

MACVIA Clinical Decision Algorithm in Allergic Rhinitis in adolescents and adults

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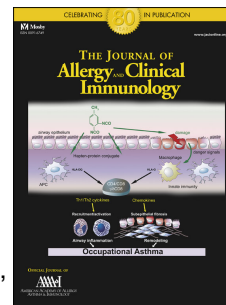
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MACVIA Clinical Decision Algorithm in Allergic Rhinitis in adolescents and adults

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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 β -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 ≤ 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's 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

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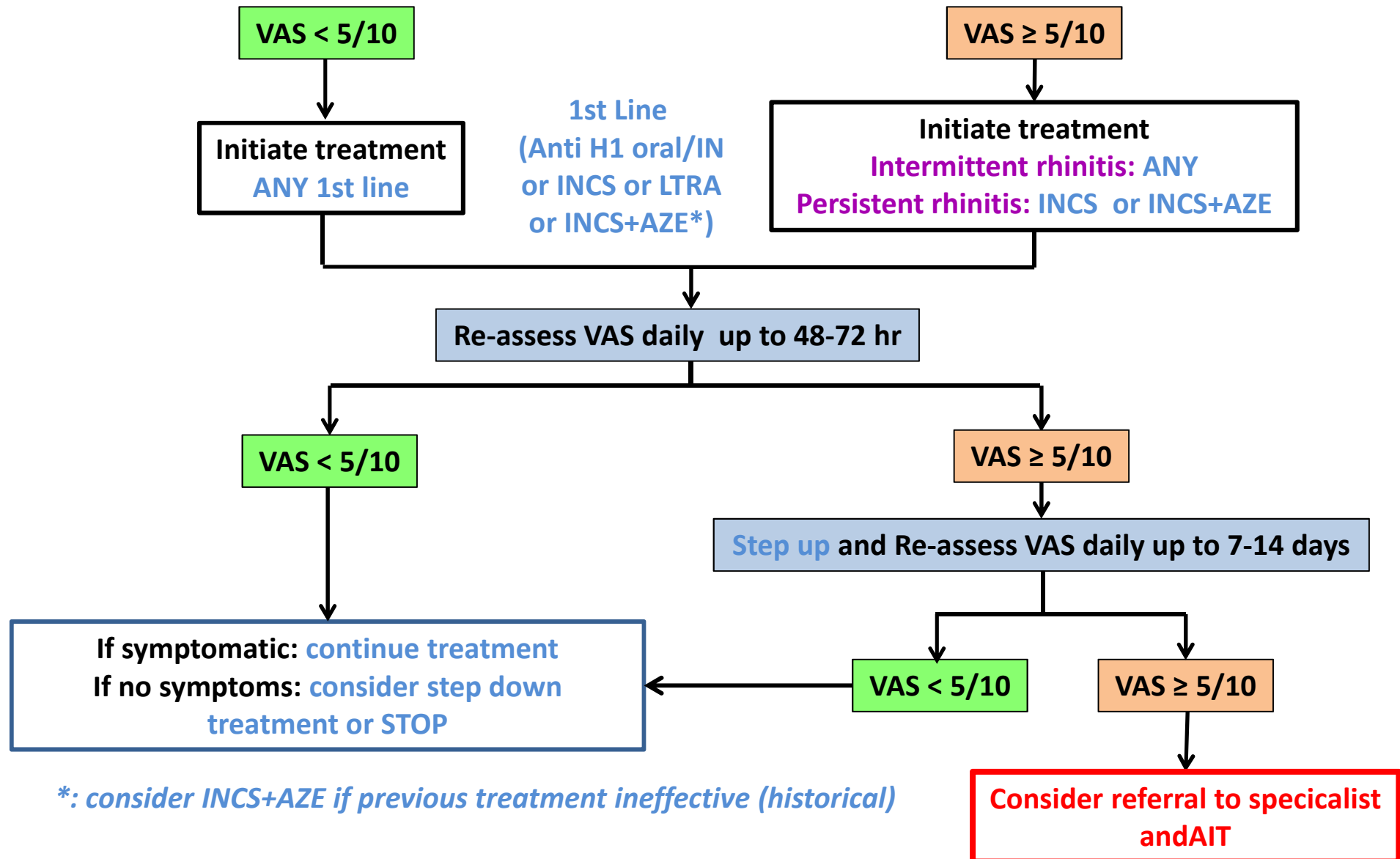
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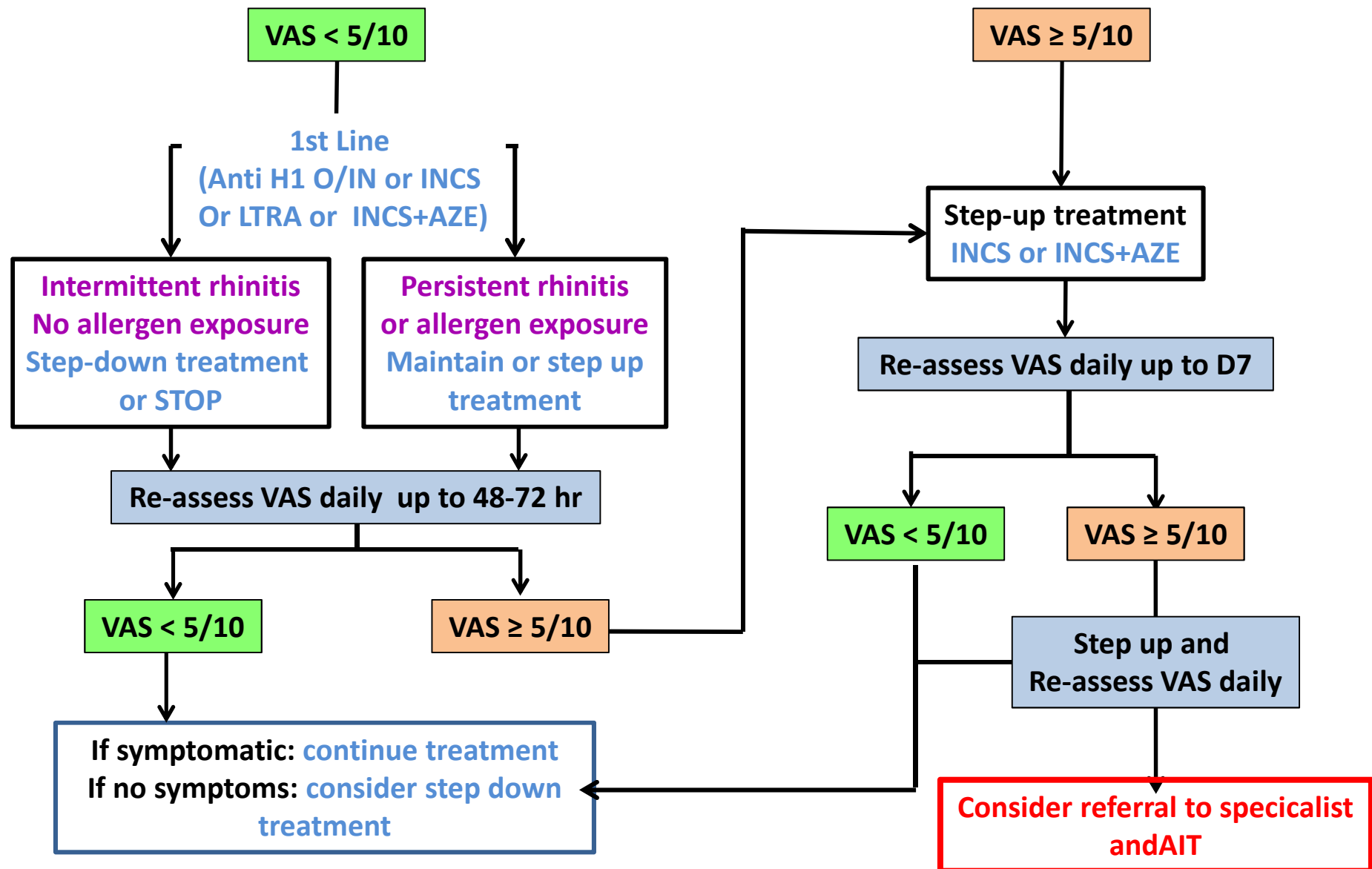
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Assessment of control in untreated symptomatic patient



Assessment of control in treated symptomatic patient



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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