



## MACVIA Clinical Decision Algorithm in Allergic Rhinitis in adolescents and adults

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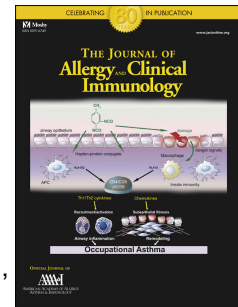
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## MACVIA Clinical Decision Algorithm in Allergic Rhinitis in adolescents and adults

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## **Short title: Clinical decision algorithm in rhinitis**

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**Key words:** allergic rhinitis, conjunctivitis, ARIA, MACVIA-LR, ICT, clinical decision support system

## Abbreviations

AHA: Active and Healthy Ageing  
 AIRWAYS ICPs: Integrated Care Pathways for Airway diseases  
 AIT: Allergen immunotherapy  
 AR: Allergic rhinitis  
 ARIA: Allergic Rhinitis and its Impact on Asthma  
 CDSS: Clinical decision support system  
 EIP: European Innovation Partnership  
 ICP: Integrated care pathway  
 MACVIA-LR: Contre les MALadies Chroniques pour un Vieillissement Actif en Languedoc-Roussillon  
 MASK: MACVIA-ARIA Sentinel network  
 QOL: Quality of life  
 SCUAD: Severe chronic Upper Airway Disease  
 VAS: Visual analogue scale

## Summary

The selection of pharmacotherapy for patients with allergic rhinitis depends on several factors, including age, prominent symptoms, symptom severity, control of allergic rhinitis, patient preferences and cost. Allergen exposure and resulting symptoms vary and treatment adjustment is required. Clinical decision support systems (CDSS) may be beneficial for the assessment of disease control. Clinical decision support systems 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. 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 (MASK: MACVIA-ARIA Sentinel network). A clinical decision support system is currently being developed to optimize allergic rhinitis control. An algorithm developed by consensus is presented in this paper. This algorithm should be confirmed by appropriate trials.

## Introduction

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 (1). Allergen exposure and resulting symptoms varying daily, AR patients would benefit from regular monitoring of their symptoms to facilitate treatment adjustment. Clinical decision support systems (CDSS) may be beneficial for the accomplishment of this task by assessing disease control, for example in response to treatment (2). A CDSS is a health information technology system designed to assist health care professionals and patients with clinical decision-making tasks. Knowledge-based CDSSs consist of three parts: the knowledge base, an inference engine, and a mechanism to communicate (3, 4). 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. CDSS 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 (1). Thus, CDSS should help to optimize treatment.

MACVIA-LR (Fighting chronic diseases for active and healthy ageing, <http://macvia.crlanguedocroussillon.fr>) is one of the reference sites of the European Innovation Partnership on Active and Healthy Ageing (7). It initiated the project AIRWAYS ICPs (integrated care pathways for airway diseases) (8) and the allergy sentinel network MASK (MACVIA-ARIA Sentinel Network) (2). A knowledge-based CDSS is currently being developed to optimize AR control. The communication mechanism of MASK uses interconnected tablets and cell phones (5, 6). The proposed algorithm of the MACVIA-CDSS is presented in this paper.

## Control of allergic rhinitis and rhino-conjunctivitis

In asthma, the treatment strategy is based on disease control and current treatment (9-11). 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 (12) including the combination of inhaled corticosteroid and fast-onset long-acting  $\beta$ -agonist inhaler as maintenance and reliever therapy (13).

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 (2, 14, 15). Measures of AR control include symptom scores, patients' self-administered visual analogue scales (VAS), objective measures of nasal obstruction, a recent modification of the ARIA severity classification, and patients' reported outcomes such as QOL or scores with several items (16, 17). However, the challenges of managing AR are increased by the fact that patients do not often recognise their AR symptoms or confuse them with those of asthma (18). 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 in order to: (i) improve patient satisfaction and concordance to treatment, and (ii) 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 (19). The ultimate goal of AR control is to reduce the costs incurred by AR (20-23).

A step-up/step-down approach to AR pharmacotherapy, based on patient response, may hold the potential for optimal AR control and cost of treatment (1). MASK has proposed that electronic daily monitoring using VAS may help patients to achieve optimal control of AR symptoms (2). Well-controlled AR is defined as VAS score  $\leq 2$  out of 10. VAS cut-off values to step up or down treatment

were proposed by comparison to pain VAS scores and step-up schemes or from literature in the field of allergy (Online supplement 1) (24-26).

## Recommendations for the treatment of allergic rhinitis and rhinoconjunctivitis

The treatment of AR also requires the consideration of (i) the type (rhinitis, conjunctivitis and/or asthma) and severity of symptoms, (ii) the relative efficacy of the treatment, (iii) speed of onset of action of treatment, (iv) current treatment, (v) historic response to treatment, (vi) patient preference, (vi) interest to self-manage and (viii) resource use. Guidelines (27) and various statements by experts for AR pharmacotherapy usually propose the approach summarized in Box 1.

### Box 1: Summary of recommendations for the treatment of allergic rhinitis and conjunctivitis used in the algorithm

- Oral or intra-nasal H1-anti-histamines are less effective than intra-nasal corticosteroids for the control of all rhinitis symptoms (28-33).
- Leukotriene receptor antagonists are usually considered to be less effective than oral H1-anti-histamines (30, 34, 35).
- Comparisons between oral and intra-nasal H1-anti-histamines differ between recommendations, thus no definite conclusions have yet been reached.
- The 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 intra-nasal H1-antihistamine or glucocorticoid is considered inadequate (1, 34-37).
- Intra-nasal anti-histamines and intra-nasal corticosteroids are effective for ocular symptoms with no significant difference between them (38, 39). However, the combination of azelastine and fluticasone propionate was more effective than fluticasone propionate alone (36, 37).
- In most studies, combinations of oral anti-histamines or leukotriene receptor antagonists and intra-nasal corticosteroids are in general not more effective than monotherapy with intra-nasal corticosteroids (40, 41).
- Intra-ocular H1 anti-histamines or cromones are effective for ocular symptoms (42). The importance of decongestants is debatable (30). However, efficacy of treatment varies with individual patient response.
- In clinical practice, intra-nasal corticosteroids need a few days to be fully effective, whereas intra-nasal H1 anti-histamines or combined intra-nasal fluticasone and azelastine are rapidly effective (43).
- All recommended medications are considered to be safe at the usual dosage. First-generation oral H1-antihistamines are sedating and should be avoided (44).
- Oral or nebulized corticosteroids may be helpful in severe patients uncontrolled by other treatment, although studies are lacking in AR (45).
- Further studies are needed in pre-school children to make more firm recommendations possible, although recent studies show the efficacy of oral H1 anti-histamines (46).

Allergen immunotherapy appears to be as effective as pharmacotherapy (47, 48) but is also regarded as a disease modifier intervention with the potential of altering the natural history of allergic diseases (49, 50).

Non-pharmacologic interventions such as nasal filters (51) or saline have been found to be effective.

## Patients' views

Many patients with AR are not satisfied with their current treatment (52-54), and this results in frequent non-adherence to therapy (55, 56). In some studies, most patients were satisfied with their treatment but full control was rarely achieved (54, 57-59). Despite the vast availability of treatment options, most patients are "very interested" in finding a new medication (56, 60) and around 25% are "constantly" trying different medications to find one that "works" (56). Patients want more effective

treatments that can control all their symptoms, including ocular ones (61, 62), and a more rapid onset of action (63).

Some patients feel that their healthcare provider does not understand their allergy treatment needs or does not take their allergy symptoms seriously (52). Many patients self-medicate using over-the-counter (OTC) drugs for a long period of time and usually only consult a physician when their treatment is ineffective (58). In one study, patients chose a step down therapy to speed up the control of symptoms (64).

Patients' individual preference for an oral or an intra-nasal route treatment needs to be considered (52, 64, 65). In addition, health care professionals need to inform the patient of the relative benefits and harms of each prescribed treatment in order to support their decision making.

## Algorithm decision aid

A step-up/step-down individualized approach to AR pharmacotherapy may hold the potential for optimal control of AR symptoms while minimizing side effects and costs (1). However,

- As in asthma, treated and untreated patients should be considered differently (Figures 1 and 2).
- Most patients have received a previous treatment that should guide health care professionals with regards to the current prescription.
- Patterns of use of medication 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:**

- 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.
- Costs.

### Step-up approach:

- Step 1, for mild symptoms, intranasal or oral non-sedating H1-antihistamine.
- Step 2, for moderate-severe symptoms and/or persistent AR, intranasal corticosteroids. The dose of some intra-nasal corticosteroids can be increased according to the package insert.
- Step 3, for patients with uncontrolled symptoms at step 2 (current or historical), combination of intra-nasal corticosteroids and intra-nasal H1-antihistamines. However, depending on the physicians' experience, other therapeutic strategies may be used.
- Step 4: It is possible that an additional short course of oral steroids may help to establish control and continue control by Step 3. Intra-ocular cromones or H1-anti-histamines may be added to improve the control of ocular symptoms.
- Treatment should be re-assessed quickly (e.g. 1 to 7 days) to confirm control using a step-up approach.
- Patients uncontrolled at Step 3 should be considered as having severe chronic upper airway disease (SCUAD) (66, 67) and may benefit from specialist referral and assessment for allergy workup and nasal examination (68). For example, specialist referral should be considered if there is failure to reduce VAS <5/10 after 10-14 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 may 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 two weeks or for the duration

of the pollen season or other specific allergen exposure. In the patient with persistent rhinitis, a longer course of treatment is often needed. It is of course important to assess concordance with agreed regimens, as treatment failure may 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 the different countries and on resources. These issues have not been approached in the present paper due to their variability between countries. Algorithms, inherently, are a combination of individual decision nodes that represent separate recommendations. They require testing as a complete algorithm and comparison to 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 the available evidence. The current algorithm is being developed by MASK (2) for a CDSS that will be available on Apple and Android and that will provide opportunities for evaluation.

**Figure 1: Step-up algorithm in untreated patients using visual analogue scale (adolescents and adults)**

*The proposed algorithm considers the treatment steps and patient's preference*

*VAS levels in ratio*

*If remaining ocular symptoms, add intra-ocular treatment*

**Figure 2: Step-up algorithm in treated patients using visual analogue scale (adolescents and adults)**

*The proposed algorithm considers the treatment steps and patient's preference*

*VAS levels in ratio*

*If remaining ocular symptoms, add intra-ocular treatment*



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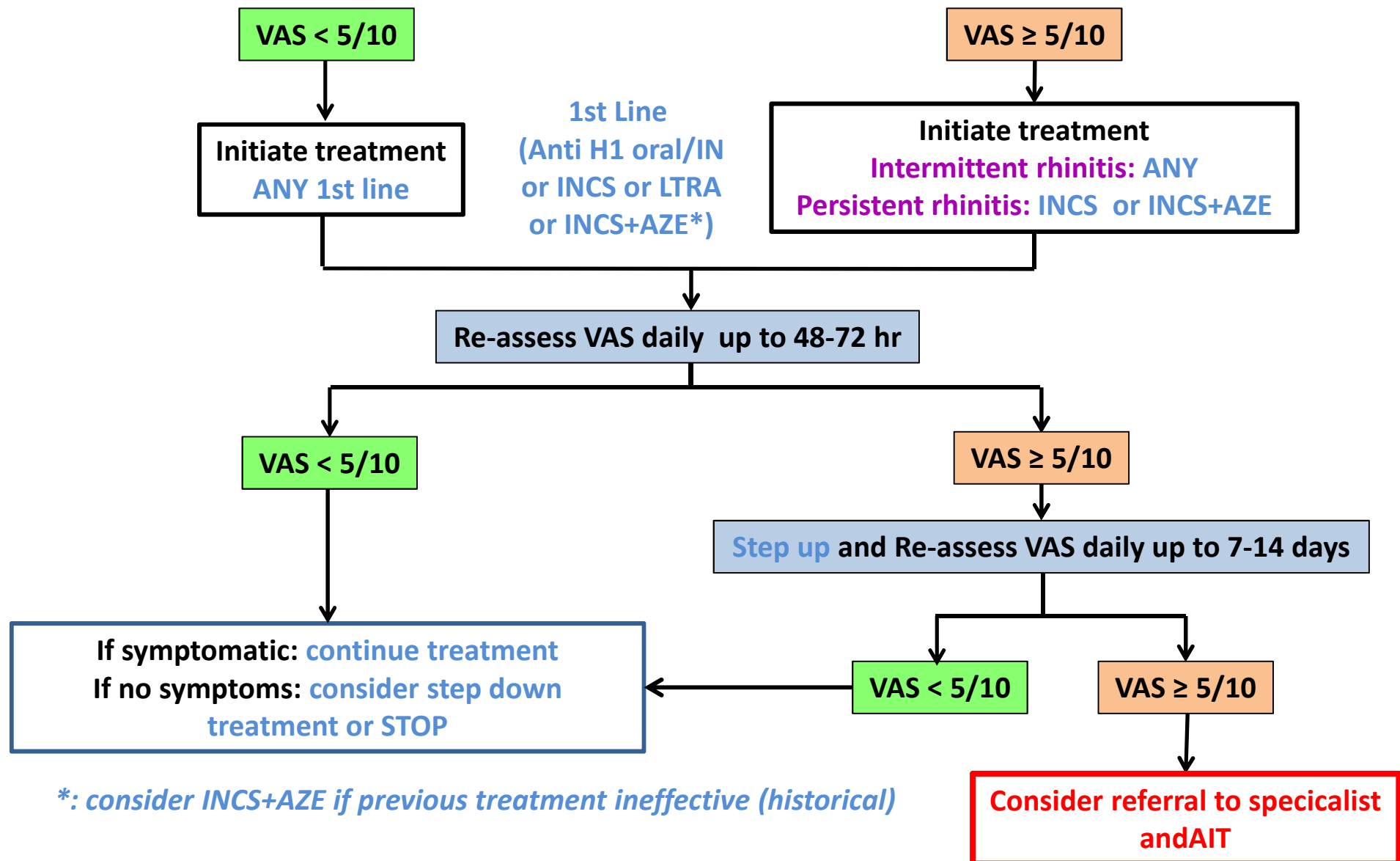


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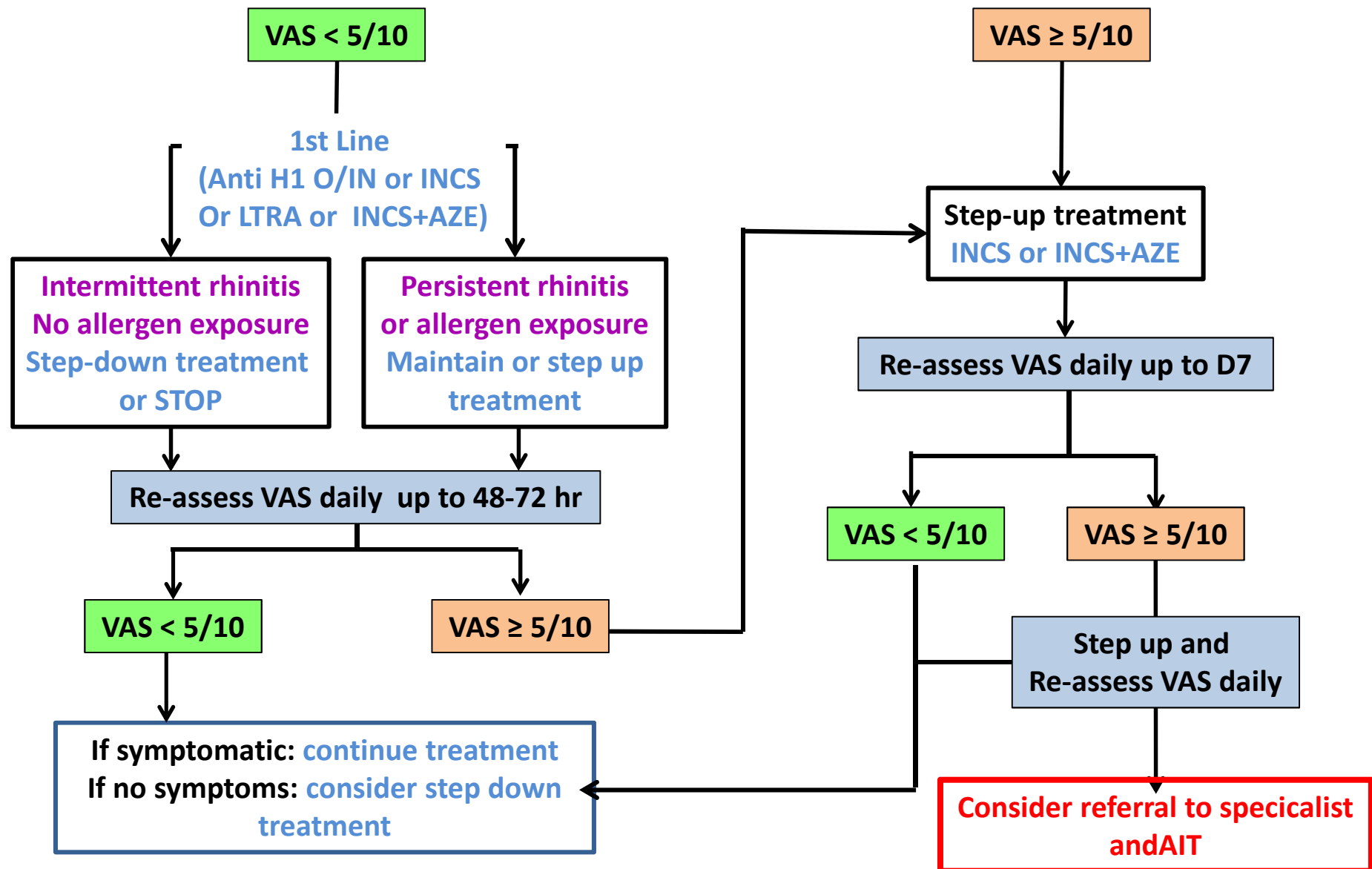
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# Assessment of control in untreated symptomatic patient



# Assessment of control in treated symptomatic patient



## ONLINE SUPPLEMENT

### Rationale for using VAS in the algorithm

Certain differences between groups in their VAS scores or changes in score may have no clinical relevance, even if they achieve statistical significance. A wide range of Minimally Clinically Important Differences (MCID) in change scores on the pain VAS have been reported (69) using different methods. MCID ranged from nine to 30 mm (out of 100 mm) in emergency departments (70-74). In other settings changes of 33% (75) and 31 mm (76) have been shown as clinically meaningful. In endometriosis pain MCID was set at 10 mm (77). The MCID for fatigue VAS was around 10 mm in a large rheumatoid arthritis clinical practice and similar to that seen in clinical trials (78). The MCID in VAS pain score does not differ with gender, age and cause-of-pain groups (71) or with the severity of pain being experienced (79). However, the linearity of the pain VAS is found in some (80) but not all studies (69, 81, 82). Pain VAS measurement error has been reported up to 20 mm (83, 84). Consequently, change scores and the calculations of aspects such as MCID may 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 meets the strict requirements of the Rasch model, including unidimensionality, and that it is internally valid (69). However, pain VAS does not behave linearly and the MCID may under- or overestimate true change during repeated pain VAS (85).

In allergic rhinitis, there is to our knowledge, a single study that has estimated MCID in VAS during treatment (25). Using receiver operating characteristic (ROC) curve analysis, an appropriate method for the estimation of MCID, the established cut-off variation of 23 mm for VAS was associated with a cut-off variation of 0.5 for RQLQ. Sensitivity analysis with RQLQ and TSS6 scales confirmed the aptitude of the cut-off value (23 mm) to discriminate changes in symptoms and quality-of-life. The MCID was the same whatever the baseline VAS level (25). A level of over 23 mm appears to be a relevant cutoff. VAS changes appear to encompass both symptoms and disease-specific QOL (25, 86). Another study, CARAT (Control of Allergic Rhinitis and Asthma Test (87, 88)), approximated the VAS-MCID. In CARAT, the MCID is 4 (range 0-30) (89). The real life study of Demoly et al in primary care (25) used the same methods as a cluster randomized trial carried out in specialist practices (24). Both studies, carried out in France in large populations, showed a very similar change in VAS levels during treatment depending on total symptom scores and RQLQ. These studies suggest that the cutoff of 23 mm (25) is appropriate to find a clinically significant difference.

VAS levels appear to be similar in different countries in severe intermittent or persistent rhinitis. VAS can be used in all age groups including preschool children (guardian evaluation) (90) and the elderly (91). Furthermore, it can be used in a wide variety of languages (91-98). VAS levels vary with the ARIA classification in many languages (94, 99, 100, 101). A VAS level of 50 (over 100 mm) is suggestive of moderate-severe AR (62, 102, 103) although in some studies the cutoff was of over 60 mm (95). VAS was used to define SCUAD (24). Thus, the MCID found in two large French populations may be generalized to other countries with different languages and cultures across the life cycle. However, future studies should refine this cutoff level.

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