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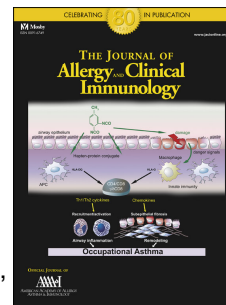


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# Accepted Manuscript

MACVIA Clinical Decision Algorithm in Allergic Rhinitis in adolescents and adults

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

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

157

## 158 **Abbreviations**

159

160 AHA: Active and Healthy Ageing

161 AIRWAYS ICPs: Integrated Care Pathways for Airway diseases

162 AIT: Allergen immunotherapy

163 AR: Allergic rhinitis

164 ARIA: Allergic Rhinitis and its Impact on Asthma

165 CDSS: Clinical decision support system

166 EIP: European Innovation Partnership

167 ICP: Integrated care pathway

168 MACVIA-LR: Contre les MALadies Chroniques pour un Vieillissement Actif en Languedoc-Roussillon

169 MASK: MACVIA-ARIA Sentinel network

170 QOL: Quality of life

171 SCUAD: Severe chronic Upper Airway Disease

172 VAS: Visual analogue scale

173

## 174 **Summary**

175

176 The selection of pharmacotherapy for patients with allergic rhinitis depends on several factors,  
177 including age, prominent symptoms, symptom severity, control of allergic rhinitis, patient preferences  
178 and cost. Allergen exposure and resulting symptoms vary and treatment adjustment is required.  
179 Clinical decision support systems (CDSS) may be beneficial for the assessment of disease control.  
180 Clinical decision support systems should be based on the best evidence and algorithms to aid patients  
181 and health care professionals to jointly determine the treatment and its step-up or step-down strategy  
182 depending on AR control. MACVIA-LR (Fighting chronic diseases for active and healthy ageing) one  
183 of the reference sites of the European Innovation Partnership on Active and Healthy Ageing, has  
184 initiated an allergy sentinel network (MASK: MACVIA-ARIA Sentinel network). A clinical decision  
185 support system is currently being developed to optimize allergic rhinitis control. An algorithm  
186 developed by consensus is presented in this paper. This algorithm should be confirmed by appropriate  
187 trials.

## 188 Introduction

189 The selection of pharmacotherapy for patients with allergic rhinitis (AR) depends on several factors  
190 such as age, prominent symptoms, symptom severity, control of AR, patient preferences, availability  
191 of treatment and cost (1). Allergen exposure and resulting symptoms varying daily, AR patients would  
192 benefit from regular monitoring of their symptoms to facilitate treatment adjustment. Clinical decision  
193 support systems (CDSS) may be beneficial for the accomplishment of this task by assessing disease  
194 control, for example in response to treatment (2). A CDSS is a health information technology system  
195 designed to assist health care professionals and patients with clinical decision-making tasks.  
196 Knowledge-based CDSSs consist of three parts: the knowledge base, an inference engine, and a  
197 mechanism to communicate (3, 4). The knowledge base contains the rules and associations of  
198 compiled data. The inference engine combines the rules from the knowledge base with the patient's  
199 data. The communication mechanism allows the system to show the results to the user as well as have  
200 input into the system. CDSS should be based on the best evidence and algorithms to aid patients and  
201 health care professionals to jointly determine the treatment and its step-up or step-down strategy  
202 depending on AR control (1). Thus, CDSS should help to optimize treatment.

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

## 210 Control of allergic rhinitis and rhino-conjunctivitis

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

216 The symptoms of AR can cause considerable morbidity in physical and emotional comfort as well as  
217 in functional capacity and quality-of-life (QOL). The control and severity of AR have been defined in  
218 a similar manner to asthma (2, 14, 15). Measures of AR control include symptom scores, patients'  
219 self-administered visual analogue scales (VAS), objective measures of nasal obstruction, a recent  
220 modification of the ARIA severity classification, and patients' reported outcomes such as QOL or  
221 scores with several items (16, 17). However, the challenges of managing AR are increased by the fact  
222 that patients do not often recognise their AR symptoms or confuse them with those of asthma (18).  
223 Therefore it is important for patients to be able to use an AR symptom scoring system that is simple to  
224 use and rapidly responsive to change.

225 As is the case for asthma, the best control of AR should be achieved as early as possible in order to: (i)  
226 improve patient satisfaction and concordance to treatment, and (ii) reduce the consequences of AR  
227 including symptoms, reduced QOL, and school and work absenteeism. Untreated AR can impair  
228 driving ability and put patients at risk (19). The ultimate goal of AR control is to reduce the costs  
229 incurred by AR (20-23).

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

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

## 236 **Recommendations for the treatment of allergic rhinitis and rhino-** 237 **conjunctivitis**

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

### 243 **Box 1: Summary of recommendations for the treatment of allergic rhinitis and conjunctivitis used** 244 **in the algorithm**

- |     |   |
|-----|---|
| 245 | • Oral or intra-nasal H1-anti-histamines are less effective than intra-nasal corticosteroids for the control of all |
| 246 | rhinitis symptoms (28-33).  |
| 247 | • Leukotriene receptor antagonists are usually considered to be less effective than oral H1-anti-histamines         |
| 248 | (30, 34, 35).   |
| 249 | • Comparisons between oral and intra-nasal H1-anti-histamines differ between recommendations, thus no               |
| 250 | definite conclusions have yet been reached.   |
| 251 | • The combined intranasal fluticasone propionate and azelastine hydrochloride in a single device is more            |
| 252 | effective than monotherapy and is indicated for patients when monotherapy with either intra-nasal H1-               |
| 253 | antihistamine or glucocorticoid is considered inadequate (1, 34-37).  |
| 254 | • Intra-nasal anti-histamines and intra-nasal corticosteroids are effective for ocular symptoms with no             |
| 255 | significant difference between them (38, 39). However, the combination of azelastine and fluticasone                |
| 256 | propionate was more effective than fluticasone propionate alone (36, 37) .  |
| 257 | • In most studies, combinations of oral anti-histamines or leukotriene receptor antagonists and intra-nasal         |
| 258 | corticosteroids are in general not more effective than monotherapy with intra-nasal corticosteroids (40, 41).       |
| 259 | • Intra-ocular H1 anti-histamines or cromones are effective for ocular symptoms (42). The importance of             |
| 260 | decongestants is debatable (30). However, efficacy of treatment varies with individual patient response.            |
| 261 | • In clinical practice, intra-nasal corticosteroids need a few days to be fully effective, whereas intra-nasal H1   |
| 262 | anti-histamines or combined intra-nasal fluticasone and azelastine are rapidly effective (43).                      |
| 263 | • All recommended medications are considered to be safe at the usual dosage. First-generation oral H1-              |
| 264 | antihistamines are sedating and should be avoided (44).   |
| 265 | • Oral or nebulized corticosteroids may be helpful in severe patients uncontrolled by other treatment,              |
| 266 | although studies are lacking in AR (45).  |
| 267 | • Further studies are needed in pre-school children to make more firm recommendations possible, although            |
| 268 | recent studies show the efficacy of oral H1 anti-histamines (46).   |

269  
270 Allergen immunotherapy appears to be as effective as pharmacotherapy (47, 48) but is also regarded as  
271 a disease modifier intervention with the potential of altering the natural history of allergic diseases (49,  
272 50).

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

## 274 **Patients' views**

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

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

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

287 Patients' individual preference for an oral or an intra-nasal route treatment needs to be considered (52,  
288 64, 65). In addition, health care professionals need to inform the patient of the relative benefits and  
289 harms of each prescribed treatment in order to support their decision making.

## 290 **Algorithm decision aid**

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

- 293 • As in asthma, treated and untreated patients should be considered differently (Figures 1 and 2).
- 294 • Most patients have received a previous treatment that should guide health care professionals with  
295 regards to the current prescription.
- 296 • Patterns of use of medication in previously-treated patients should be evaluated when future  
297 treatment is initiated.

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

- 299 • Efficacy of previous treatments.
- 300 • Adherence to treatment
- 301 • The patient's preference (route of administration, fear of side effects and experience of the patient  
302 regarding the treatment).
- 303 • Possible side effects or harms.
- 304 • Costs.

305 **Step-up approach:**

- 306 • Step 1, for mild symptoms, intranasal or oral non-sedating H1-antihistamine.
- 307 • Step 2, for moderate-severe symptoms and/or persistent AR, intranasal corticosteroids. The dose  
308 of some intra-nasal corticosteroids can be increased according to the package insert.
- 309 • Step 3, for patients with uncontrolled symptoms at step 2 (current or historical), combination of  
310 intra-nasal corticosteroids and intra-nasal H1-antihistamines. However, depending on the  
311 physicians' experience, other therapeutic strategies may be used.
- 312 • Step 4: It is possible that an additional short course of oral steroids may help to establish control  
313 and continue control by Step 3. Intra-ocular cromones or H1-anti-histamines may be added to  
314 improve the control of ocular symptoms.
- 315 • Treatment should be re-assessed quickly (e.g. 1 to 7 days) to confirm control using a step-up  
316 approach.
- 317 • Patients uncontrolled at Step 3 should be considered as having severe chronic upper airway  
318 disease (SCUAD) (66, 67) and may benefit from specialist referral and assessment for allergy  
319 workup and nasal examination (68). For example, specialist referral should be considered if there  
320 is failure to reduce VAS <5/10 after 10-14 days assuming the patient is adherent to therapy.
- 321 • At all times, patient adherence and intranasal device technique mastery should be regarded as  
322 potential for lack of treatment effect.

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

327 The duration of treatment is determined by the type of rhinitis (intermittent or persistent). In the  
328 patient with intermittent rhinitis, treatment should be continued daily for two weeks or for the duration

329 of the pollen season or other specific allergen exposure. In the patient with persistent rhinitis, a longer  
330 course of treatment is often needed. It is of course important to assess concordance with agreed  
331 regimens, as treatment failure may be a result of poor patient concordance.

### 332 **Conclusion**

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

343

344

345

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

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

349 *VAS levels in ratio*

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

351

352

353

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

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

357 *VAS levels in ratio*

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

359

ACCEPTED MANUSCRIPT

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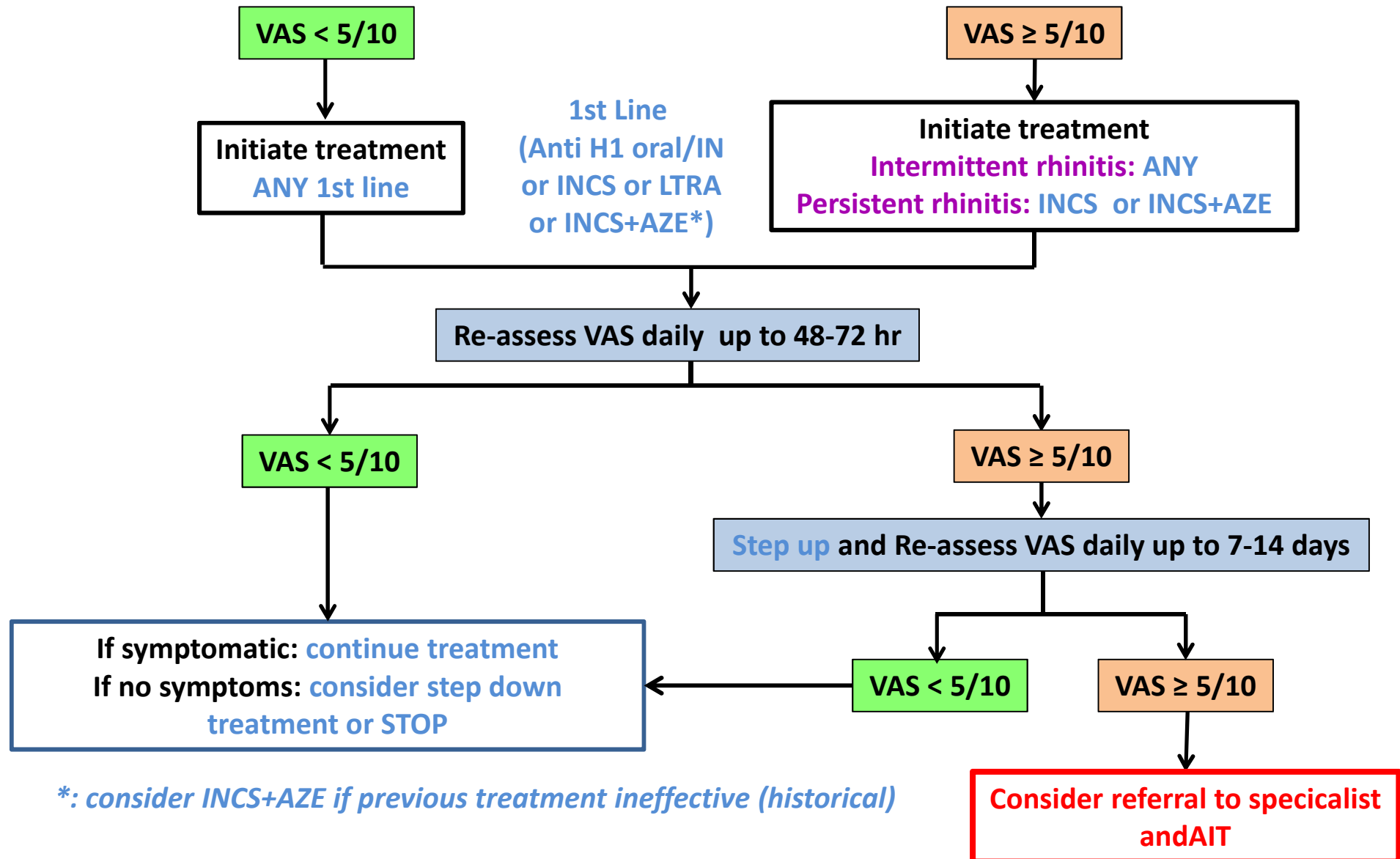


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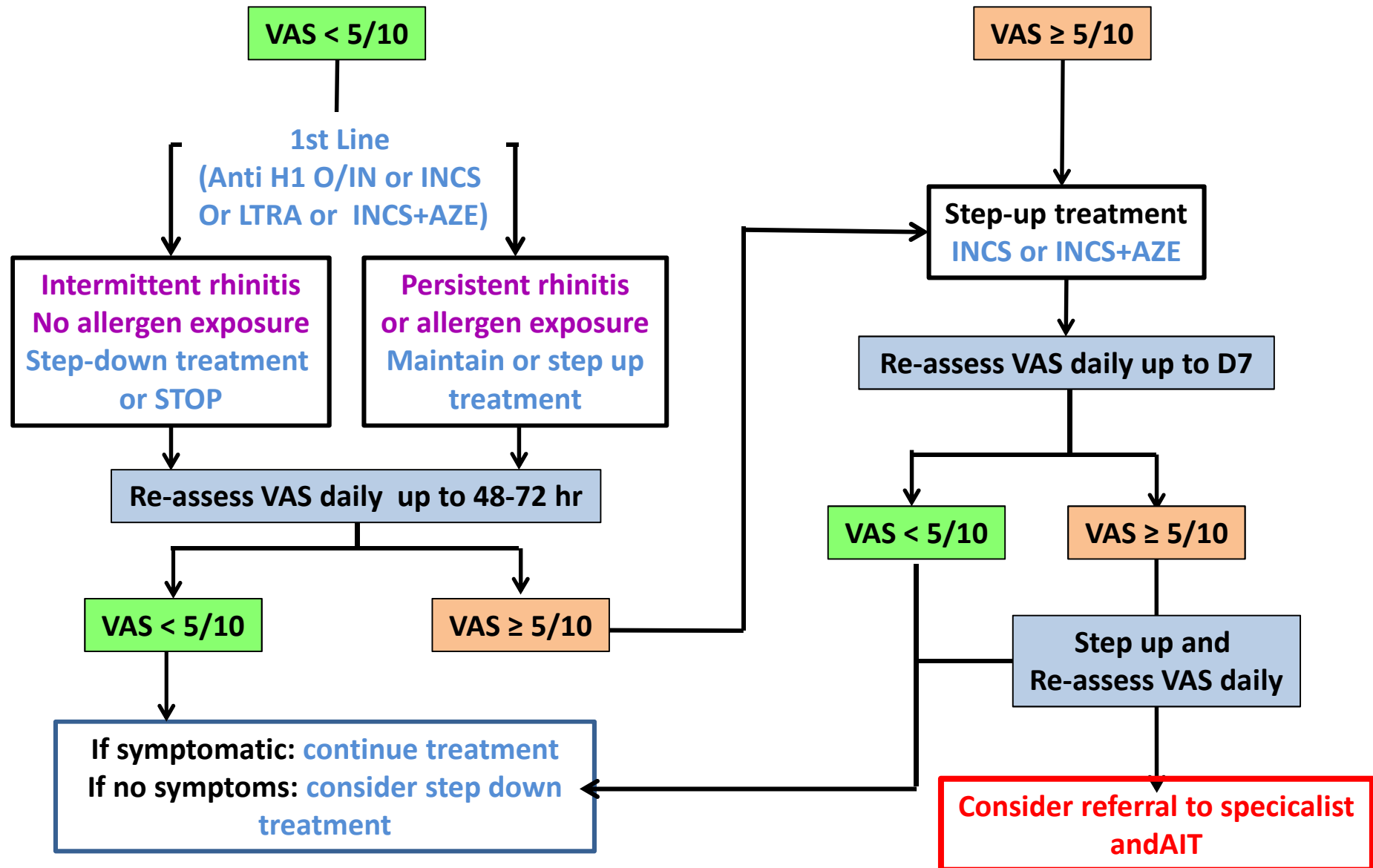
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- 542
- 543

# Assessment of control in untreated symptomatic patient



# Assessment of control in treated symptomatic patient



## 1 ONLINE SUPPLEMENT

### 3 Rationale for using VAS in the algorithm

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

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

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

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