

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

Jean Bousquet, Holger J. Schünemann, Peter W. Hellings, Sylvie Arnavielhe, Claus Bachert, Anna Bedbrook, Karl-Christian Bergmann, Sinthia Bosnic-Anticevich, Jan Brozek, Moises Calderon, et al.

### ▶ To cite this version:

Jean Bousquet, Holger J. Schünemann, Peter W. Hellings, Sylvie Arnavielhe, Claus Bachert, et al.. MACVIA Clinical Decision Algorithm in Allergic Rhinitis in adolescents and adults. Journal of Allergy and Clinical Immunology, 2016, 10.1016/j.jaci.2016.03.025. hal-01310973

## HAL Id: hal-01310973 https://hal.sorbonne-universite.fr/hal-01310973

Submitted on 3 May 2016

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

## Accepted Manuscript

MACVIA Clinical Decision Algorithm in Allergic Rhinitis in adolescents and adults

Jean Bousquet, MD, Holger J. Schu<sup>¬</sup>nemann, MD, Peter W. Hellings, MD, Sylvie Arnavielhe, PhD, Claus Bachert, MD, Anna Bedbrook, BSc, Karl-Christian Bergmann, MD, Sinthia Bosnic-Anticevich, PhD, Jan Brozek, MD, Moises Calderon, MD, G. Walter Canonica, MD, Thomas B. Casale, MD, Niels H. Chavannes, MD, Linda Cox, MD, Henry Chrystyn, PhD, Alvaro A. Cruz, MD, Ronald Dahl, MD, Giuseppe De Carlo, Dr, Pascal Demoly, MD, Philippe Devillier, MD, Gérard Dray, PhD, Monica Fletcher, MSc, Wytske J. Fokkens, MD, Joao Fonseca, MD, Sandra N. Gonzalez-Diaz, MD, Lawrence Grouse, MD, Thomas Keil, MD, Piotr Kuna, MD, Désirée Larenas-Linnemann, MD, Karin C. Lodrup Carlsen, MD, Eli O. Meltzer, MD, Joaquim Mullol, MD, Antonella Muraro, MD, Robert Naclerio, MD, Susanna Palkonen, MD, Nikolaos G. Papadopoulos, MD, Giovanni Passalacqua, MD, David Price, MD, Dermot Ryan, MD, Boleslaw Samolinski, MD, Glenis K. Scadding, MD, Aziz Sheikh, MD, Arunas Valiulis, MD, Erkka Valovirta, MD, Samantha Walker, PhD, Magnus Wickman, MD, Arzu Yorgancioglu, MD, Torsten Zuberbier, MD, on behalf of the MASK study group



PII: S0091-6749(16)30148-8

DOI: 10.1016/j.jaci.2016.03.025

Reference: YMAI 12064

To appear in: Journal of Allergy and Clinical Immunology

Received Date: 30 October 2015

Revised Date: 5 February 2016

Accepted Date: 15 March 2016

Please cite this article as: Bousquet J, Schu<sup>–</sup>nemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A, Bergmann K-C, Bosnic-Anticevich S, Brozek J, Calderon M, Canonica GW, Casale TB, Chavannes NH, Cox L, Chrystyn H, Cruz AA, Dahl R, De Carlo G, Demoly P, Devillier P, Dray G, Fletcher M, Fokkens WJ, Fonseca J, Gonzalez-Diaz SN, Grouse L, Keil T, Kuna P, Larenas-Linnemann D, Lodrup Carlsen KC, Meltzer EO, Mullol J, Muraro A, Naclerio R, Palkonen S, Papadopoulos NG, Passalacqua G, Price D, Ryan D, Samolinski B, Scadding GK, Sheikh A, Valiulis A, Valovirta E, Walker S, Wickman M, Yorgancioglu A, Zuberbier T, on behalf of the MASK study group, MACVIA Clinical Decision Algorithm in Allergic Rhinitis in adolescents and adults, *Journal of Allergy and Clinical Immunology* (2016), doi: 10.1016/j.jaci.2016.03.025.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1		MACVIA Clinical Decision Algorithm in Allergic Rhinitis in
2		adolescents and adults
2		
3		
4		
5	Bou	squet J (1-3), Schünemann HJ (4), Hellings PW (5), Arnavielhe S (6), Bachert C (7), Bedbrook A (2),
6	Bei	rgmann KC (8), S Bosnic-Anticevich (9), Brozek J (4), Calderon M (10), Canonica GW (11), Casale T
7	(	12), Chavannes NH (13), Cox L (14), H Chrystyn (15), Cruz AA (16), Dahl R (17), De Carlo G (18),
8	D	emoly P (19, 20), Devillier P (21), Dray G (22), Fletcher M (23), Fokkens WJ (24), Fonseca J (25),
9	Gon	zalez-Diaz S (26), Grouse L (27), Keil T (28), Kuna P(29), Larenas-Linnemann D (30), Lodrup Carlsen
10		KC (31), Meltzer EO (32), Mullol J (33), Muraro A (34), Naclerio RN (35), Palkonen S (18),
11	Ра	padopoulos N (36), Passalacqua G (11), Price D (37), Ryan D (38), Samolinski B (39), Scadding GK
12	(4)	0), Sheikh A (41), Valiulis A (42), Valovirta E (43), Walker S (44), Wickman M (45), Yorgancioglu A
13		(46), Zuberbier T (8) on behalf of the MASK study group*
14		
15		
16	1.	University Hospital, Montpellier, France
17 18	2.	MACVIA-LR, Contre les MAladies Chroniques pour un Vleillissement Actif en Languedoc-Roussillon, European
19	3.	INSERM. VIMA : Ageing and chronic diseases. Epidemiological and public health approaches. U1168. Paris. and UVSO.
20	-	UMR-S 1168, Université Versailles St-Quentin-en-Yvelines, France
21	4.	Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada
22 23	5. c	Laboratory of Clinical Immunology, Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium
24	0. 7.	Unner Airways Research Laboratory, ENT Dent, Ghent University Hospital, Ghent, Belaium
25	8.	Allergy-Centre-Charité at the Department of Dermatology, Charité - Universitätsmedizin Berlin, Berlin, Germany;
26		Secretary General of the Global Allergy and Asthma European Network (GA2LEN)
27	9.	Woolcock Institute of Medical Research, University of Sydney and Sydney Local Health District, Glebe, NSW, Australia
20 29	10. 11	Imperial College London - National Heart and Lung Institute, Royal Brompton Hospital NHS, London, UK. Alleray and Respiratory Diseases Clinic, DIML University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy
30	12.	Division of Allergy/Immunology, University of South Florida, Tampa, USA
31	13.	Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands
32	14.	Department of Medicine, Nova Southeastern University, Davie, Florida, USA.
33 34	15. 16	RIRL, 5a Coles Lane, Oakington, Cambridge, UK ProAR – Nucleo de Excelencia em Asma, Federal University of Babia, Brasil and GARD Executive Committee
35	10. 17.	Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark
36	18.	EFA European Federation of Allergy and Airways Diseases Patients' Associations, Brussels, Belgium
37	19.	EPAR U707 INSERM, Paris and EPAR UMR-S UPMC, Paris VI, Paris, France
30 30	20.	Department of Respiratory Diseases, Montpellier University Hospital, France Laboratoire de Pharmacologie Respiratoire LIPRES EA220, Hôpital Each, Surespes Université Versailles Saint-Quentin
40	21.	France
41	22.	Ecole des Mines, Alès, France
42	23.	Education for Health, Warwick, UK
43 11	24. 25	Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, Netherlands
45	25.	· Alleray Unit Instituto CUE Porto e Hospital CUE Porto Porto Portugal · Health Information and Decision Sciences
46		Department - CIDES, Faculdade de Medicina, Universidade do Porto, Porto, Portugal ; Faculdade de Medicina da
47		Universidade do Porto, Rua Dr. Plácido da Costa, s/n, 4200-450 Porto, Portugal.
48	26.	Universidad Autónoma de Nuevo León, Mexico
49 50	27. 28	University of Washington School of Medicine, Faculty of the Department of Neurology, USA
51	20.	Institute for Clinical Epidemiology and Biometry, University of Wuerzburg, Germany
52	29.	Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, Poland
53	30.	Clínica de Alergia, Asma y Pediatría, Hospital Médica Sur, México
ว4 55	31.	Usio University Hospital, Department of Paediatrics, Oslo, and University of Oslo, Faculty of Medicine, Institute of
56	32.	Alleray and Asthma Medical Group and Research Center. San Dieao. California. USA.
57	33.	Unitat de Rinologia i Clínica de l'Olfacte, Servei d'ORL, Hospital Clínic, Clinical & Experimental Respiratory
58		Immunoallergy, IDIBAPS, Barcelona, Spain.

- Food Allergy Referral Centre Veneto Region, Department of Women and Child Health, Padua General University 34 60 Hospital, Padua, Italy
- 61 35. Section of Otolaryngology-Head and Neck Surgery, The University of Chicago Medical Center and The Pritzker School of 62 63 Medicine, The University of Chicago, Illinois.
- 36. Center for Pediatrics and Child Health, Institute of Human Development, Royal Manchester Children's Hospital, 64 University of Manchester, Manchester M13 9WL, UK. Allergy Department, 2nd Pediatric Clinic, Athens General 65 Children's Hospital "P&A Kyriakou," University of Athens, Athens 11527, Greece. 66
  - 37. Academic Centre of Primary Care, University of Aberdeen, Aberdeen ; Research in Real-Life, Cambridge, UK.
- 67 Honorary Clinical Research Fellow, Allergy and Respiratory Research Group, The University of Edinburgh, Edinburgh, 38. 68 1 IK
- 69 70 39. Department of Prevention of Envinronmental Hazards and Allergology, Medical University of Warsaw, Poland
  - 40. The Royal National TNE Hospital, University College London, UK
- 71 72 73 74 Allergy and Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Medical 41. School, UK
  - 42. Vilnius University Clinic of Children's Diseases, Vilnius, Lithuania
  - 43. Dept. of Lung Diseases and Clinical Allergology, University of Turku, Finland.
- 75 44. Asthma UK, Mansell street, London, UK
- 76 Sachs' Children's Hospital, Stockholm; Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden 45.
- 77 46. Celal Bayar University Department of Pulmonology, Manisa, Turkey and GARD Executive Committee 78

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

81

79

59

#### 82 Address for correspondence

- 83
- 84 Professor Jean Bousquet
- 85 CHRU Arnaud de Villeneuve, Département de Pneumologie, 371 Avenue du Doyen Gaston Giraud,
- 86 34295 Montpellier Cedex 5, France Tel +33 611 42 88 47 jean.bousquet@orange.fr
- 87

#### Authors with degrees : 88

Bousquet Jean, MD Schünemann Holger J, MD Hellings Peter W, MD Arnavielhe Sylvie, PhD Bachert Claus, MD Bedbrook Anna, BSc Bergmann Karl-Christian, MD Bosnic-Anticevitch Sinthia, PhD Brozek Jan, MD Calderon Moises, MD Canonica G. Walter, MD Casale Thomas B, MD Chavannes Niels H, MD Cox Linda, MD Chrystyn Henry, PhD Cruz Alvaro A., MD Dahl Ronald, MD De Carlo Giuseppe, Dr Demoly Pascal, MD Devillier Philippe, MD Dray Gérard, PhD Fletcher Monica, MSc Fokkens Wytske J, MD Fonseca Joao, MD Gonzalez-Diaz Sandra N., MD Grouse Lawrence, MD Keil Thomas, MD Kuna Piotr, MD Larenas-Linnemann Désirée, MD

Lodrup Carlsen Karin C., MD Meltzer Eli O., MD Mullol Joaquim, MD Muraro Antonella, MD Naclerio Robert, MD Palkonen Susanna, MD Papadopoulos Nikolaos G, MD Passalacqua Giovanni, MD Price David, MD Ryan Dermot, MD Samolinski Boleslaw, MD Scadding Glenis K, MD Sheikh Aziz, MD Valiulis Arunas, MD Valovirta Erkka, MD Walker Samantha, PhD Wickman Magnus, MD Yorgancioglu Arzu, MD Zuberbier Torsten, MD

### 89 Working group members:

90 91 92 93 94 95 96 97 98 Aberer Werner, MD Adachi Mitsuru, MD Agache Ioana, MD Akdis Cezmi A., MD Akdis Mubeccel, MD Annesi-Maesano Isabella, MD Ansotegui Ignacio J, MD Anto Josep M., MD Arshad S. Hasan, MD 99 Baiardini Ilaria, MD 100 Baigenzhin Abay K, MD 101 Barbara Cristina, MD 102 Bateman Eric D., MD 103 Beghé Bianca, MD 104Bel Elisabeth H., MD 105Ben Kheder Ali, MD 106 Bennoor Kazi S., MD 107 Benson Michael, MD 108 Bernstein David, MD 109 Bewick Michael, MD 110 Bieber Thomas, MD 111 Bindslev-Jensen Carsten, MD 112 Bjermer Leif, MD 113 Blain Hubert, MD 114 Boner Attilio, MD 115 Bonini Matteo, MD 116 Bonini Sergio, MD 117 Bosse Isabelle, MD 118 Bouchard Jacques, MD 119 Boulet Louis-Philippe, MD 120 Bourret Rodolphe A., PhD 121 Bousquet Philippe J., MD Braido Fulvio, MD Briggs Andrew H., PhD Brightling Christopher E., MD Buhl Roland, MD 126 Burney Peter, MD 127 Bush Andrew, MD 128 Caballero-Fonseca Fernando, MD 129 Caimmi Davide P., MD 130 Camargos Paulo, MD 131 Camuzat Thierry, Mr

132 133 134 Carlsen Kai-Hakon, MD Carr Warner, MD Casale Thomas B., Md 135 Cepeda Sarabia Alfonso M Chatzi Leda, PhD 137 Chen Yuzhi, MD 138 Chiron Raphaël, MD 139 Chkhartishvili Ekaterine, MD 140 Chuchalin Alexander, MD 141 Ciprandi Georgio, MD 142 Cirule Ieva 143 Correia de Sousa Jaime, MD 144 Costa David, MD 145 Crooks George, MD 146 Custovic Adnan, MD 147Dahlen Sven-Erik, MD 148 Darsow Ulf, MD 149 De Blay Frédéric, MD 150De Manuel Keenoy Esteban, MD 151 Dedeu Tony, MD 152Deleanu Diana, MD Denburg Judah, MD Didier Alain, MD Dinh-Xuan Anh-Tuan, MD Dokic Dejan, Md Douagui Habib B., MD Dubakiene Ruta, MD Durham Stephen, MD Dykewicz Mark, MD El-Gamal Yehia, MD Emuzyte Regina, MD Fink Wagner Antje, PhD Fiocchi Alessandro, MD Forastiere Francesco, MD Gamkrelidze Amiran, MD Gemicioğlu Bilun, MD Gereda Jose E., MD Gerth van Wijk Roy, MD Gotua Maia, MD Grisle Ineta, MD Guzmán M. Antonieta, MD Haahtela Tari, Md Heinrich Joachim, PhD Hellquist-Dahl Birthe, PhD Horak Friedrich. MD Howarth Peter H., MD Humbert Marc, MD Hyland Michael, PhD Ivancevich Juan-Carlos, MD Jares Edgardo J., MD Johnston Sebastian L, MD Jonquet Olivier, MD Joos Guy, MD Jung Ki-Suck, MD Just Jocelyne, MD Jutel Marek, MD Kaidashev Igor P., MD Kaitov Musa, MD Kalayci Omer, MD Kalyoncu Fuat, Md Keith Paul, Md Khaltaev Nikolai, MD Kleine-Tebbe Jorg, MD

Klimek Ludger, MD Koffi N'Goran Bernard, MD Kolek Vitezlav, MD Koppelman Gerard H., MD Kowalski Marek, MD Kull Inger, PhD Kvedariene Violeta, MD Lambrecht Bart, MD Lau Susanne, MD Laune Daniel, PhD Le Thi Tuyet Lan, MD Li Jing, MD Lieberman Philippe, MD Lipworth Brian J., MD Louis Renaud, MD Magard Yves, MD Magnan Antoine, MD Mahboub Bassam, MD Majer Ivan, MD Makela Mika, MD Manning Peter J., MD Masjedi Mohamad, R., MD Maurer Marcus, MD Mavale-Manuel Sandra, MD Melén Erik, MD Melo-Gomes Elisabete, MD Mercier Jacques, MD Merk Hans, MD Miculinic Neven, MD Mihaltan Florin, MD Milenkovic Branislava, MD Mohammad Yousser, MD Molimard Mathieu, MD Momas Isabelle, PhD Montilla-Santana Anna, MD Morais-Almeida Mario, MD Mösges Ralph, MD Nadif Rachel, PhD Namazova-Baranova Leyla, MD Neffen Hugo, MD Nekam Kristof, MD Neou Angelos, MD Niggemann Bodo, MD Nyembue Dieudonné, MD O'Hehir Robyn, MD Ohta Ken, MD Okamoto Yoshitaka, MD Okubo Kim, MD Ouedraogo Solange, MD Paggiaro Pier-Luigi, MD Pali-Schöll Isabella, MD Palmer Stephen, MSc Panzner Petr, Md Papi Alberto, MD Park Hae-Sim, MD Pavord Ian, MD Pawankar Ruby, MD Pfaar Oliver, MD Picard Robert, PhD Pigearias Bernard, MD Pin Isabelle, MD

Plavec Davor, MD Pohl Wofgang, MD Popov Todor, MD Postma Dirkje S., MD Potter Paul, MD Poulsen Lars K., PhD Rabe Klaus, F., MD Raciborski Filip, PhD Radier Pontal Françoise, MD Reitamo Sakari, MD Repka-Ramirez Maria-Susana, MD Robalo-Cordeiro Carlos, MD Roberts Graham, MD Rodenas Francisco, PhD Rolland Christine, MD Roman Rodriguez Miguel, MD Romano Antonino, MD Rosado-Pinto José, MD Rosario Nelson A., MD Rosenwasser Larry, MD Rottem Menachem, MD Sanchez-Borges Mario, MD Sastre-Dominguez Joaquim, MD Schmid-Grendelmeier Peter, MD Serrano Eli, MD Simons F. Estelle R., MD Sisul Juan-Carlos, MD Skrindo Ingebjorg, MD Smit Henriette A., PhD Solé Dirceu, MD Sooronbaev Talant, MD Spranger Otto, Mr Stelmach Rafael, MD Strandberg Timo, MD Sunyer Jordi, MD Thijs Carel, MD Todo-Bom Ana-Maria, MD Triggiani Massimo, MD Valenta Rudolf, MD Valero Antonio L., MD van Hage Marianne, MD Vandenplas Olivier, MD Vezzani Giorgio, MD Vichyanond Pakit, MD Viegi Giovanni, MD Wagenmann Martin, MD Wahn Ulrich, MD Wang De Yun, MD Williams Dennis, PhD Wright John, MD Yawn Barbara P., MD Yiallouros Panaviotis, MD Yusuf Osman M., MD Zar Heather J., MD Zernotti Mario, MD Zhang Luo, MD Zhong Nanshan, Md Zidarn Mihaela, MD

153 154

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

- 156 system
- 157

#### 158 Abbreviations

- 159
- 160 AHA: Active and Healthy Ageing
- AIRWAYS ICPs: Integrated Care Pathways for Airway diseases
- AIT: Allergen immunotherapy
- 161 162 163 164 AR: Allergic rhinitis
- 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
- MASK: MACVIA-ARIA Sentinel networK
- 169 170 171 QOL: Quality of life
- 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.

MACVIA-LR (Fighting chronic diseases for active and healthy ageing, <u>http://macvia.cr-</u> languedocroussillon.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.

### 210 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 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.

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-

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.

#### Patients' views 274

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

treatments that can control all their symptoms, including ocular ones (61, 62), and a more rapid onsetof 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-thecounter (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.

### 290 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.

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

- Efficacy of previous treatments.
- **300** Adherence to treatment
- The patient's preference (route of administration, fear of side effects and experience of the patient regarding the treatment).
- **303** Possible side effects or harms.
- **304** 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's 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.</li>
- 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

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
347 348	and adults) The proposed glassithm considers the treatment stops and patient's preference
340	VAS levels in ratio
350	If remaining ocular symptoms, add intra-ocular treatment
351	ij i cinalning ocalal oymptomoj ada mila ocalal el cathelle
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	

### 360 **References**

- 361
- Meltzer EO. Pharmacotherapeutic strategies for allergic rhinitis: matching treatment to symptoms,
   disease progression, and associated conditions. Allergy Asthma Proc. 2013;34(4):301-11.
- Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW, et al.
   MACVIA-ARIA Sentinel Network for allergic rhinitis (MASK-rhinitis): The new generation guideline implementation. Allergy. 2015.
- 367
  3. Berlin A, Sorani M, Sim I. A taxonomic description of computer-based clinical decision support
  368 systems. J Biomed Inform. 2006;39(6):656-67.
- 369
  4. Berner E. Clinical decision support systems: State of the Art. Rockville, MD: Agency for
  370
  4. Healthcare Research and Quality. U.S. Department of Health and Human Services; 2009.
- Bourret R, Bousquet J. An integrated approach to telemonitoring noncommunicable diseases: best practice from the European innovation partnership on active and healthy ageing. World Hosp Health Serv. 2013;49(3):25-8.
- Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW, et al.
  MACVIA-ARIA Sentinel Network for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation. Allergy. 2015;70(11):1372-92.
- 377 7. Bousquet J, Hajjam J, Piette F, Jean-Bart B, Wlosik C, Robine JM, et al. [The French reference sites of the European Innovation Partnership on active and healthy ageing]. Presse Med.
  379 2013;42(12):1558-61.
- Bousquet J, Addis A, Adcock I, Agache I, Agusti A, Alonso A, et al. Integrated care pathways for airway diseases (AIRWAYS-ICPs). Eur Respir J. 2014;44(2):304-23.
- 382
  9. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma383 Summary Report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94-138.
- 384 10. O'Byrne PM, Reddel HK, Eriksson G, Ostlund O, Peterson S, Sears MR, et al. Measuring asthma
   385 control: a comparison of three classification systems. Eur Respir J. 2010;36(2):269-76.
- Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J. 2015.
- Thomas A, Lemanske RF, Jr., Jackson DJ. Approaches to stepping up and stepping down care in asthmatic patients. J Allergy Clin Immunol. 2011;128(5):915-24; quiz 25-6.
- 390 13. Patel M, Pilcher J, Beasley R. Combination ICS/fast-onset LABA inhaler as maintenance and
   391 reliever therapy: the future for uncontrolled adult asthma? Expert Rev Respir Med.
   392 2013;7(5):451-4.
- 393 14. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al.
  394 Uniform definition of asthma severity, control, and exacerbations: document presented for the
  395 World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol.
  396 2010;126(5):926-38.
- 397 15. Asthma WHOCCf, Rhinitis, Bousquet J, Anto JM, Demoly P, Schunemann HJ, et al. Severe
   398 chronic allergic (and related) diseases: a uniform approach--a MeDALL--GA2LEN--ARIA
   399 position paper. Int Arch Allergy Immunol. 2012;158(3):216-31.
- 400 16. Schatz M, Meltzer EO, Nathan R, Derebery MJ, Mintz M, Stanford RH, et al. Psychometric
  401 validation of the rhinitis control assessment test: a brief patient-completed instrument for
  402 evaluating rhinitis symptom control. Ann Allergy Asthma Immunol. 2010;104(2):118-24.
- 403
  403 17. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. Clin Exp Allergy. 2011;41(6):860-8.
- 405
  18. Nolte H, Nepper-Christensen S, Backer V. Unawareness and undertreatment of asthma and allergic rhinitis in a general population. Respir Med. 2006;100(2):354-62.
- 407
  407
  408
  408
  409
  409
  409
  409
  409
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
  400
- 409 20. Hellgren J, Cervin A, Nordling S, Bergman A, Cardell LO. Allergic rhinitis and the common cold--high cost to society. Allergy. 2010;65(6):776-83.
- 21. Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK. Economic burden of
  inadequate management of allergic diseases in the European Union: a GA(2) LEN review.
  Allergy. 2014;69(10):1275-9.

- Lamb CE, Ratner PH, Johnson CE, Ambegaonkar AJ, Joshi AV, Day D, et al. Economic impact
  of workplace productivity losses due to allergic rhinitis compared with select medical conditions
  in the United States from an employer perspective. Curr Med Res Opin. 2006;22(6):1203-10.
- 417
  418
  418
  418
  418
  418
  418
  419
  418
  419
  419
  419
  418
  419
  419
  419
  419
  410
  410
  410
  410
  411
  411
  412
  412
  413
  414
  415
  414
  415
  415
  416
  417
  417
  418
  418
  419
  419
  419
  419
  419
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
  410
- 420
  421 Bousquet PJ, Bachert C, Canonica GW, Casale TB, Mullol J, Klossek JM, et al. Uncontrolled
  421 allergic rhinitis during treatment and its impact on quality of life: a cluster randomized trial. J
  422 Allergy Clin Immunol. 2010;126(3):666-8 e1-5.
- 423 25. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients
  424 treated for allergic rhinitis: an observational prospective study in primary care: Asthma and
  425 Rhinitis. Clin Exp Allergy. 2013;43(8):881-8.
- 426 26. Ohta K, Jean Bousquet P, Akiyama K, Adachi M, Ichinose M, Ebisawa M, et al. Visual analog
  427 scale as a predictor of GINA-defined asthma control. The SACRA study in Japan. J Asthma.
  428 2013;50(5):514-21.
- Padjas A, Kehar R, Aleem S, Mejza F, Bousquet J, Schunemann HJ, et al. Methodological rigor
  and reporting of clinical practice guidelines in patients with allergic rhinitis: QuGAR study. J
  Allergy Clin Immunol. 2014;133(3):777-83 e4.
- 432 28. Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S, et al. BSACI
  433 guidelines for the management of allergic and non-allergic rhinitis. Clin Exp Allergy.
  434 2008;38(1):19-42.
- 435 29. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008;122(2 Suppl):S1-84.
- 438 30. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic
  439 Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol.
  440 2010;126(3):466-76.
- 441 31. Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2013;68(9):1102-16.
- 444 32. Scadding GK. Optimal management of allergic rhinitis. Arch Dis Child. 2015;100(6):576-82.
- 445 33. Larenas-Linnemann D, Mayorga-Butron JL, Sanchez-Gonzalez A, Ramirez-Garcia A, Medina446 Avalos M, Figueroa-Morales MA, et al. [ARIA Mexico 2014. Adaptation of the Clinical Practice
  447 Guide ARIA 2010 for Mexico. Methodology ADAPTE]. Rev Alerg Mex. 2014;61 Suppl 1:S3448 S116.
- 449 34. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice
  450 guideline: allergic rhinitis executive summary. Otolaryngol Head Neck Surg. 2015;152(2):197451 206.
- 452 35. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice
  453 guideline: Allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152(1 Suppl):S1-43.
- 454 36. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Double-blind,
  455 placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann
  456 Allergy Asthma Immunol. 2010;105(2):168-73.
- 457 37. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, et al. A novel intranasal
  458 therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin
  459 Immunol. 2012;129(5):1282-9 e10.
- 460 38. Fokkens WJ, Jogi R, Reinartz S, Sidorenko I, Sitkauskiene B, van Oene C, et al. Once daily
  461 fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen.
  462 Allergy. 2007;62(9):1078-84.
- 39. Bielory L, Chun Y, Bielory BP, Canonica GW. Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis. Allergy. 2011;66(5):686-93.
- 40. Anolik R, Mometasone Furoate Nasal Spray With Loratadine Study G. Clinical benefits of
  466 combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with
  467 mometasone furoate in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol.
  468 2008;100(3):264-71.

- 469 41. Esteitie R, deTineo M, Naclerio RM, Baroody FM. Effect of the addition of montelukast to
  470 fluticasone propionate for the treatment of perennial allergic rhinitis. Ann Allergy Asthma
  471 Immunol. 2010;105(2):155-61.
- 472 42. Castillo M, Scott NW, Mustafa MZ, Mustafa MS, Azuara-Blanco A. Topical antihistamines and
  473 mast cell stabilisers for treating seasonal and perennial allergic conjunctivitis. Cochrane Database
  474 Syst Rev. 2015;6:CD009566.
- 475 43. Meltzer E, Ratner P, Bachert C, Carr W, Berger W, Canonica GW, et al. Clinically Relevant
  476 Effect of a New Intranasal Therapy (MP29-02) in Allergic Rhinitis Assessed by Responder
  477 Analysis. Int Arch Allergy Immunol. 2013;161(4):369-77.
- 478
  44. Church MK, Maurer M, Simons FE, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, et al.
  479
  479 Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. Allergy. 2010.
- 480
  45. Wang C, Lou H, Wang X, Wang Y, Fan E, Li Y, et al. Effect of budesonide transnasal 481 nebulization in patients with eosinophilic chronic rhinosinusitis with nasal polyps. J Allergy Clin 482 Immunol. 2015;135(4):922-29 e6.
- 483
  46. Mullol J, Bousquet J, Bachert C, Canonica GW, Gimenez-Arnau A, Kowalski ML, et al. Update 484 on rupatadine in the management of allergic disorders. Allergy. 2015;70 Suppl 100:1-24.
- 485
  47. Matricardi PM, Kuna P, Panetta V, Wahn U, Narkus A. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: A comparison based on meta-analyses. J Allergy 487
  487
  487
  487
- 488 48. Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis.
  490 BMC Med. 2014;12:71.
- 49. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol. 2015;136(3):556-68.
- 50. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment
  of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results
  from a randomized double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol.
  2015.
- 497 51. Kenney P, Hilberg O, Pedersen H, Nielsen OB, Sigsgaard T. Nasal filters for the treatment of 498 allergic rhinitis: a randomized, double-blind, placebo-controlled crossover clinical trial. J Allergy 499 Clin Immunol. 2014;133(5):1477-80, 80 e1-13.
- 500 52. Marple BF, Fornadley JA, Patel AA, Fineman SM, Fromer L, Krouse JH, et al. Keys to
  501 successful management of patients with allergic rhinitis: focus on patient confidence, compliance,
  502 and satisfaction. Otolaryngol Head Neck Surg. 2007;136(6 Suppl):S107-24.
- 503 53. Ciprandi G, Incorvaia C, Scurati S, Puccinelli P, Soffia S, Frati F, et al. Patient-related factors in
  rhinitis and asthma: the satisfaction with allergy treatment survey. Curr Med Res Opin.
  2011;27(5):1005-11.
- 506 54. Frati F, Dell'Albani I, Passalacqua G, Bonini S, Rossi O, Senna G, et al. A survey of clinical features of allergic rhinitis in adults. Med Sci Monit. 2014;20:2151-6.
- 508 55. Turner RR, Testa MA, Hayes JF, Su M. Validation of the allergic rhinitis treatment satisfaction and preference scale. Allergy Asthma Proc. 2013;34(6):551-7.
- 56. Baena-Cagnani CE, Canonica GW, Zaky Helal M, Gomez RM, Compalati E, Zernotti ME, et al.
  The international survey on the management of allergic rhinitis by physicians and patients (ISMAR). World Allergy Organ J. 2015;8(1):10.
- 513 57. Demoly P, Aubier M, de Blay F, Wessel F, Clerson P, Maigret P. Evaluation of patients'
  514 expectations and benefits in the treatment of allergic rhinitis with a new tool: the patient benefit
  515 index the benefica study. Allergy Asthma Clin Immunol. 2015;11(1):8.
- 516 58. Fromer LM, Blaiss MS, Jacob-Nara JA, Long RM, Mannion KM, Lauersen LA. Current Allergic
  517 Rhinitis Experiences Survey (CARES): Consumers' awareness, attitudes and practices. Allergy
  518 Asthma Proc. 2014;35(4):307-15.
- 519 59. Zicari AM, Indinnimeo L, De Castro G, Incorvaia C, Frati F, Dell'Albani I, et al. A survey on features of allergic rhinitis in children. Curr Med Res Opin. 2013;29(5):415-20.
- 521 60. Demoly P, Chiriac AM, Berge B, Rostin M. Reasons for prescribing second generation
  522 antihistamines to treat allergic rhinitis in real-life conditions and patient response. Allergy
  523 Asthma Clin Immunol. 2014;10(1):29.

- 524 61. Virchow JC, Kay S, Demoly P, Mullol J, Canonica W, Higgins V. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients--an observational, cross sectional study in four countries in Europe. J Med Econ. 2011;14(3):305-14.
- 527 62. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of Allergic Rhinitis
  528 Symptoms on Quality of Life in Primary Care. Int Arch Allergy Immunol. 2013;160(4):393-400.
- 529 63. Valovirta E, Myrseth SE, Palkonen S. The voice of the patients: allergic rhinitis is not a trivial disease. Curr Opin Allergy Clin Immunol. 2008;8(1):1-9.
- 64. Hellings PW, Dobbels F, Denhaerynck K, Piessens M, Ceuppens JL, De Geest S. Explorative
  study on patient's perceived knowledge level, expectations, preferences and fear of side effects for
  treatment for allergic rhinitis. Clin Transl Allergy. 2012;2(1):9.
- 65. Green RJ, Davis G, Price D. Concerns of patients with allergic rhinitis: the Allergic Rhinitis Care
  Programme in South Africa. Prim Care Respir J. 2007;16(5):299-303.
- 66. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs in severe chronic upper airway disease (SCUAD). J Allergy Clin Immunol. 2009;124(3):428-33.
- 67. Hellings PW, Fokkens WJ, Akdis C, Bachert C, Cingi C, Dietz de Loos D, et al. Uncontrolled
  allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy. 2013;68(1):1-7.
- 540 68. Mullol J, Bartra J, del Cuvillo A, Izquierdo I, Munoz-Cano R, Valero A. Specialist-based
  541 treatment reduces the severity of allergic rhinitis. Clin Exp Allergy. 2013;43(7):723-9.
- 542 543

# Assessment of control in untreated symptomatic patient



# Assessment of control in treated symptomatic patient



### 1 **ONLINE SUPPLEMENT**

2

### 3 Rationale for using VAS in the algorithm

4

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. MCDI 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 MCDI in VAS during 21 treatment (25). Using receiver operating characteristic (ROC) curve analysis, an appropriate method 22 for the estimation of MCDI, the established cut-off variation of 23 mm for VAS was associated with a 23 cut-off variation of 0.5 for ROLQ. Sensitivity analysis with ROLQ 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-MCDI. 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 MCDI 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.

- 41 42
- 42 43

- 46
  2. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med. 1996;27(4):485-9.
- 48
   3. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med. 1998;5(11):1086-90.
- 4. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001;38(6):633-8.

Kersten P, White PJ, Tennant A. Is the pain visual analogue scale linear and responsive to change?
 An exploration using Rasch analysis. PLoS One. 2014;9(6):e99485.

- 52 5. Gallagher EJ, Bijur PE, Latimer C, Silver W. Reliability and validity of a visual analog scale for 53 acute abdominal pain in the ED. Am J Emerg Med. 2002;20(4):287-90.
- 54 6. Lee JS, Hobden E, Stiell IG, Wells GA. Clinically important change in the visual analog scale after 55 adequate pain control. Acad Emerg Med. 2003;10(10):1128-30.
- 56 7. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a 57 reanalysis of two clinical trials of postoperative pain. J Pain. 2003;4(7):407-14.
- 58 8. Auffinger BM, Lall RR, Dahdaleh NS, Wong AP, Lam SK, Koski T, et al. Measuring surgical 59 outcomes in cervical spondylotic myelopathy patients undergoing anterior cervical discectomy and 60 fusion: assessment of minimum clinically important difference. PLoS One. 2013;8(6):e67408.
- 61 9. Bourdel N, Alves J, Pickering G, Ramilo I, Roman H, Canis M. Systematic review of 62 endometriosis pain assessment: how to choose a scale? Hum Reprod Update. 2015;21(1):136-52.
- 63 10.Khanna D, Pope JE, Khanna PP, Maloney M, Samedi N, Norrie D, et al. The minimally important 64 difference for the fatigue visual analog scale in patients with rheumatoid arthritis followed in an 65 academic clinical practice. J Rheumatol. 2008;35(12):2339-43.
- 66 11.Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does 67 not differ with severity of pain. Emerg Med J. 2001;18(3):205-7.
- 68 12. Myles PS, Troedel S, Boquest M, Reeves M. The pain visual analog scale: is it linear or nonlinear? 69 Anesth Analg. 1999;89(6):1517-20.
- 70 13.Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann 71 Emerg Med. 2001;38(6):639-43.
- 72 14.Emshoff R, Bertram S, Emshoff I. Clinically important difference thresholds of the visual analog 73 scale: a conceptual model for identifying meaningful intraindividual changes for pain intensity. 74 Pain. 2011;152(10):2277-82.
- 75 15.Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute 76 pain. Acad Emerg Med. 2001;8(12):1153-7.
- 16.DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate 77 78 postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg. 79 1998:86(1):102-6.
- 80 17.Kersten P, Kucukdeveci AA, Tennant A. The use of the Visual Analogue Scale (VAS) in 81 rehabilitation outcomes. J Rehabil Med. 2012;44(7):609-10.
- 82 18.Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients 83 treated for allergic rhinitis: an observational prospective study in primary care: Asthma and 84 Rhinitis. Clin Exp Allergy. 2013;43(8):881-8.
- 85 19.Bousquet PJ, Combescure C, Klossek JM, Daures JP, Bousquet J. Change in visual analog scale 86 score in a pragmatic randomized cluster trial of allergic rhinitis. J Allergy Clin Immunol. 87 2009;123(6):1349-54.
- 88 20. Azevedo P, Correia de Sousa J, Bousquet J, Bugalho-Almeida A, Del Giacco SR, Demoly P, et al. 89 Control of Allergic Rhinitis and Asthma Test (CARAT): dissemination and applications in primary 90 care. Prim Care Respir J. 2013;22(1):112-6.
- 91 21. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M, et 92 al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. 93 Allergy. 2010;65(8):1042-8.
- 94 22. van der Leeuw S, van der Molen T, Dekhuijzen PN, Fonseca JA, van Gemert FA, Gerth van Wijk 95 R, et al. The minimal clinically important difference of the control of allergic rhinitis and asthma 96 test (CARAT): cross-cultural validation and relation with pollen counts. NPJ Prim Care Respir 97 Med. 2015;25:14107.
- 98 23. Bousquet PJ, Bachert C, Canonica GW, Casale TB, Mullol J, Klossek JM, et al. Uncontrolled 99 allergic rhinitis during treatment and its impact on quality of life: a cluster randomized trial. J 100 Allergy Clin Immunol. 2010;126(3):666-8 e1-5.
- 101 24. Morais-Almeida M, Santos N, Pereira AM, Branco-Ferreira M, Nunes C, Bousquet J, et al. 102 Prevalence and classification of rhinitis in preschool children in Portugal: a nationwide study. 103 Allergy. 2013;68(10):1278-88.
- 25.Morais-Almeida M, Pite H, Pereira AM, Todo-Bom A, Nunes C, Bousquet J, et al. Prevalence and 104 105 classification of rhinitis in the elderly: a nationwide survey in Portugal. Allergy. 2013;68(9):1150-7.

- 26.Bousquet J, Bachert C, Canonica GW, Mullol J, Van Cauwenberge P, Bindslev Jensen C, et al.
  Efficacy of desloratadine in intermittent allergic rhinitis: a GALEN study. Allergy. 2009;64(1516-23).
- 27.Bousquet J, Bachert C, Canonica GW, Mullol J, Van Cauwenberge P, Jensen CB, et al. Efficacy of
  desloratadine in persistent allergic rhinitis a GA(2)LEN study. Int Arch Allergy Immunol.
  2010;153(4):395-402.
- 28.Ohta K, Bousquet PJ, Aizawa H, Akiyama K, Adachi M, Ichinose M, et al. Prevalence and impact
  of rhinitis in asthma. SACRA, a cross-sectional nation-wide study in Japan. Allergy.
  2011;66(10):1287-95.
- 29.Larenas-Linnemann D, Dinger H, Shah-Hosseini K, Michels A, Mosges R. Over diagnosis of
   persistent allergic rhinitis in perennial allergic rhinitis patients: a nationwide study in Mexico. Am J
   Rhinol Allergy. 2013;27(6):495-501.
- 30.Shao J, Cui YX, Zheng YF, Peng HF, Zheng ZL, Chen JY, et al. Efficacy and safety of sublingual
  immunotherapy in children aged 3-13 years with allergic rhinitis. Am J Rhinol Allergy.
  2014;28(2):131-9.
- 31.Wei H, Zhang Y, Shi L, Zhang J, Xia Y, Zang J, et al. Higher dosage of HIFU treatment may lead
  to higher and longer efficacy for moderate to severe perennial allergic rhinitis. Int J Med Sci.
  2013;10(13):1914-20.
- 32. Tatar EC, Surenoglu UA, Saylam G, Isik E, Ozdek A, Korkmaz H. Is there any correlation between
   the results of skin-prick test and the severity of symptoms in allergic rhinitis? Am J Rhinol Allergy.
   2012;26(1):e37-9.
- 33.Bousquet PJ, Bousquet-Rouanet L, Co Minh HB, Urbinelli R, Allaert FA, Demoly P. ARIA
  (Allergic Rhinitis and Its Impact on Asthma) Classification of Allergic Rhinitis Severity in Clinical
  Practice in France. Int Arch Allergy Immunol. 2007;143(3):163-9.
- 34.del Cuvillo A, Montoro J, Bartra J, Valero A, Ferrer M, Jauregui I, et al. Validation of ARIA
  duration and severity classifications in Spanish allergic rhinitis patients The ADRIAL cohort
  study. Rhinology. 2010;48(2):201-5.
- 35.Rouve S, Didier A, Demoly P, Jankowsky R, Klossek JM, Anessi-Maesano I. Numeric score and
   visual analog scale in assessing seasonal allergic rhinitis severity. Rhinology. 2010;48(3):285-91.
- 36.Baiardini I, Braido F, Brandi S, Tarantini F, Bonini S, Bousquet PJ, et al. The impact of GINA
  suggested drugs for the treatment of asthma on Health-Related Quality of Life: a GA(2)LEN
  review. Allergy. 2008;63(8):1015-30.
- 37.Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of Allergic Rhinitis Symptoms
   on Quality of Life in Primary Care. Int Arch Allergy Immunol. 2013;160(4):393-400.
- 38.Yamamoto H, Yamada T, Sakashita M, Kubo S, Susuki D, Tokunaga T, et al. Efficacy of
  prophylactic treatment with montelukast and montelukast plus add-on loratadine for seasonal
  allergic rhinitis. Allergy Asthma Proc. 2012;33(2):e17-22.

144