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Jean Bousquet, Josep M. Anto, Pascal Demoly, Holger J. Schünemann, Alkis Togias, Mübeccel Akdis, Charles Auffray, Claus Bachert, Thomas Bieber, Philippe J. Bousquet, et al.

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# Severe chronic allergic (and related) diseases: a uniform approach – a MeDALL-GA<sup>2</sup>LEN-ARIA Position Paper

In collaboration with the WHO Collaborating Center for Asthma and Rhinitis

J Bousquet,<sup>\*/\*\*/ \*\*\*/S/€1/2</sup> JM Anto,<sup>\*/\*\*/3/4/5/6</sup> P Demoly,<sup>\*/\*\*\*/S/7/8</sup> HJ Schünemann,<sup>\*/\*\*\*/9</sup> A Togias<sup>10</sup>, M Akdis,<sup>\*/\*\*/11</sup> C Auffray,<sup>\*\*/12</sup> C Bachert,<sup>\*/\*\*/\*\*\*\*/13</sup> T Bieber,<sup>\*/14</sup> PJ Bousquet,<sup>\*/\*\*\*/S/1</sup> KH Carlsen,<sup>\*/\*\*/\*\*\*\*/15</sup> TB Casale,<sup>\*/\*\*/16</sup> AA Cruz,<sup>\*/\*\*\*/17</sup> T Keil,<sup>\*/\*\*/18</sup> KC Lodrup-Carlsen,<sup>\*/\*\*/\*\*\*\*/15</sup> M Maurer,<sup>\*/\*\*/\*\*\*\*/19</sup> K Ohta,<sup>\*/\*\*/20</sup> NG Papadopoulos,<sup>\*/\*\*\*/21</sup> M Roman Rodriguez<sup>22</sup>, B Samolinski,<sup>\*/\*\*/23</sup> I Agache,<sup>\*/\*\*/24</sup> A Andrianarisoa,<sup>€/25</sup> I Annesi-Maesano,<sup>\*/\*\*/ \*\*\*/26</sup> F Ballester<sup>27</sup>, CE Baena-Cagnani,<sup>\*/\*\*/28/29</sup> X Basagaña,<sup>\*/\*\*/3/4/5</sup> ED Bateman,<sup>\*/\*\*/30</sup> EH Bel,<sup>\*/31</sup> A Bedbrook,<sup>\*/\*\*/ \*\*\*/S/7</sup> B Beghue,<sup>\*/\*\*/32</sup> M Beji,<sup>€/33</sup> A Ben Kheder,<sup>\*/\*\*/€/34</sup> M Benet,<sup>\*/\*\*/3/4/5</sup> KS Bennoor,<sup>\*/\*\*/35</sup> KC Bergmann,<sup>\*/\*\*\*/19</sup> F Berrissoul,<sup>€/36</sup> C Bindslev Jensen,<sup>\*/\*\*/ \*\*\*/37</sup> G Bleecker,<sup>38</sup> S Bonini,<sup>\*/\*\*\*/39</sup> AL Boner,<sup>40</sup> LP Boulet,<sup>\*/\*\*/€/41</sup> CE Brightling,<sup>42</sup> JL Brozek,<sup>\*/\*\*/9</sup> A Bush,<sup>43</sup> WW Busse,<sup>44</sup> PAM Camargos,<sup>\*/\*\*/45</sup> GW Canonica,<sup>\*/\*\*\*/46</sup> W Carr,<sup>\*/\*\*/47</sup> A Cesario,<sup>48/49</sup> YZ Chen,<sup>\*/\*\*/50</sup> A Chin-Suorn,<sup>€/36</sup> A Chiriac,<sup>\*/\*\*/1</sup> DJ Costa,<sup>\*/\*\*/51</sup> L Cox,<sup>52</sup> A Custovic,<sup>\*/\*\*/53</sup> R Dahl,<sup>\*/\*\*/54</sup> U Darsow,<sup>\*/55</sup> T Didi,<sup>€/55A</sup> WK Dolen,<sup>56</sup> H Douagui,<sup>\*/\*\*/57</sup> R Dubakiene,<sup>\*/\*\*\*/58</sup> A El-Meziane,<sup>€/59</sup> J Fonseca,<sup>\*/\*\*/60</sup> WJ Fokkens,<sup>\*/\*\*\*/61</sup> E Fthenou,<sup>\*/\*\*/62</sup> A Gamkrelidze,<sup>\*/\*\*/63</sup> J Garcia-Aymerich,<sup>\*/\*\*/3/4/5/6</sup> R Gerth van Wijk,<sup>\*/\*\*/64</sup> E Gimeno,<sup>\*/\*\*/3</sup> S Guerra,<sup>\*/\*\*/3/4/5/64A</sup> T Haahtela,<sup>\*/\*\*/\*\*\*\*/65</sup> H Haddad,<sup>€/66</sup> P Hellings,<sup>\*/\*\*/67</sup> B Hellquist-Dahl,<sup>\*/\*\*/54</sup> C Hohmann,<sup>\*/\*\*/18</sup> P Howarth,<sup>\*/\*\*\*/68</sup> JO Hourihane,<sup>69</sup> M Humbert,<sup>\*/\*\*/70</sup> B Jacquemin,<sup>\*/2/71</sup> J Just,<sup>72</sup> O Kalayci,<sup>\*/\*\*/73</sup> MA Kaliner,<sup>74</sup> F Kauffmann,<sup>\*/\*\*/2/71</sup> M Kerckhof,<sup>\*/\*\*/75</sup> G Khayat,<sup>€/76</sup> B Koffi N'Goran,<sup>\*/\*\*/€/77</sup> M Kogevinas,<sup>\*/\*\*/3/4/5/77A</sup> GH Koppelman,<sup>\*/\*\*/78</sup> ML Kowalski,<sup>\*/\*\*/\*\*\*\*/79</sup> I Kull,<sup>\*/\*\*/80/81</sup> P Kuna,<sup>\*/\*\*/82</sup> D Larenas,<sup>\*/\*\*/83</sup> I Lavi,<sup>\*/\*\*/3</sup> LT Le,<sup>\*/\*\*/84</sup> P Lieberman,<sup>85</sup> B Lipworth,<sup>\*/\*\*/86</sup> B Mahboub,<sup>\*/\*\*/87</sup> MJ Makela,<sup>\*/\*\*/\*\*\*\*/65</sup> F Martin,<sup>€/88</sup> FD Martinez,<sup>\*/\*\*/€/94</sup> GD Marshall,<sup>90</sup> A Mazon,<sup>€/27</sup> E Melen,<sup>\*/\*\*/91</sup> EO Meltzer,<sup>\*/\*\*/92</sup> F Mihaltan,<sup>\*/\*\*/€/93</sup> Y Mohammad,<sup>\*/\*\*/€/94</sup> A Mohammadi,<sup>\*/\*\*/95</sup> I Momas,<sup>\*/\*\*/96</sup> M Morais-Almeida,<sup>\*/\*\*/97</sup> J Mullol,<sup>\*/\*\*\*/98</sup> A Muraro,<sup>99</sup> R Naclerio,<sup>\*/\*\*/100</sup> S Nafti,<sup>€/101</sup> L Namazova-Baranova,<sup>\*/\*\*\*/102</sup> MC Nawijn,<sup>\*/\*\*/103</sup> D Nyembue,<sup>\*/\*\*/104</sup> S Oddie,<sup>\*/\*\*/105/106</sup> R O'Hehir,<sup>\*/\*\*/107</sup> Y Okamoto,<sup>108</sup> MP Orru,<sup>\*/\*\*/109</sup> C Ozdemir,<sup>\*/\*\*/110</sup> GS Ouedraogo,<sup>\*/\*\*/111</sup> S Palkonen,<sup>\*/\*\*/\*\*\*\*/112</sup> P Panzner,<sup>\*/\*\*/113</sup> G Passalacqua,<sup>\*/\*\*\*/46</sup> R Pawankar,<sup>\*/\*\*/114</sup> B Pigearias,<sup>€/115</sup> I Pin,<sup>\*/\*\*/116/117</sup> M Pinart,<sup>\*/\*\*/3</sup> C Pison,<sup>\*/\*\*/118/119/120</sup> TA Popov,<sup>\*/\*\*/121/122</sup> D Porta,<sup>\*/\*\*/123</sup> DS Postma,<sup>\*/\*\*/124</sup> D Price,<sup>\*/\*\*/125</sup> KF Rabe,<sup>\*/\*\*/126</sup> J Ratomaharo,<sup>€/127</sup> S Reitamo,<sup>\*/\*\*/65</sup> D Rezagui,<sup>€/128</sup> J Ring,<sup>\*/\*\*\*/129</sup> R Roberts,<sup>130</sup> J Roca,<sup>\*/\*\*/131</sup> B Rogala,<sup>\*/\*\*\*/132</sup> A Romano,<sup>\*/\*\*\*/133</sup> J Rosado-Pinto,<sup>\*/\*\*/134</sup> D Ryan,<sup>135/136</sup> M Sanchez-Borges,<sup>\*/\*\*/137</sup> GK Scadding,<sup>\*/\*\*/138</sup> A Sheikh,<sup>139</sup> FER Simons,<sup>\*/\*\*/140</sup> V Siroux,<sup>\*/\*\*/141/142</sup> P Schmid-Grendelmeier,<sup>\*/\*\*\*/143</sup> HA Smit,<sup>\*/\*\*/144</sup> T Sooronbaev,<sup>\*/\*\*/145</sup> RT Stein,<sup>3/145A</sup> PJ Sterk,<sup>\*/\*\*/31/127</sup> J Sunyer,<sup>\*/\*\*/3/4/5/6</sup> I Terreehorst,<sup>\*/\*\*\*/146</sup> E Toskala,<sup>\*/\*\*/\*\*\*\*/147</sup> Y Tremblay,<sup>€/148</sup> R Valenta,<sup>\*/\*\*/149</sup> D Valeyre,<sup>€/150</sup> O Vandenplas,<sup>\*/\*\*/151</sup> C van Weel,<sup>\*/\*\*/152</sup> M Vassilaki,<sup>\*/\*\*/62</sup> R Varraso,<sup>\*/2/71</sup> G Viegi,<sup>\*/\*\*\*/153</sup> DY Wang,<sup>\*/\*\*/154</sup> M Wickman,<sup>\*/\*\*/155</sup> D Williams,<sup>\*/\*\*/156</sup> S Wöhrl,<sup>\*/157</sup> J Wright,<sup>\*/\*\*/105</sup> A Yorgancioglu,<sup>\*/\*\*/158</sup> OM Yusuf,<sup>\*/\*\*/159</sup> HJ Zar,<sup>\*/\*\*/160</sup> ME Zernotti,<sup>\*/\*\*/28</sup> M Zidarn,<sup>161</sup> N Zhong,<sup>\*/\*\*/162</sup> T Zuberbier,<sup>\*/\*\*/\*\*\*\*/19/163</sup>

\*: Member of GA<sup>2</sup>LEN (Global Allergy and Asthma European Network, Grant Agreement FP6)

\*\* : Member of MeDALL (Mechanisms of the Development of ALLergy, Grant Agreement FP7 N°264357, MeDALL paper N°5)

\*\*\* : Member of ARIA (Allergic Rhinitis and its Impact on Asthma)

§ : WHO Collaborating Center for Asthma and Rhinitis (Montpellier)

€ : Espace Francophone de Pneumologie (Société de Pneumologie de Langue Française)

- 1- University Hospital, Department of Respiratory Diseases, Hôpital Arnaud de Villeneuve, Montpellier, France
- 2- Inserm, CESP Centre for research in Epidemiology and Population Health, U1018, Respiratory and Environmental Epidemiology team, Villejuif, France
- 3- Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
- 4- Municipal Institute of Medical Research (IMIM-Hospital del Mar), Barcelona, Spain
- 5- CIBER Epidemiología y Salud Pública (CIBERESP), Spain
- 6- Universitat Pompeu Fabra (UPF), Barcelona, Spain.
- 7- WHO Collaborating Center for Asthma and Rhinitis, Montpellier, France
- 8- University Hospital of Montpellier - Inserm U657, Hôpital Arnaud de Villeneuve, Montpellier, France
- 9- Department of Clinical Epidemiology & Biostatistics and Medicine, McMaster University, Hamilton, Canada
- 10- National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA
- 11- Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland
- 12- Functional Genomics and Systems Biology for Health, CNRS Institute of Biological Sciences, Villejuif, France
- 13- URL (Upper Airways research Laboratory), University Hospital Ghent, Belgium
- 14- Department of Dermatology and Allergy, University Medical Center, Bonn, Germany
- 15- University of Oslo; Oslo University Hospital, Department of Paediatrics, Oslo, Norway
- 16- Division of Allergy and Immunology, Department of Medicine, Creighton University, Omaha, Nebraska, USA
- 17- ProAR - FMB, Federal University of Bahia School of Medicine, Salvador, Brazil
- 18- Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany
- 19- Allergy-Centre-Charité at the Dept. of Dermatology, Charité – University Medicine Berlin, Germany
- 20- Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan
- 21- Allergy Dpt, 2nd Pediatric Clinic, University of Athens, Greece
- 22- Son Pisa Primary Care Centre, IB-Salut Balearic Health Service, Palma de Mallorca, Spain
- 23- Department of Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Poland
- 24- Faculty of Medicine, Transylvania University, Brasov, Romania
- 25- Public Hospital Medical Service, Ministry of Health, Antananarivo, Madagascar
- 26- EPAR U707 INSERM, Paris ; EPAR UMR-S UPMC, Paris VI, Paris France
- 27- University of Valencia and Center for Public Health Research (CSISP), Valencia, Spain
- 28- Faculty of Medicine, Catholic University, Cordoba, Argentina ;
- 29- School of Specialization, Respiratory Medicine, University of Genoa, Italy
- 30- Health Sciences Faculty, University of Cape Town, South Africa
- 31- Department of Pulmonology, Academic Medical Centre, University of Amsterdam, The Netherlands
- 32- Divisions of Human Genetics Infection, Inflammation and Repair, School of Medicine, University of Southampton, UK.
- 33- Service de Pneumologie Allergologie, Centre Hospitalo-Universitaire de la Rabta, Tunis, Tunisia
- 34- Hopital A Mami, Ariana, Tunisia
- 35- National Institute of Diseases of Chest & Hospital, Mohakhali, Dhaka, Bangladesh
- 36- AIR KHMER, Cambodia
- 37- Odense University Hospital - Denmark
- 38- Wake Forest University Health Sciences, Winston-Salem, NC, USA
- 39- Institute of Neurobiology and Molecular Medicine – CNR, Rome, Italy and Department of Medicine, Second University of Naples, Naples, Italy
- 40- Department of Paediatrics, University of Verona, Verona, Italy
- 41- Institut de cardiologie et de pneumologie de l'Hôpital Laval and Université Laval, Quebec, Canada
- 42- Institute for Lung Health, Leicester, UK
- 43- Department of Paediatric Respiratory Medicine, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College, London, UK
- 44- Professor of Medicine, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; George R. and Elaine Love Professor, Chair - Dept of Medicine, University of Wisconsin, School of Medicine and Public Health, Madison, WI, USA
- 45- Dept of Pediatrics, Medical School, Federal University of Minas Gerais, Belo Horizonte, Brazil
- 46- Allergy & Respiratory Diseases, DIMI, Department of Internal Medicine, University of Genoa, Genoa, Italy
- 47- Southern California Research, Mission Viejo, California, USA

- 48- Deputy Scientific Director, IRCCS San Raffaele Pisana, Roma, Italy and  
49- Department of Thoracic Surgery, Catholic University, Rome, Italy  
50- National Cooperative Group of Pediatric Research on Asthma. Asthma Clinic and Education Center of the Capital Institute of Pediatrics, Peking, China  
Center for Asthma Research and Education, Beijing, P.R.China  
51- Primary Care Dept., Montpellier I University, France  
52- Nova Southeastern University Osteopathic College of Medicine, Davie, Florida, USA  
53- University of Manchester, Manchester, UK  
54- Aarhus University Hospital, Denmark  
55- Department of Dermatology and Allergy Biederstein, Technische Universität München, München, Germany  
55A- Service de pneumologie, Centre Hospitalier de la Région d'Annecy, Annecy, France  
56- Medical College of Georgia, Augusta, GA, USA  
57- Service de pneumo-allergologie, Centre Hospitalo-Universitaire de Béni-Messous, Algiers, Algeria  
58- Vilnius University Faculty of Medicine, Lithuania, GA2LEN collaborating centre  
59- Société Marocaine des Maladies Respiratoires, BP 1828, Derb Ghellaf, Casablanca, Maroc AND Centre of Respiratory Diseases and Allergy, Centre commercial Nadia, Casablanca, Maroc  
60- Biostatistics and Medical Informatics Department & CINTESIS, and Allergy Division, Porto University, Portugal ; Allergy, Hospital S. Joao & Instituto, CUF; CINTESIS, Porto University Medical School  
61- Department of Otorhinolaryngology, University of Amsterdam, The Netherlands  
62- Department of Social Medicine, Faculty of Medicine, University of Crete, Heraklion, Crete, Greece  
63- WHO CO in Georgia, Tbilisi, Georgia  
64- Section of Allergology, Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands  
64A- University of Arizona, Tucson, AZ, USA  
65- Department of Dermatology, Skin and Allergy Hospital, Helsinki University Hospital, Finland  
66- Association Franco-Libanaise de Pneumologie (AFLP) and Service de pneumologie, Centre Hospitalier Tarbes- Lourdes, Bigorre, France  
67- Department of Otorhinolaryngology, Head, and Neck Surgery, University Hospitals Leuven, Belgium  
68- University of Southampton, England  
69- University College Cork, Ireland, UK  
70- Université Paris-Sud, Service de Pneumologie, Hôpital Antoine-Béclère, Clamart, France  
71- University Paris Sud 11, UMRS 1018, Villejuif, France  
72- Groupe Hospitalier Trousseau-La Roche-Guyon, Centre de l'Asthme et des Allergies, APHP, Université Paris 6, France  
73- Hacettepe University School of Medicine, Pediatric Allergy and Asthma Unit, Hacettepe, Ankara, Turkey  
74- George Washington University School of Medicine, Washington DC - Institute for Asthma and Allergy, Chevy Chase, MD, USA  
75- Department of Epidemiology, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands  
76- Service de Pneumologie, Hôtel-Dieu de France & Faculté de Médecine, Université Saint-Joseph, Beyrouth, Liban  
77- Service des Maladies Respiratoires, Centre Hospitalière Universitaire, Abidjan, Ivory Coast  
77A- Department of Nutrition, National School of Public Health, Athens, Greece  
78- Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands  
79- Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, Poland  
80- Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden  
81- Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden  
82- Barlicki University Hospital, Medical University of Lodz, Poland  
83- Allergy Department, Hospital Médica Sur, Mexicocity, Mexico  
84- University of Medicine and Pharmacy, Hochiminh City, Vietnam  
85- University of Tennessee College of Medicine, Memphis Tennessee, USA  
86- Asthma and Allergy Research Group, University of Dundee, UK  
87- Pulmonary and allergy unit, Dubai Health Authority and University of Sharjah, UAE  
88- Compiègnes, Association Franco-Vietnamienne de Pneumologie  
89- Arizona Respiratory Center, University of Arizona, Tucson, AZ, USA  
90- Division of Clinical Immunology and Allergy, University of Mississippi Medical Center, Jackson, MS USA  
91- Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden  
Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden  
92- Allergy & Asthma Medical Group & Research Center, University of California, San Diego, USA

- 93- Institute of Pneumology Marius Nasta, Bucharest, Romania
- 94- Tishreen University School of Medicine, Department of Internal Medicine, Lattakia, Syria
- 95- Association Franco-Marocaine de Pathologie Thoracique (AFMAPATH), Marrakech, Morocco
- 96- Paris Descartes University, Department of Public health and biostatistics, EA 4064 and Paris municipal Department of social action, childhood, and health, Paris, France
- 97- Immunoallergy Department, CUF-Descobertas Hospital, Lisbon, Portugal
- 98- Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic, IDIBAPS. Barcelona, Catalonia, Spain
- 99- Department of Pediatrics - University of Padua, Padua, Italy
- 100- Professor and Chief of OHNS, University of Chicago, Chicago, Illinois, USA
- 101- Mustapha Hospital, Algiers, Algeria
- 102- Scientific Center for Children's Health RAMS, Moscow, Russia
- 103- Laboratory of Allergology and Pulmonary Diseases, Department of Pathology and Medical Biology, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
- 104- Kinshasa University, Congo
- 105- Bradford Institute for Health Research, Bradford Teaching Hospitals Foundation Trust, Bradford, UK
- 106- Bradford Neonatology, Bradford Royal Infirmary, Bradford, UK
- 107- Alfred Hospital and Monash University, Melbourne, Australia
- 108- Dept. of Otorhinolaryngology, Chiba University Hospital, Chiba, Japan
- 109- Pharmacist, Italy
- 110- Marmara University, Seher, Yildizi Sokak 16/10 Etiler, Istanbul, Turkey
- 111- Centre Hospitalier Universitaire Pédiatrique Charles de Gaulle, Ouagadougou, Burkina Faso, West Africa
- 112- EFA European Federation of Allergy and Airways Diseases Patients' Associations, Brussels, Belgium
- 113- Charles University Prague, Medical School and Hospital in Plzen, Dept. of Allergy and Clin. Immunology, Plzen, Czech Republic
- 114- Nippon Medical School, Bunkyo-ku, Tokyo, Japan
- 115- NICE and Société de Pneumologie de Langue Française, France
- 116- CHU de Grenoble;
- 117- INSERM, U823, Institut Albert Bonniot, Grenoble; University Joseph Fourier, Grenoble, France
- 118- Department of Pulmonology, University Hospital of Grenoble;
- 119- Inserm 884;
- 120- University of Grenoble, France
- 121- Clinic of Allergy and Asthma, Medical University Sofia, Bulgaria  
Clinic of Allergy
- 122- Asthma, Alexander's University Hospital, Sofia, Bulgaria
- 123- Department of Epidemiology, Regional Health Service Lazio Region, Rome, Italy
- 124- Department of Pulmonology, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
- 125- GPIAG, University of Aberdeen, Aberdeen, Scotland
- 126- Department of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands
- 127- PNEUMALGA and Société de Pneumologie de l'Océan Indien
- 128- Association Franco-Algérienne de Pneumologie (**AFAP**)
- 129- Technische Universität München - Germany
- 130- University of Wisconsin School of Medicine & Public Health, Madison, USA
- 131- Institut Clínic del Tòrax, Hospital Clínic, IDIBAPS, CIBERES, Universitat de Barcelona, Spain
- 132- Silesian University School of Medicine, Zabrze, Poland
- 133- Department of Internal Medicine and Geriatrics, UCSC-Allergy Unit, Complesso Integrato Columbus, Rome, Italy.
- 134- Immunoallergy Department, Hospital da Luz, Lisboa, Portugal  
Hospital Dona Estefânia, Lisboa, Portugal
- 135- Woodbrook Medical Centre, Loughborough, England
- 136- Clinical Research Fellow, University of Aberdeen, Scotland
- 137- Department of Allergy and Clinical Immunology, Centro Medico-Docente La Trinidad, Caracas, Venezuela
- 138- Royal National TNE Hospital, University College London, UK
- 139- Centre for Population Health Sciences, The University of Edinburgh, Medical School, Edinburgh, UK
- 140- Faculty of Medicine, University of Manitoba, Canada
- 141- INSERM, U823, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Grenoble;
- 142- Université Joseph Fourier, Grenoble, France
- 143- Allergy Unit, Dept. of Dermatology, University Hospital, Zuerich, Switzerland

- 144- Julius Center of Health Sciences and Primary Care, University Medical Center Utrecht, University of Utrecht, Utrecht, the Netherlands
- 145- National Centre Cardiology and Internal Medicine, Bishkek, Kyrgyzstan
- 145A- School of Medicine, Pontificia Universidade Católica RGS, Porto Alegre, RS - Brazil
- 146- Dept of ENT and Paediatrics, AMC hospital, Amsterdam, the Netherlands
- 147- Finnish Institute of Occupational Health, Helsinki, Finland
- 148- Department of Obstetric and Gynecology, Axis in Reproduction, Perinatal and Child Health, Faculty of medicine, Laval University, Quebec, Canada
- 149- Christian Doppler Laboratory for Allergy Research, Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria
- 150- Université Paris 13, PRES Sorbonne-Paris-Cité and Assistance publique-Hôpitaux de Paris, Avicenne hospital, Bobigny, France
- 151- University Hospital of Mont-Godinne, Catholic University of Louvain, Yvoir, Belgium
- 152- Department of Primary and Community Care, Radboud University Nijmegen Medical Centre, HB Nijmegen, The Netherlands
- 153- CNR Institutes of Biomedicine and Molecular Immunology (IBIM), Palermo, and of Clinical Physiology (IFC), Pisa, Italy
- 154- Yong Loo Lin School of Medicine, National University of Singapore, Republic of Singapore
- 155- Sachs' Children's Hospital, Stockholm; Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
- 156- School of Pharmacy, University of North Carolina, North Carolina, USA
- 157- Medical University of Vienna, Department of Dermatology, Division of Immunology, Allergy and Infectious Diseases (DIAID), Wien, Austria
- 158- Celal Bayar University School of Medicine Dept. of Pulmonology, Manisa, Turkey
- 159- The Allergy & Asthma Institute, Islamabad, Pakistan
- 160- Department of Paediatrics and Child Health, University of Cape Town, South Africa  
School of Child and Adolescent Health, Red Cross Childrens Hospital, University of Cape Town, South Africa
- 161- University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia
- 162- Guangzhou Institute of Respiratory Diseases and State Key Laboratory of Respiratory Diseases, Guangzhou Medical College, Guangzhou, China
- 163- Secretary General of the Global Allergy and Asthma European Network (GA2LEN), Network of Excellence, Charité - Universitätsmedizin Berlin, Berlin, Germany

### **Corresponding author**

Jean Bousquet  
Centre Hospitalier Universitaire, Montpellier  
34295- Montpellier-Cedex 05  
Phone : +33-611-42-88-47  
Email : jean.bousquet@inserm.fr

## **Abstract**

Concepts of disease severity, activity, control and responsiveness to treatment are linked but different. Severity refers to the loss of function of the organs induced by the disease process or to the occurrence of severe acute exacerbations. Severity may vary over time and needs regular follow up. Control is the degree to which therapy goals are currently met. These concepts have evolved over time for asthma in guidelines, task forces or consensus meetings. The aim of this paper is to generalize the approach of the uniform definition of severe asthma presented to WHO for chronic allergic and associated diseases (rhinitis, chronic rhinosinusitis, chronic urticaria, atopic dermatitis) in order to have a uniform definition of severity, control and risk, usable in most situations. It is based on the appropriate diagnosis, availability and accessibility of treatments, treatment responsiveness and associated factors such as co-morbidities and risk factors. This uniform definition will allow a better definition of the phenotypes of severe allergic (and related) diseases for clinical practice, research (including epidemiology), public health purposes, education and the discovery of novel therapies.

## **Key words**

IgE, allergy, severity, control, risk, asthma, rhinitis, rhinosinusitis, urticaria, atopic dermatitis

## Abbreviations

ACQ: Asthma Control Questionnaire  
ACT: Asthma Control Test  
AD: Atopic dermatitis  
ARIA: Allergic Rhinitis and its Impact on Asthma  
ATS: American Thoracic Society  
CRS: Chronic rhinosinusitis  
CRSsNP: Chronic rhinosinusitis without nasal polyps  
CRSwNP: Chronic rhinosinusitis with nasal polyps  
EASI: Eczema Area and Severity Index  
EPR3: Expert report 3  
ERS: European Respiratory Society  
FP: Framework Programme  
GA<sup>2</sup>LEN: Global Allergy and Asthma European Network (FP6)  
GINA: Global initiative for asthma  
LMIC: Low and middle-income country  
MeDALL: Mechanisms of the Development of Allergy (FP7)  
NAEPP: National Asthma Education Prevention Program  
POEM: Patient-oriented Eczema Measure  
SCORAD: SCORing Atopic Dermatitis  
SCUAD: Severe chronic upper airway disease  
U-BIOPRED: Unbiased BIOMarkers for the PREDiction of respiratory disease outcomes  
VAS: Visual analogue scale  
WAO: World Allergy Organization  
WHO: World Health Organization

**4926 words**

## Introduction

Allergic diseases represent the world's most common chronic disease. Several mechanisms are involved, but many result from IgE-mediated reactions (1). Not all sensitized patients are symptomatic (2) and symptom severity varies from mild to severe and from intermittent to persistent whereas exacerbations may occur in any patient regardless of severity. Most patients have an early onset of symptoms but the clinical phenotypes of allergic diseases may vary with age (3).

Acute, IgE-mediated, severe reactions (e.g. anaphylaxis (4)) occurring in patients sensitized to drugs (5), foods (6) or hymenoptera venoms (7) may be life-threatening. Many types of acute non-IgE-mediated allergic diseases or non-allergic diseases (1) such as aspirin hypersensitivity, hereditary angioedema (8), cold urticaria (9) or skin reactions such as DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) or Lyell syndrome (10) may also be life-threatening. Acute allergic (and related) diseases will not be considered in this document.

Major IgE-mediated chronic diseases include rhinitis (and conjunctivitis) (11), asthma (12), atopic dermatitis (13) and gastro-intestinal diseases. However, allergy is not the only mechanism involved (14-17). The present document will propose the definition of the severity of allergic and related (non-allergic origin) diseases: asthma, rhinitis (conjunctivitis), rhinosinusitis (18-20), atopic dermatitis and chronic urticaria (21, 22). Occupational diseases will not be considered in this document. Atopic and vernal conjunctivitis are severe diseases which may affect the vision. They will be considered in an update of this document.

Co-morbidities play a major role in severity, adding to the complexity of the disease and its management (11). However, in the current document, each disease will be considered separately since certain patients may have a severe disease (e.g. rhinitis) associated with a milder one (e.g. asthma).

Concepts of disease severity, activity, control and responsiveness to treatment are linked. Severity refers to the loss of function of the organs induced by the disease process. It may vary over time and needs regular follow up. Activity refers to the current level of activation of the biological network

perturbations that cause the disease and their clinical consequences. Control is the degree to which therapy goals are currently met. Disease activity and control can be viewed as opposites.

These concepts have evolved over time for asthma in the development of guidelines (23, 24), task forces (25) or consensus meetings (26). Up to 2006, asthma was classified by severity alone. Then, newer GINA guidelines replaced “grading by severity” with “grading by control” using the same items. Neither classification seems adequate when employed in isolation, nor is the classification of asthma by control alone sufficient (26). The NAEPP-EPR3 guidelines (23) made key suggestions combining impairment, response to treatment and risks. This concept was adopted by GINA (27). The uniform definition of severe asthma presented to WHO (28) was based on the NAEPP-EPR3 approach (23).

The aim of this paper is to generalize the approach of the uniform definition of severe asthma presented to WHO (28) for allergic and related diseases in order to develop a uniform definition of severity, control and risk, usable in most situations. This uniform definition will enable a better definition of severe allergic (and related) diseases for clinical practice, research (including epidemiology), public health purposes, education and the discovery of novel therapies (Table I).

## **1. Severity, control, response to treatment and risk in asthma**

The stratification and grading of asthma severity includes several components (Table 2). The most useful concept of asthma severity is based on the intensity of the treatment required to obtain control (26).

### **1.1. Control**

The level of asthma control incorporates current clinical control and exacerbations over the past 6 to 12 months (26). The measurement of current asthma control may be assessed by individual outcome measures such as daily or nocturnal symptoms, symptoms linked to activities or exercise, monitoring of peak flow or pulmonary function, as-needed use of relievers, and exacerbations. Used individually, these measures cannot accurately assess asthma control. A composite measure reflecting all key endpoints is more relevant (30) and has been used in guidelines (23, 2008 #27059, 31) (Table 3).

**Several scores for the control of asthma** have been validated and translated into many languages in adults and adolescents. Examples are:

- The Royal College of Physicians' three questions (32).
- The Juniper's Asthma Control Questionnaire (ACQ), based on 6 questions (ACQ6) and FEV<sub>1</sub> (ACQ7) (33). ACQ6 is more predictive than ACQ7 for asthma control (34).
- The Asthma Control Test (ACT), based on 5 questions (35, 36).

**In children**, a few asthma control questionnaires have been validated (37, 38).

None of these questionnaires appropriately assess **exacerbations** that are of importance in the assessment of the control of asthma and deserve further attention.

**Biomarkers** hold promise to capture complementary information regarding diagnosis and risk, but need to be validated with regard to control. Biomarkers are either not readily available or completely unavailable in most practice settings (39).

Although asthma therapy is primarily aimed at controlling the disease, the control level of asthma is independent of the step of asthma treatment. Control can be achieved at any severity level. A patient under total control may still have severe disease (e.g. an oral corticosteroid-treated patient). Patients achieving control with treatment have a lower risk of exacerbation than those who are uncontrolled (39).

## **1.2. Response to treatment**

Responsiveness to treatment has been demonstrated in studies assessing risk reduction during treatment. Studies at the community level show a considerable reduction of hospitalizations and deaths using appropriate management (40). Successful studies have been carried out in low- and middle-income countries (LMICs) (41, 42) or in deprived populations (43). The concept is therefore applicable to all populations and all countries. In the NAEPP-EPR3 guidelines (23), **resistance to therapy** is defined as uncontrolled asthma despite high-dose inhaled corticosteroids. For the INNOVATE trial (omalizumab), the European Medical Agency requested the assessment of asthma control in patients treated by inhaled corticosteroids and long-acting  $\beta$ -agonists (44).

### **1.3. Risk**

The concept of asthma risk (23) is intended to capture:

- The likelihood of future asthma exacerbations.
- Progressive loss of pulmonary function over time (or for children, reduced lung growth).
- Risk of adverse effects from treatment, which should always be considered carefully.

These domains respond differentially to treatment. The assessment of risk domain is more difficult than the evaluation of control.

### **1.4. Definition of asthma severity and control**

The definition of asthma severity, control and exacerbations proposed to WHO (28) took guidelines (23, 24) and the 2008 ATS/ERS Task Force report into consideration (26) (Figure 1). The recent consensus by U-BIOPRED (Unbiased BIOMarkers for the PREDiction of respiratory disease outcomes) from the Innovative Medicines Initiative (IMI) distinguishes severe asthma from alternative diagnoses by providing a stepwise algorithm to single out severe refractory asthma from difficult asthma based on insufficient therapy, poor treatment adherence and/or co-morbidity (45).

In patients appropriately diagnosed, severe asthma is defined by the level of current clinical control and risks as: “Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)” (28).

This proposal also includes wheezing disorders in pre-school children although there is dispute as to the age at which the label “asthma” can properly be applied (46, 47). A consensus has been proposed (48), but the conclusions are still under discussion.

## **2. Uniform approach to the severity of chronic allergic (and related) diseases**

Severe allergic (and related) diseases include 7 groups, each carrying different public health perspectives and challenges (Figure 2):

- **Diagnosis** is the first step, but it is not always easy as certain diseases may overlap (e.g. wheezing in preschool children).
- **Control** should be monitored in all patients with a diagnosis of chronic allergic disease using available tests. Control should be regularly evaluated and treatment adapted to its level.
- **Responsiveness to treatment** is the ease with which disease control is achieved by therapeutic interventions. For asthma or allergic rhinitis, effective treatments are available for most patients. Some diseases (e.g. some phenotypes of non-allergic rhinitis or urticaria) are more difficult to control.
- **Availability and affordability of the treatment:** The management of allergic disease depends on the context of national (or regional), economic and health provider settings and facilities, the health system as well as individual and societal variables (beliefs, cultural and socio-economic determinants). In high-income countries, treatments are available and, for most patients, affordable. However, in many LMICs and in some deprived areas of high-income countries, essential medicines may be available but are rarely affordable (50) although they should be in formularies. Even if medications are affordable, health professional knowledge concerning their optimal use is fragmented and requires training. Furthermore, the health system often lacks infrastructure for early diagnosis, follow up and education as well as legislation for appropriate referral.
- **Re-assessment of the diagnosis of the disease:** In patients who are uncontrolled despite optimal treatment, all reasonable efforts to eliminate other diagnoses must be made. Patients may suffer from a mild disease that is considered to be severe because it is underlined by another disease (e.g. wheezing in cystic fibrosis). It may be difficult to ascribe the differential severity to the allergic disease or the underlying one. On the other hand, there may be a degree of overdiagnosis which could lead to a false impression of severe disease.
- **Difficult-to-treat severe disease** represents a category in which partial or poor response to treatment reflects factors other than the disease alone. Issues to address in such cases include:

- Poor adherence to treatment.
- Incorrect inhalation technique.
- Adverse environmental circumstances such as passive smoke or allergen exposure.
- Psychosocial issues.
- And co-morbidities which cannot be controlled.

Any or all of these factors can be very important in any chronic disease.

- **Patients with treatment-dependent severe disease** are those who require the highest level of recommended treatment to maintain control. This requirement for high doses of medication and multiple medications suggests a component of treatment resistance or insensitivity. Although the disease is controlled, the patients are at risk of exacerbations if treatment is inappropriately reduced or becomes unavailable.
- **Patients with treatment-resistant severe disease** are those who are partially or poorly controlled despite the highest recommended treatment provided according to the guidelines existing in the country (or if guidelines do not exist, the highest controller medications available in the country). This insensitivity may not be an absolute phenomenon, but varies from patient to patient and with time.
- **Severity should be re-assessed at regular intervals** as it may change over time.

### 3. Severe allergic and related diseases

#### 3.1. Allergic and non-allergic rhinitis (and rhino-conjunctivitis)

Allergic rhinitis is an IgE-mediated reaction of the nasal mucosa. It is often associated with conjunctivitis (rhino-conjunctivitis) (11). Non-allergic rhinitis represents a group of heterogeneous diseases in which no IgE-mediated reaction can be demonstrated (17). Unmet clinical needs are clear in allergic and non-allergic rhinitis (51).

### **3.1.1. Control**

Control and severity are not well delineated in rhinitis. Using the new definition, measures of the control of allergic rhinitis include symptom scores, visual analogue scales (VAS) (52), objective measures of nasal obstruction such as peak inspiratory flow measurements, acoustic rhinometry and rhinomanometry (53), a recent modification of the ARIA severity classification (54), or patients' reported outcomes such as quality-of-life (11, 55, 56). More recently, a score with several items was proposed (57). It appears in rhinitis that a simple measure such as VAS may be sufficient to appreciate the control of the disease (58) and is particularly relevant to primary (59) or pharmacy care (60). The level of control of allergic rhinitis is assessed independent of the treatment step (52, 61).

### **3.1.2. Responsiveness to treatment**

Most patients with allergic rhinitis can be controlled using guideline-based treatment. However, among patients with moderate to severe symptoms who comply with an adequate treatment according to guidelines, up to 20% continue to be impaired by their symptoms. The GA<sup>2</sup>LEN-ARIA-WAO task force has proposed the new appellation of Severe Chronic Upper Airways Disease (SCUAD) for these cases where patients' symptoms are not sufficiently controlled despite their pharmacological treatment (51, 62). However, SCUAD applies to all nasal diseases irrespective of the allergic component. Allergic conjunctivitis is frequently associated with pollen-induced rhinitis but it is more difficult to control than rhinitis (63).

The efficacy of the treatment of non-allergic rhinitis is variable (17). It is heterogeneous in etiologies and inconsistently benefits from treatments which are effective in allergic rhinitis (64, 65).

### **3.1.3. Re-assessment of the diagnosis of the disease**

Many different conditions can mimic allergic and non-allergic rhinitis (66). Local allergic reactions with nasal but not systemic IgE antibodies (67) may be more important than initially thought. Misdiagnosis (e.g. nasal tumors, granulomas, cerebrospinal rhinorrhea) may lead to adverse outcomes if the patient is not appropriately re-assessed and reviewed.

### **3.1.4. Risk**

Allergic rhinitis impairs work (68, 69) and school performance (70, 71). Moreover, sedation may be enhanced using H<sub>1</sub>-antihistamines with sedative properties (72). The major long-term risk of allergic and non-allergic rhinitis is the development of asthma (73).

## **3.2. Chronic rhinosinusitis (CRS)**

### **3.2.1. Control**

Control and severity are not well delineated in CRS. Using the new definition, it is proposed that an overall symptom score measured by VAS may more accurately monitor control, and could be combined with disease specific (18, 74) and generic health status assessment instruments (18).

### **3.2.2. Responsiveness to treatment**

Responsiveness to treatment differs in CRS without nasal polyps (CRSsNP) and in CRS with nasal polyps (CRSwNP) (75-77). The principle of SCUAD also applies to CRS (51).

The pathophysiology of CRSsNP is poorly understood (19) and treatment options are limited to topical corticosteroids (18). According to clinical experience and reports, sinus surgery improves symptoms in the short-term in 65-90% of the cases.

In CRSwNP, symptoms may be controlled by topical corticosteroid treatment in mild to moderate localized disease (78-80). However, in severe polyposis and asthma co-morbidity, repeated courses of intranasal and/or oral corticosteroids are usually insufficient in controlling symptoms. Repeated sinus surgeries may be needed with inconsistent clinical benefits (81).

### **3.2.3. Re-assessment of the diagnosis of the disease**

The differential diagnosis includes all forms of rhinitis, as well as underlying sinus diseases such as cystic fibrosis, primary ciliary dyskinesia, non-invasive fungal sinusitis, allergic fungal sinus disease and invasive forms (18). Sinus headache needs to be differentiated from neurological, ocular or facial pains. Other rare diagnoses are Wegener's, other granulomas disease, cocaine abuse or lymphomas. Any unilateral obstruction, pain and bleeding has to be investigated by a specialist to exclude malignancies, inverted papilloma, meningoceles and other serious conditions (82).

#### **3.2.4. Risk**

Very rarely, acute complications with a spread of the disease into the orbit, the meninges, the brain or frontal bone (osteomyelitis) may develop in the course of acute exacerbations of the disease. Mucocoeles develop slowly as long-term complications after surgery, but can also develop spontaneously.

About 10-15% of the CRSsNP and up to 45% of the CRSwNP patients present or will develop comorbid asthma, which may be severe (83). CRSwNP may also develop into a systemic disease such as aspirin-exacerbated respiratory disease (84), or Churg-Strauss syndrome (85). Allergic fungal sinus disease may be accompanied by allergic bronchopulmonary aspergillosis (ABPA).

Repeated courses of oral corticosteroids in patients with persistent CRS may affect bone metabolism and lead to HPA-axis dysfunction (79, 86).

### **3.3. Chronic urticaria**

Urticaria describes the spontaneous or inducible occurrence of wheals and flares often accompanied by pruritus which generally subside within hours, while new lesions occur. Chronic urticaria is a group of spontaneous or inducible diseases characterized by symptom persistence or reoccurrence over 6 weeks (21, 87) with several clinical unmet needs (88). Angioedema describes a deep swelling in the dermis which can be accompanied by pain and predominantly involves soft tissues, e.g. in the face (eyelids, lips) or genital area.

#### **3.3.1. Control**

Control and severity are not well delineated in chronic urticaria (88). Using the new definition, control can be assessed by the daily number of wheals and by the intensity of the pruritus as assessed using the weekly urticaria activity score (UAS7) (89) and/or the chronic urticaria quality of life questionnaire (CU-Q2oL) (90, 91). Patient diaries and health-related quality of life instruments can be used.

#### **3.3.2. Responsiveness to treatment**

In chronic urticaria, symptomatic treatment is the rule since causal treatment is rarely effective (22, 88). Chronic urticaria can be fully controlled in a minority of patients by following the guideline-recommended step-up approach. The aim of the treatment in chronic urticaria is the absence of symptoms, i.e. the complete protection from the reoccurrence of wheals, pruritus, and angioedema. This can be achieved in less than half of all patients by using licensed doses of non-sedating oral H<sub>1</sub>-antihistamines, the guideline-recommended first step therapy and only in-label treatment option (92).

### **3.3.3. Re-assessment of the diagnosis of the disease**

Urticaria vasculitis and auto-inflammatory disorders (e.g. cryopyrin-associated periodic syndrome (CAPS) (93), Schnitzler syndrome (94)), mastocytosis (95) and hereditary or other complement associated disease (8) must be considered in patients with chronic spontaneous urticaria who present with wheals and signs of systemic inflammation or recurrent angioedema without wheals. These diseases are associated with a high risk of severe morbidity and mortality.

### **3.3.4. Risk**

The risks in chronic inducible urticaria are different from those in chronic spontaneous urticaria and are specific for each inducible urticaria. In general, low thresholds for trigger intensity and for trigger exposure time are indicators of high disease activity (96).

Some inducible urticarias such as cold urticaria and exercise-induced urticaria can induce severe systemic reactions including anaphylactic shock which may lead to death (e.g. swimming in cold water).

Chronic spontaneous urticaria patients are at risk of developing comorbidities such as autoimmune disorders (e.g. autoimmune thyroiditis) (97).

Since many patients cannot be controlled using recommended doses of medications, uncontrolled patients often develop depression and anxiety (98).

Many chronic urticaria patients are at risk of experiencing adverse effects of their therapy since they often receive doses higher than those recommended as well as the off-label use of other medications.

## **3.4. Atopic dermatitis**

### **3.4.3. Control**

Several severity tests of current atopic dermatitis (AD) have been published. Three measurements (SCORing Atopic Dermatitis [SCORAD] (99), Eczema Area and Severity Index [EASI] (100), and Patient-oriented Eczema Measure [POEM]) have been tested sufficiently and performed adequately (101). Other scoring systems such as the Langeland-Rajka score have been designed to include information about the recent past (3 months) of the disease (102). Besides the objective parameters such as erythema or excoriations, the more subjective aspect of pruritus/itching is of great importance in the evaluation of the disease since it also reflects the severity. SCORAD also includes a VAS component for this particular symptom. Furthermore, SCORAD has been used to classify AD into 3 main severity forms: mild (<15), moderate (>15 and <40) and severe (>40). Recently, a patient-oriented version of SCORAD (PO-SCORAD) was proposed and validated, allowing the estimation of severity by the patients themselves or the caregivers of affected children (103). These scoring systems only provide a snapshot of the current disease situation for a given patient at a defined time point (104) and should be more appropriately considered as control tests.

Impaired QOL is common in AD, both in children (patients and caregivers) and adults. Impaired QOL may be observed in infants (105). Several QOL measures (disease-specific and generic) have been used (106).

### **3.4.4. Responsiveness to treatment**

Most cases of patients seemingly resistant to the treatment are certainly explained by a lack of correct implementation of the guidelines (107, 108). This can be improved by an intense treatment under supervision and adapted educational programs. Thus, as in other chronic diseases, the responsiveness and control of the disease is tightly dependent on the compliance of the patients/parents. However, truly therapy-resistant AD severe cases exist, which may be explained by a particular genetic predisposition. There are currently no studies available having addressed this issue, but it is estimated that no more than 5% of AD belong to this group (13).

### **3.4.5. Re-assessment of the diagnosis of the disease**

Depending on the age of onset, AD can be misdiagnosed (107, 108). In preschool children, the spectrum of differential diagnosis is very wide including either common diseases such as psoriasis or rather rare conditions such as Schwachman Diamond's syndrome (also named Burke-Syndrome) agammaglobulinaemia, ataxia telangiectasia (109) and histiocytic disorders (110). In adults, other diseases such as seborrheic dermatitis or cutaneous T cell lymphoma have to be excluded (111).

### **3.4.6. Risk**

Atopic dermatitis during infancy is a risk factor for other atopic diseases occurring later in childhood (112-114). This is probably the case for about 30% of AD patients, mostly with early onset, i.e. in infancy. During the first year of life, atopic dermatitis is mostly related to food allergy, but very often spontaneously improves after one to two years. Children with early onset, a filagrin mutation and having food allergy (mainly peanut) have almost a 100% risk of developing allergic asthma (115).

On the other hand, about 30% of adult patients seem to develop specific IgE against self-proteins, suggesting an autoimmune form of AD in adulthood for which allergen avoidance is therefore meaningless (116).

Due to a strongly impaired innate immunity response of the epidermal barrier in AD, these patients have a high risk of developing superinfections with bacteria such as *Staphylococcus aureus*, fungi such as *Malassezia sympodialis* or herpes simplex virus or causing eczema herpeticum, a severe complication of AD (117, 118).

The increased permeability of the skin associated with chronic inflammation may also favor sensitization to haptens, causing increasing rates of allergic contact dermatitis (119).

## **4. Application to children**

### **4.1 Severe problematic asthma**

Severe problematic asthma is probably as common in children as in adults, with approximately 4-5 % of children with asthma (120). Phenotypes of severe problematic asthma differ in children and in adults (121, 122). A proposal with a 4-step procedure for the diagnosis and assessment of severe problematic asthma in childhood has recently been published (123). The steps include (a) a full diagnostic work-up that may exclude other chronic lung diseases which may mimic severe asthma; (b) a multidisciplinary assessment to identify factors of importance including co-morbidities; (c) an assessment of the pattern of inflammation and (d) a documentation of the level of corticosteroid responsiveness.

## **4.2 Allergic rhinoconjunctivitis and chronic rhinosinusitis**

For children, there is an increasing awareness that rhinitis may start in very early childhood, but definitions and control measures are largely lacking. Treatment challenges are frequently more pronounced in children, with sparse documentation of pharmacological intervention in severe disease, which is often part of complex atopic disease presentation.

It is difficult to diagnose allergic rhinitis/conjunctivitis in preschool children. Furthermore, children of this age have frequent infections of the upper airways, and management is challenging due to a lack of guidelines, co-morbidities and a lack of objective parameters to guide diagnosis.

There are specific problems in childhood/adolescence such as general symptoms of malaise occurring during important school and university examinations in the spring pollen season (124).

In children, it may be difficult to distinguish between persistent non-allergic rhinitis and rhinitis associated with recurrent respiratory tract infections.

Cystic fibrosis or primary ciliary dyskinesias are important to rule out in patients suspected of chronic rhinosinusitis.

## **5. Importance of a uniform approach**

### **5.1. Subphenotyping severe/uncontrolled diseases**

Allergic diseases represent complex multi-dimensional diseases with marked heterogeneity depending on environmental factors and socio-economic determinants. Tools to phenotype individual disease subtypes are now being developed in order to characterize the various patterns of triggers that induce symptoms, different clinical presentations of the disease, and different inflammatory markers. This is the case for asthma (US SARP: Severe Asthma Research Program (125, 126), U-BIOPRED, (45, 127) and allergic disease onset (MeDALL, Mechanisms of the Development of ALLergy, FP7, (49)) but more research is needed to identify allergic disease subphenotypes or endophenotypes (128) based on severity.

Phenotyping subtypes can be used to characterize and predict disease severity, progression, and response to treatment, and may help identify unique targets for treatment (26). Heterogeneity also exists within each dimension of the disease (e.g. eosinophils and asthma severity) (129, 130), across diseases (e.g. eosinophils in asthma and COPD) and in relation to co-morbidities (131, 132). Phenotypes may also change over time.

Phenotype heterogeneity may reflect a priori defined hypotheses or lead to the generation of novel hypotheses through multiple logistic regression (131, 133), cluster analysis (126, 132) or free scale networks. However, a uniform definition applied worldwide is needed, and then detailed subphenotyping of severe allergic diseases may be approached (28).

### **5.2. Clinical practice**

A uniform definition provides a framework to decide who needs targeting for treatment or improved treatment (28). It will help in the delivery of appropriate health care through better organization for diagnosis and treatment in primary care and/or specialist clinics. A multidisciplinary approach is recommended in patients with severe allergic diseases (39). For this, the use of a common language across primary, secondary and tertiary care is important. A major challenge is that their *functional*

differentiation of level of care turns into a segregation of patient flows. The use in guidelines of the same definitions and criteria across the board of health care will facilitate a smooth transfer of patients from primary care to more specialized care and back, according to their needs. Communication with patients or parents of patients should be focused on providing information on the need for therapy and the consequent use of therapy, as well as on the risks of not complying with these recommendations.

### **5.3. Personalized medicine**

The main challenge for allergic diseases in the 21<sup>st</sup> century is to understand their complexity. Identification of the underlying mechanisms will help the prognosis, diagnosis and treatment of disease (49) as well as the transition to predictive, preventive, personalized and participatory (P4) medicine (134). The uniform approach of severity is perfectly embedded within this new paradigm.

### **5.4. Registries for severe allergic (and related) diseases**

Severe asthma registries provide a foundation upon which to generate a greater understanding of public health needs, to define phenotypic heterogeneity to inform the design of research studies and to improve overall clinical care (28). Registries will help in the surveillance of severe allergic diseases. Data from the registries may provide evidence of inadequacies in the control of diseases. The establishment of an internationally-agreed definition of severe allergic (and related) diseases will provide the opportunity to develop a single registry in order to capture core information in both developed and developing countries. This is particularly relevant to the worldwide changing demography of allergic diseases.

### **5.5. Clinical trials**

For clinical trials, it is essential to have clarity as to what definitions have been used - severity assessed before treatment or after treatment, and in this case, which treatment was used. In addition, clinical trials should consider co-morbidities and confounding conditions necessary for the adequate assessment of clinical responses (e.g. smoking and asthma) or effectiveness of different therapeutic approaches.

## **5.6. Registration of medicines and reimbursement**

Controlled trials designed with a uniform approach of severity (135) will be more easily evaluated by the agencies for approval and by the Health Technology Assessment agencies (such as NICE) for reimbursement.

## **5.7. Research on mechanisms and genetics**

More research into severe allergic diseases is urgently needed. Many large collaborative studies are already ongoing for severe asthma (125-127), but not for the other diseases. A uniform definition and a collaborative approach to epidemiological, genetic and mechanistic research are important. Different levels of phenotype characterization (granularity) can be applied to assess phenotypic characterization in patients with severe allergic (and related) diseases. For the success of such approaches, it is important to develop global partnerships and platforms to ensure the application of standard methodology and protocols to promote the collection and sharing of samples and data through appropriate infrastructure in different countries (28).

## **5.8. Epidemiology**

In epidemiologic population studies, standardized definitions are fundamental. It is often difficult to assess severity since many patients are undertreated. The uniform definition of severe allergic (and related) diseases accounts for these patients and articulates time frames for the appropriate assessment of severity and control. Thus, the definition will facilitate epidemiological research, understand modifiable risk factors and enable comparisons across studies in different populations. Control usually refers to events occurring recently (over the last 2-4 weeks) whereas severity refers to those occurring over a long period of time (e.g. 6-12 months).

## **5.9. Public health planning**

For public health purposes, a uniform definition of severe allergic (and related) diseases is needed to identify the prevalence, burden and costs incurred by severe patients in order to improve quality of

care and optimize health care planning and policies. This definition will provide support for more precise calculations on the needs and costs of medications in a country.

### **5.10.Developed and developing countries**

A uniform definition of severe allergic (and related) diseases should be applicable to the local and geographical conditions of all countries, phenotypes, risk factors, availability and affordability to treatment differing widely around the world. Research must be planned to evaluate the phenotypes of “severe” allergic (and related) diseases from different countries.

### **5.11.Development of novel therapies**

For treatment-resistant severe allergic (and related) diseases, more detailed cellular and molecular phenotyping is needed to identify new targets for the development of novel therapies and to improve current therapies in a cost-effective manner. Ultimately, novel therapies studied in clinical trials should help define the pathogenesis of the diseases and determine the importance of the treatment in large patient populations or in sub-populations of patients based on the concept of distinct phenotypes.

## **Conclusions**

It is likely that a uniform definition of severe allergic diseases will help in a better understanding of phenotypes but there is a need for a validation process of the proposed definition for severe chronic allergic diseases across different populations and countries with different income, age groups and different disease phenotypes.

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**Table 1: Goals of the current paper**

- The current document develops a common strategy to the severity of chronic allergic (and related) diseases taken individually.
- It does not consider acute allergic reactions such as anaphylaxis.
- It does not take into account co-morbidities (29).
- It is intended to be used by all stakeholders involved in the management or research of allergic (and related) diseases.

**Table 2: Components contributing to asthma severity**

From (23) and (28)

- 1- Level of control
  - Current clinical control (impairment): Symptoms, health status and functional limitations over previous 2-4 weeks
  - Severe exacerbations over previous 6-12 months (use of oral or systemic corticosteroids)
- 2- Level of current treatment prescribed
- 3- Inhalation technique and compliance to treatment
- 4- Responsiveness to treatment
- 5- Exposure to aggravating factors
- 6- Risk

**Table 3: Level of asthma control in patients ≥ 5 years of age**

From (28) (Adapted from GINA 2006 (31) and 2007 NAEPP-EPR3 (23))

Any of the components places the patient in the category

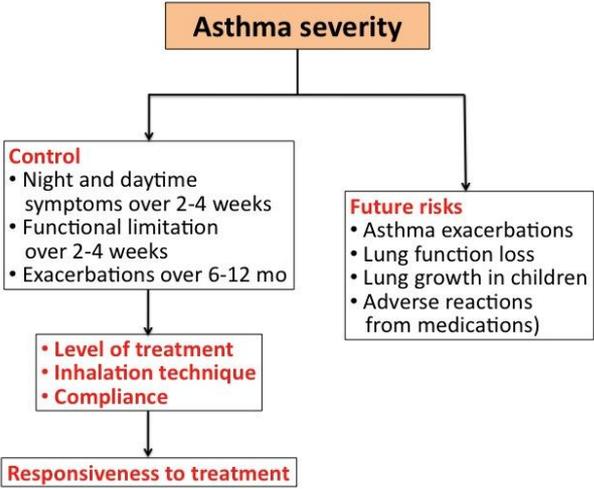
Control level	Well controlled**	Partially controlled**	Poorly controlled**
Daytime symptoms in the past 2-4 weeks	≤ 2 days / week but not more than once a day	> 2 days / week Or more than once a day but ≤ 2 days / week	Throughout the day
Limitations of activities in the past 2-4 weeks	None	Some limitation	Extremely limited
Nocturnal symptoms/awakenings in the past 2-4 weeks	None	≤ 2 nights / week	> 2 nights / week
Need for short-acting inhaled β <sub>2</sub> -agonists in the past 2-4 weeks	≤ 2 days per week	> 2 days per week	Several times a day
Lung function FEV <sub>1</sub> or PEF* FEV <sub>1</sub> /FVC (<11 yrs of age)	≥ 80% predicted or personal best ≥ 80%	60-79% predicted or personal best 75-79%	<60% predicted or personal best <75%
Exacerbation(s) (requiring oral or systemic corticosteroids)***	0-1/ yr	2/yr	Frequent (>2/yr)
Consider severity and interval since last exacerbation			

\*: FEV<sub>1</sub> or PEF may be ≥ 80% predicted in patients with severe persistent asthma

\*\* : \* For well controlled asthma, all components should be present; for partially or poorly controlled asthma, any of the components places the patient in the category

\*\*\*: At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control of severity.

Figure 1: Evaluation of asthma severity (from (23))



**Figure 2: Uniform approach for the definition of severe allergic (and related) diseases**

(adapted from (49))

