons between oral and intranasal H<sub>1</sub>-antihistamines differ between recommendations, and thus no definite conclusions have yet been reached.
- Combined intranasal fluticasone propionate and azelastine hydrochloride in a single device is more effective than monotherapy and is indicated for patients when monotherapy with either an intranasal H<sub>1</sub>-antihistamine or glucocorticoid is considered inadequate.<sup>1,34-37</sup>
- Intranasal antihistamines and intranasal corticosteroids are effective for ocular symptoms, with no significant difference between them.<sup>38,39</sup> However, the combination of azelastine and fluticasone propionate was more effective than fluticasone propionate alone.<sup>36,37</sup>
- In most studies, combinations of oral antihistamines or leukotriene receptor antagonists and intranasal corticosteroids are in general not more effective than monotherapy with intranasal corticosteroids.<sup>40,41</sup>
- Intraocular H<sub>1</sub>-antihistamines or cromones are effective for ocular symptoms.<sup>42</sup> The importance of decongestants is debatable.<sup>30</sup> However, the efficacy of treatment varies with individual patient response.
- In clinical practice, intranasal corticosteroids need a few days to be fully effective, whereas intranasal H<sub>1</sub>-antihistamines or combined intranasal fluticasone and azelastine are rapidly effective.<sup>43</sup>
- All recommended medications are considered safe at the usual dosage. First-generation oral H<sub>1</sub>-antihistamines are sedating and should be avoided.<sup>44</sup>
- Oral or nebulized corticosteroids can be helpful in patients with severe disease whose symptoms are uncontrolled by other treatment, although studies are lacking in patients with AR.<sup>45</sup>
- Further studies are needed in preschool children to make more firm recommendations possible, although recent studies show the efficacy of oral H<sub>1</sub>-antihistamines.<sup>46</sup>

The symptoms of AR can cause considerable morbidity in physical and emotional comfort, as well as in functional capacity and quality of life (QOL). The control and severity of AR have been defined in a similar manner to asthma.<sup>2,14,15</sup> Measures of AR control include symptom scores, patients' self-administered visual analog scales (VASs), objective measures of nasal obstruction, a recent modification of the Allergic Rhinitis and its Impact on Asthma severity classification, and patients' reported outcomes, such as QOL or scores with several items.<sup>16,17</sup> However, the challenges of managing AR are increased by the fact that patients do not often recognize their AR symptoms or confuse them with those of asthma.<sup>18</sup> Therefore it is important for patients to be able to use an AR symptom scoring system that is simple to use and rapidly responsive to change.

As is the case for asthma, the best control of AR should be achieved as early as possible to (1) improve patient satisfaction and concordance to treatment and (2) reduce the consequences of AR, including symptoms, reduced QOL, and school and work absenteeism. Untreated AR can impair driving ability and put patients at risk.<sup>19</sup> The ultimate goal of AR control is to reduce the costs incurred by AR.<sup>20-23</sup>

A step-up/step-down approach to AR pharmacotherapy based on patient response might hold potential for optimal AR control and cost of treatment.<sup>1</sup> MASK has proposed that electronic daily monitoring with VASs might help patients achieve optimal control of AR symptoms.<sup>2</sup> Well-controlled AR is defined as a VAS score of 2 or less of 10. VAS cutoff values to step up or down treatment were proposed by comparison with pain VAS scores and step-up schemes or from the literature in the field of allergy (see the [additional material](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).<sup>24-26</sup>

## RECOMMENDATIONS FOR THE TREATMENT OF AR AND RHINOCONJUNCTIVITIS

The treatment of AR also requires the consideration of (1) the type (rhinitis, conjunctivitis, and/or asthma) and severity of

symptoms, (2) the relative efficacy of the treatment, (3) the speed of onset of action of treatment, (4) current treatment, (5) historic response to treatment, (6) patient's preference, (7) interest to self-manage, and (8) resource use. Guidelines<sup>27</sup> and various statements by experts for AR pharmacotherapy usually propose the approach summarized in [Box 1](#).<sup>28-46</sup>

Allergen immunotherapy appears to be as effective as pharmacotherapy<sup>47,48</sup> but is also regarded as a disease modifier intervention with the potential of altering the natural history of allergic diseases.<sup>49,50</sup> Nonpharmacologic interventions, such as nasal filters<sup>51</sup> or saline, have been found to be effective.

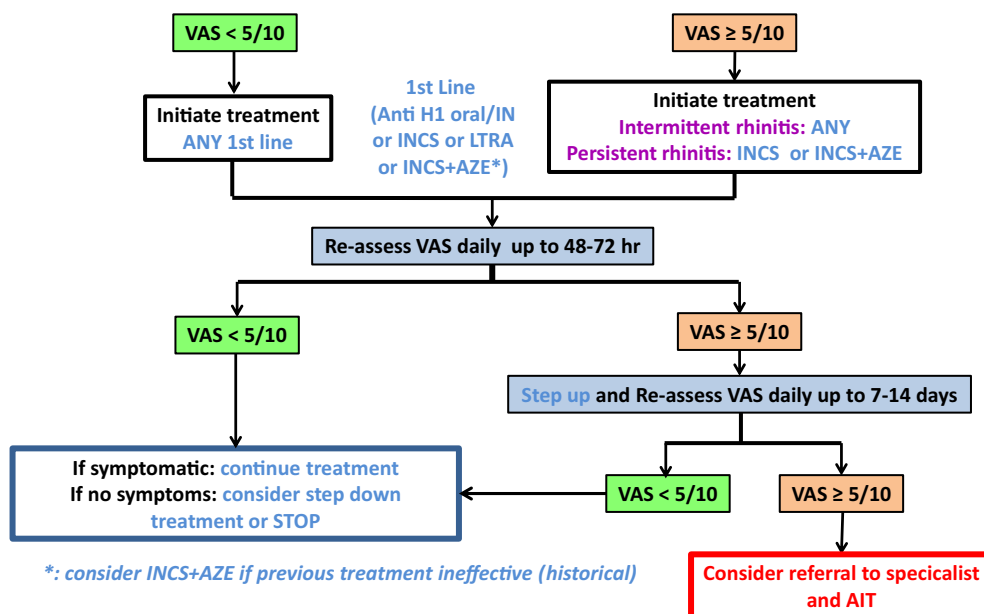
## PATIENTS' VIEWS

Many patients with AR are not satisfied with their current treatment,<sup>52-54</sup> and this results in frequent nonadherence to therapy.<sup>55,56</sup> In some studies, most patients were satisfied with their treatment, but full control was rarely achieved.<sup>54,57-59</sup> Despite the vast availability of treatment options, most patients are "very interested" in finding a new medication,<sup>56,60</sup> and around 25% are "constantly" trying different medications to find one that "works."<sup>56</sup> Patients want more effective treatments that can control all their symptoms, including ocular ones,<sup>61,62</sup> and a more rapid onset of action.<sup>63</sup>

Some patients believe that their health care provider does not understand their allergy treatment needs or does not take their allergy symptoms seriously.<sup>52</sup> Many patients self-medicate with over-the-counter drugs for a long period of time and usually only consult a physician when their treatment is ineffective.<sup>58</sup> In one study, patients chose a step-down therapy to speed up the control of symptoms.<sup>64</sup>

A patient's individual preference for an oral or intranasal route treatment needs to be considered.<sup>52,64,65</sup> In addition, health care professionals need to inform the patient of the relative benefits and harms of each prescribed treatment to support their decision making.

## Assessment of control in untreated symptomatic patient



**FIG 1.** Step-up algorithm in untreated patients using the VAS (adolescents and adults). The proposed algorithm considers the treatment steps and patient preference and VAS levels in ratio. If ocular symptoms remain, add intraocular treatment.

### ALGORITHM DECISION AID

A step-up/step-down individualized approach to AR pharmacotherapy might hold the potential for optimal control of AR symptoms while minimizing side effects and costs.<sup>1</sup> However, the following should be considered:

- as in asthmatic patients, treated and untreated patients should be considered differently (Figs 1 and 2);
- most patients have received a previous treatment that should guide health care professionals with regard to the current prescription; and
- patterns of medication use in previously treated patients should be evaluated when future treatment is initiated.

The step-up or step-down strategy should be discussed with the patient and should consider the following:

- efficacy of previous treatments;
- adherence to treatment;
- the patient's preference (route of administration, fear of side effects, and experience of the patient regarding the treatment);
- possible side effects or harms; and
- costs.

The step-up approach consists of the following:

- *Step 1:* For mild symptoms, use intranasal or oral non-sedating H<sub>1</sub>-antihistamines.
- *Step 2:* For moderate-to-severe symptoms and/or persistent AR, use intranasal corticosteroids. The dose of some intranasal corticosteroids can be increased according to the package insert.
- *Step 3:* For patients with uncontrolled symptoms at step 2 (current or historical), use a combination of intranasal

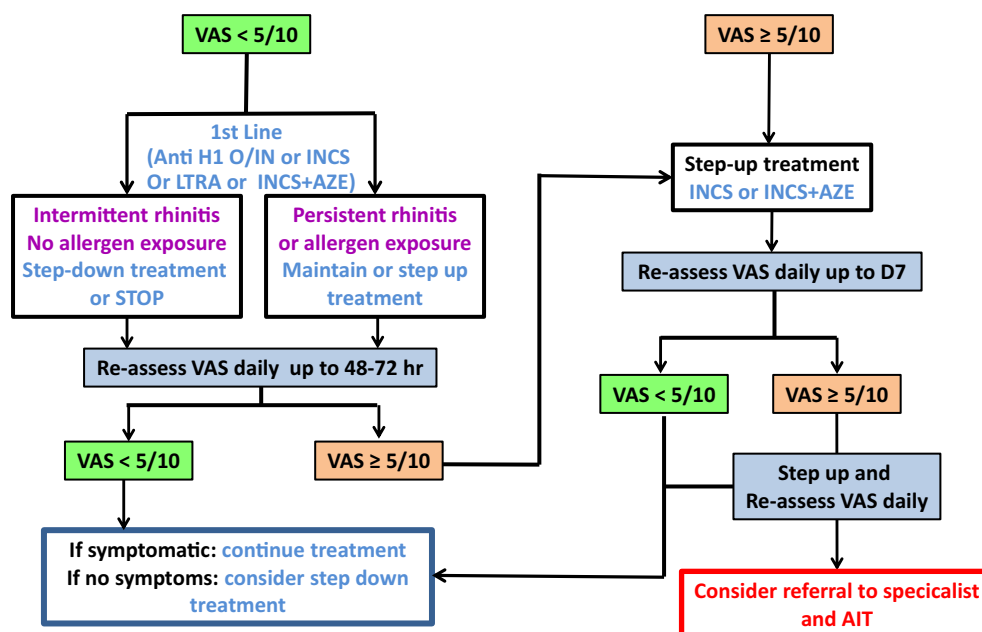
corticosteroids and intranasal H<sub>1</sub>-antihistamines. However, depending on the physicians's experience, other therapeutic strategies can be used.

- *Step 4:* It is possible that an additional short course of oral steroids might help to establish control and continue control by step 3. Intraocular cromones or H<sub>1</sub>-antihistamines can be added to improve the control of ocular symptoms.
- Treatment should be reassessed quickly (eg, 1-7 days) to confirm control by using a step-up approach.
- Patients whose symptoms are uncontrolled at step 3 should be considered as having severe chronic upper airway disease<sup>66,67</sup> and might benefit from specialist referral and assessment for allergy workup and nasal examination.<sup>68</sup> For example, specialist referral should be considered if there is failure to reduce the VAS score to less than 5 of 10 after 10 to 14 days, assuming the patient is adherent to therapy.
- At all times, patient adherence and intranasal device technique mastery should be regarded as potential for lack of treatment effect.

Alternatively, a step-down approach can be used, and step 3 treatment should be considered as the first option in patients with a previous treatment failure or resistance to monotherapy. After a few days of achieving complete control, consideration could be given to treatment reduction. However, the step-down approach is based on consensus, and more data are needed.

The duration of treatment is determined by the type of rhinitis (intermittent or persistent). In the patient with intermittent rhinitis, treatment should be continued daily for 2 weeks or for the duration of the pollen season or other specific allergen exposure. In the patient with persistent rhinitis, a longer course

## Assessment of control in treated symptomatic patient



**FIG 2.** Step-up algorithm in treated patients using the VAS (adolescents and adults). The proposed algorithm considers the treatment steps and patient preference and VAS levels in ratio. If ocular symptoms remain, add intraocular treatment.

of treatment is often needed. Of course, it is important to assess concordance with agreed regimens because treatment failure can be a result of poor patient concordance.

## CONCLUSION

We propose a simple algorithm to step up or step down AR treatment globally. However, its use varies depending on the availability of medications in different countries and depending on resources. These issues have not been approached in the present article because of their variability between countries. Inherently, algorithms are a combination of individual decision nodes that represent separate recommendations. They require testing as a complete algorithm and comparison with alternative strategies to explore whether the combination of these separate recommendations leads to more benefit than harm when applied in practice. Thus this algorithm, as with other algorithms, requires testing in large-scale trials to provide the necessary certainty in available evidence. The current algorithm is being developed by MASK<sup>2</sup> for a CDSS that will be available on Apple and Android and that will provide opportunities for evaluation.

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## RATIONALE FOR USING A VAS IN THE ALGORITHM

Certain differences between groups in their VAS scores or changes in scores might have no clinical relevance, even if they achieve statistical significance. A wide range of minimal clinically important differences (MCIDs) in change scores on the pain VAS have been reported<sup>E1</sup> by using different methods. MCIDs ranged from 9 to 30 mm (of 100 mm) in emergency departments.<sup>E2-E6</sup> In other settings, changes of 33%<sup>E7</sup> and 31 mm<sup>E8</sup> have been shown to be clinically meaningful. In patients with endometriosis, the pain MCID was set at 10 mm.<sup>E9</sup> The MCID for the fatigue VAS was around 10 mm in a large rheumatoid arthritis clinical practice and similar to that seen in clinical trials.<sup>E10</sup> The MCID in the VAS pain score does not differ with sex, age, and cause-of-pain groups<sup>E3</sup> or with the severity of pain being experienced.<sup>E11</sup> However, the linearity of the pain VAS is found in some<sup>E12</sup> but not all<sup>E1,E13,E14</sup> studies. Pain VAS measurement error has been reported to be up to 20 mm.<sup>E15,E16</sup> Consequently, change scores and the calculations of aspects, such as MCIDs, can be carefully considered by the potential lack of interval scaling of the VAS and further compromised by the magnitude of measurement error. Repeated pain VAS data meet the strict requirements of the Rasch model, including unidimensionality, and they were internally valid.<sup>E1</sup> However, the pain VAS does not behave linearly, and the MCID can underestimate or overestimate true change during repeated pain VAS.

In patients with AR, to our knowledge, there is a single study that has estimated MCIDs in the VAS during treatment.<sup>E18</sup> By using receiver operating characteristic curve analysis, an appropriate method for estimation of MCIDs, the established cutoff variation of 23 mm for the VAS was associated with a cutoff variation of 0.5 for the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Sensitivity analysis with RQLQ and Total Symptom Score 6 scales confirmed the aptitude of the cutoff value (23 mm) to discriminate changes in symptoms and QOL. The MCID was the same whatever the baseline VAS level.<sup>E18</sup> A level of more than 23 mm appears to be a relevant cutoff. VAS changes appear to encompass both symptoms and disease-specific QOL.<sup>E18,E19</sup> Another study, the Control of Allergic Rhinitis and Asthma Test,<sup>E20,E21</sup> approximated the VAS MCID. In CARAT, the MCID is 4 (range, 0-30).<sup>E22</sup> The real-life study of Demoly et al<sup>E18</sup> in primary care used the same methods as a cluster randomized trial carried out in specialist practices.<sup>E23</sup> Both studies, which were carried out in France in large populations, showed a very similar change in VAS levels during treatment depending on total symptom scores and RQLQ scores. These studies suggest that the cutoff of 23 mm<sup>E18</sup> is appropriate to find a clinically significant difference.

VAS levels appear to be similar in different countries in patients with severe intermittent or persistent rhinitis. A VAS can be used in all age groups, including preschool children (guardian evaluation)<sup>E24</sup> and the elderly.<sup>E25</sup> Furthermore, it can be used in a wide variety of languages.<sup>E25-E32</sup> VAS levels vary with the Allergic Rhinitis and its Impact on Asthma classification in many languages.<sup>E28,E33-E35</sup> A VAS level of 50 (>100 mm) is suggestive of moderate-to-severe AR,<sup>E19,E36,E37</sup> although in some studies the cutoff was greater than 60 mm.<sup>E29</sup> AVAS was used to define severe chronic upper airway disease.<sup>E23</sup> Thus the MCID found in 2 large French populations can be generalized to other countries with different languages and cultures across the lifecycle. However, future studies should refine this cutoff level.

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