

Unmet needs in severe chronic upper airway disease (SCUAD)

Jean Bousquet, MD,^{a,*†} Claus Bachert, MD,^{b,*} Giorgio W. Canonica, MD,^{c,*†} Thomas B. Casale, MD,^{d,†} Alvaro A. Cruz, MD,^e Richard J. Lockey, MD,^{f,†} and Torsten Zuberbier, MD,^{g,*} on behalf of the extended Global Allergy and Asthma European Network, World Allergy Organization and Allergic Rhinitis and its Impact on Asthma Study Group§ Montpellier, France, Ghent, Belgium, Genova, Italy, Omaha, Neb, Salvador, Brazil, Tampa, Fla, and Berlin, Germany

Although the majority of patients with chronic upper airway diseases have controlled symptoms during treatment, many patients have severe chronic upper airway diseases (SCUADs). SCUAD defines those patients whose symptoms are inadequately controlled despite adequate (ie, effective, safe, and acceptable) pharmacologic treatment based on guidelines. These patients have impaired quality of life, social functioning, sleep, and school/work performance. Severe uncontrolled allergic rhinitis, nonallergic rhinitis, chronic rhinosinusitis, aspirin-exacerbated respiratory diseases, or occupational airway diseases are defined as SCUADs. Pediatric SCUADs are still unclear. In developing countries SCUADs exist, but risk factors can differ from those seen in developed countries. Comorbidities are common in patients with SCUADs and might increase their severity. The present document is the position of a group of experts considering that SCUADs should be considered differently from mild chronic upper airway diseases. It reviews the state of the art, highlighting gaps in our knowledge, and proposes several areas for a better understanding, prevention, and management of SCUADs. This document can also serve to optimize the pharmacoeconomic evaluation of SCUADs by means of comparison with mild chronic upper airway diseases. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Severe chronic upper airway disease, rhinitis, rhinosinusitis

From ^aUniversity Hospital, Montpellier; ^bUZG, University Hospital Ghent; ^cthe Allergy and Respiratory Diseases Clinic, University of Genova; ^dCreighton University, Omaha; ^eProAR-FMB, Federal University of Bahia, Salvador; ^fJoy McCann Culverhouse, University of South Florida College of Medicine, Tampa; and ^gAllergy Centre Charité, Charité-Universitätsmedizin Berlin.

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†Members of the Board of the World Allergy Organization.

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Reprint requests: Jean Bousquet, MD, PhD, Service des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, 371, Avenue Doyen Gaston Giraud, F-34295 Montpellier Cedex 5, France. E-mail: jean.bousquet@inserm.fr.

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The upper airway includes the nasal cavity and sinuses and the pharynx, and ends at the upper level of the larynx. Chronic upper airway diseases encompass intermittent and persistent inflammatory diseases of the upper airways, excluding those induced by acute infection or anatomic abnormalities. These include allergic rhinitis (AR), nonallergic rhinitis (NAR), chronic rhinosinusitis (CRS) with and without nasal polyposis, and occupational rhinitis. These disorders are extremely common and present in all ages, all ethnic populations, and all countries. In addition to the increasing public health effect of these diseases, the socioeconomic effect is well recognized.^{1,2} Comorbidities are common and increase the complexity of the management and costs.

Although the majority of patients with chronic upper airway diseases have controlled symptoms during treatment, many patients have severe chronic upper airway diseases (SCUADs). SCUAD defines those patients whose symptoms are inadequately controlled despite adequate (ie, effective, safe, and acceptable) pharmacologic treatment based on guidelines. In some patients, SCUADs can be associated with different forms of upper airway diseases (eg, AR and NAR), and a precise diagnosis is needed. These patients have impaired quality of life, social functioning, sleep, and school/work performance.

The prevalence and costs of chronic upper airway diseases continue to grow worldwide. However, health care expenditures, especially in the field of reimbursement, have been reduced in many countries. Some chronic upper airway diseases, such as AR, are not regarded as severe diseases, reducing the possibility for reimbursement of medications. This might further increase undertreatment. Moreover, it might limit novel treatment discovery because the pharmaceutical industry will only accept the high costs for drug development if these drugs can be licensed in the future, reimbursed, and used by patients.

The present document is the position of a group of experts considering that SCUADs should be tackled with special attention and with the objective of incorporation within community-based primary care where possible and referral to specialist care when needed. It reviews the state of the art, highlighting gaps in our knowledge, and proposes several areas for a better understanding, prevention, and management of SCUADs. This document can also serve to optimize the pharmacoeconomic evaluation of SCUADs by means of comparison with mild chronic upper airway diseases.

AR Definition

Rhinitis is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms, including anterior or posterior rhinorrhea, sneezing, nasal blockage, and/or itching.

Abbreviations used

AR:	Allergic rhinitis
COPD:	Chronic obstructive pulmonary disease
CRS:	Chronic rhinosinusitis
CT:	Computed tomography
NAR:	Nonallergic rhinitis
SCUAD:	Severe chronic upper airway disease

AR, the most common form of noninfectious rhinitis, is associated with an IgE-mediated immune response against allergens.²

Prevalence and burden

AR is a global health problem that causes major illness and disability worldwide. The World Health Organization has recently estimated that at least 400 million persons worldwide have AR (without asthma), and 200 million have AR and asthma.³ It is likely that these estimates are largely underestimated.

Impairment of quality of life is seen in adults and children.² Patients might also have sleep disorders, emotional problems, and impairment in activities and social functioning. Poorly controlled symptoms of AR might contribute to sleep loss or disturbance.⁴ Moreover, H₁-antihistamines with sedative properties can increase functional disturbances in patients with AR.

AR affects school and work.² Although several economic analyses of AR have been published, there are relatively few cost-of-illness studies. The economic effect of AR is often underestimated because the direct costs of the disease are lower than those of a number of other chronic illnesses. However, the indirect costs are substantial.²

AR defined as a SCUAD

Heterogeneity of AR. Although the classification into seasonal and perennial AR is unlikely to be involved in heterogeneity, patients can be sensitized to a few allergens or to many allergens (monosensitized and polysensitized).² It is not clear whether polysensitization induces a more severe AR phenotype because of more chronic inflammation. Patients present with AR of variable severity or duration. In addition, nonallergic triggers can variably interact with inflammation induced by allergens. There are many other causes of heterogeneity that need to be better understood.

Severity and control of AR. The Allergic Rhinitis and its Impact on Asthma classification defines mild and moderate/severe AR.¹ It might be useful to consider mild, moderate, and severe AR, but at present, this classification has not led to new therapeutic algorithms. In patients with asthma, the control of the disease differs from the severity and is independent of asthma medications. Although such an independent relationship was also suspected in patients with AR, this important concept was confirmed in a recent study in which it was found that the severity of rhinitis is independent of its treatment.⁵ Thus, as for asthma, an important concept is to consider “control,” and a SCUAD should refer to patients whose symptoms are uncontrolled with treatment based on guidelines.

Current treatments are insufficient for the control of many patients. In clinical trials, symptoms are improved but many

patients still remain symptomatic. This was also found in a trial comparing guidelines and free treatment choice.⁶ It is considered that the symptoms of around 20% of patients with severe persistent rhinitis are not controlled, and some of these patients have severe symptoms, particularly associated eye symptoms.⁷ It is likely that allergen-specific immunotherapy can improve these severe symptoms that are uncontrolled by medications, but more studies are required. Novel treatments are needed, although there is insufficient research development. The definition of SCUAD might prompt the pharmaceutical industry to increase research in the field.

Unmet needs

- Define control and severity of AR and assess direct and indirect costs of SCUAD.
- Define phenotypes/genotypes in relationship to disease heterogeneity, immune responses, and inflammation and their relevance to the severity and control of AR by medications or immunotherapy.
- Find novel treatments to control symptoms in the vast majority of patients and meet the current unmet therapeutic needs.
- Perform pharmacoeconomic studies supporting the costs for the treatment of SCUAD.

NAR

Definition

NAR can be defined on the basis of chronic nasal symptoms that are not evidently caused by IgE-dependent mechanisms or specifically related to structural deformity. Several nonallergic conditions can cause symptoms similar to those of AR: infections, hormonal imbalance, physical and chemical agents, and the use of certain drugs.⁸ The allergic nature of the disease might be underappreciated in the absence of evidence of systemic IgE sensitization because local IgE production might be more common than proposed and thereby underlie disease expression.⁹ The role of infection needs to be more clearly delineated because chronic infection can lead to NAR. The nasal mucosa is frequently exposed to bacterial and viral infections. Airway epithelial cells, the primary site of infection, provide a link between the innate and specific immune response to infectious agents. The immune system has innate and adaptive components, which cooperate to protect the host against infections. Immediate activation of innate immunity relies on the detection by the host of conserved microbial motifs known as pathogen-associated molecular patterns.⁸ Moreover, NAR phenotypes are poorly understood and represent one of the major unmet needs of the field.¹⁰ It is possible that many patients have both AR and NAR.

Prevalence and burden

NAR is common. In population surveys, the prevalence of allergy among subjects with nasal symptoms is less than 50%.^{11,12} Thus NAR probably affects far more than 400 million persons worldwide. However, its prevalence is unknown. Both children and adults are affected.

NAR defined as a SCUAD

The severity of NAR and its effect on quality of life and socioeconomic burden are also a matter of discussion because more studies need to be carried out in well-defined patients with NAR.

Unmet needs

- The phenotypes/genotypes of NAR in children and adults need to be evaluated to better understand NAR prevalence, risk factors, diagnosis, and management.⁸ It is important to differentiate between infectious rhinitis, AR, and NAR because management differs for each of these cases. Genomic studies in large numbers of well-phenotyped patients are key. In these studies, patients with mild chronic upper airway diseases and SCUADs should be differentiated, and social and economic aspects should be clearly delineated.
- Links with asthma and other comorbidities need to be investigated for mild and severe NAR.
- Mechanistic studies should be carried out to better understand the disease or diseases and risk factors and to guide toward an improved diagnosis and therapy.⁸ These studies need to take into account the heterogeneity of NAR. It is possible that the epithelium, neuronal mechanisms, T and B cells, innate immunity (adjuvants), and possibly autoimmune responses play a role in NAR and also contribute to the symptoms of AR. Prospective viral epidemiology might help to differentiate between the infectious and hyperreactive components.
- The treatment of NAR is another unresolved problem. Novel treatments are needed, especially in patients with SCUAD. Many studies have found that NAR inconsistently benefits from treatments effective in patients with AR.¹³ However, patients with NAR might respond differently to treatments depending on their phenotype.

CRS AND NASAL POLYPOSIS

Definition and mechanisms

Sinusitis and rhinitis frequently coexist, and have been proposed as *rhinosinusitis*.^{14,15} However, the term rhinosinusitis is not globally accepted.¹⁶ Until recently, rhinosinusitis was classified, based on duration, into acute, subacute, and chronic. This definition did not incorporate the severity of the disease. Also, because of the long timeline of 12 weeks in CRS, it can be difficult to discriminate between recurrent acute rhinosinusitis and CRS with or without exacerbations. The severity has been classified as mild, moderate, and severe.

CRS (including nasal polyps) is an inflammation of the nose and the paranasal sinuses.¹⁴ The diagnosis of CRS cannot be determined based on symptoms alone and requires an investigation by specialists with nasal endoscopy and computed tomographic (CT) scanning. It is therefore likely that underdiagnosis is common in the general population.

Prevalence and burden

Epidemiologic data based on questionnaires for CRS are limited and difficult to assess. Because most epidemiologic studies on CRS are based on questionnaires, a large proportion of these patients might only have NAR without significant sinus involvement. According to the National Institute of Allergy and Infectious Diseases Fact Sheet, CRS is the most commonly reported chronic disease in the United States, affecting around 16% of the total population. However, the prevalence of doctor-diagnosed CRS is much lower. In Sweden, Finland, or Korea, in studies with an appropriate nasal examination, CRS/nasal polypoid prevalence is around 3% to 5%.¹⁴

CRS defined as a SCUAD

In most surveys, patients with CRS have an impaired quality of life.¹⁷ They have more bodily pain and worse social functioning than patients with chronic obstructive pulmonary disease (COPD), congestive heart failure, or back pain.¹⁸ CRS represents a significant health problem, resulting in frequent surgical procedures and a large financial burden on society.¹⁴

Unmet needs

- Well-conducted epidemiologic studies are needed to determine the real prevalence and severity of CRS (SCUAD), as well as its effect on social/professional life and costs.
- The classification of CRS (and nasal polyposis) is still unclear. Studies have shown that CRS represents several distinguishable diseases with different inflammatory and remodeling patterns.¹⁹
- The role of allergens and panallergens, such as *Staphylococcus aureus*,²⁰ needs to be better investigated.
- Some, but not all, patients with CRS are responsive to corticosteroids, and many patients still need surgery.¹⁴ Development plans are needed to determine the effectiveness of treatments.
- The identification of phenotypes/genotypes of CRS will be of interest for defining patients responding to corticosteroids and finding novel treatments to reduce unnecessary surgical interventions. Mediator and cellular mechanisms associated with severity should be identified to determine new diagnostic tools and novel therapies.

ASPIRIN HYPERSENSITIVITY

Definition, epidemiology, and burden

Aspirin hypersensitivity, defined as CRS and asthma after aspirin ingestion (Fernand-Widal triad, 1922), affects only a small percentage of the general population (0.6% to 2.5%). However, it is one of the most common adverse reactions to drugs.²¹ Moreover, certain patient groups, such as asthmatic patients, are at an increased risk. This phenomenon is not restricted to aspirin because all nonsteroidal anti-inflammatory drugs that inhibit the enzyme COX display a high incidence of cross-sensitivity.

Aspirin hypersensitivity defined as a SCUAD

Many patients with aspirin hypersensitivity present with SCUAD (extensive nasal polyposis and anosmia) associated with severe asthma, which runs a protracted course, despite the avoidance of aspirin and cross-reacting drugs. The term aspirin-exacerbated respiratory disease has recently been proposed.²² The disease prevalence might well be underestimated because there is no easily-available test that helps define those with aspirin-exacerbated respiratory disease.

The disease is responsive to corticosteroids but might require long-term treatment with oral corticosteroids. Leukotriene modifiers improve the control of asthma treated with high doses of inhaled corticosteroids.

Unmet needs

- The study of mechanisms of aspirin hypersensitivity might be of importance for finding novel therapeutic targets for the treatment of SCUAD and severe asthma.

TABLE I. Symptoms and possible causes of NAR

NAR is a chronic disease with some, but not necessarily all, of the following symptoms:
Primary symptoms
Nasal congestion
Rhinorrhea
Other associated symptoms
Postnasal drip in the absence of a pharyngeal cause of mucus hypersecretion or acid reflux disease
Throat clearing
Cough
Eustachian tube dysfunction (ear pressure/popping/pain)
Sneezing
Hyposmia or hyperosmia
Facial pressure/headache
Symptoms of NAR can be intermittent or persistent, elicited by defined triggers, or both. These triggers can include:
Cold air
Vasomotor triggers
Physical agents, including changes in climate (temperature, humidity, and barometric pressure)
Chemical agents, including strong smells (eg, perfume, cooking smells, flowers, and chemical odors)
Environmental tobacco smoke
Changes in sexual hormone levels
Pollutants and chemicals (eg, volatile organic compounds)
Exercise
Alcohol ingestion
NAR might present with concomitant conditions, such as:
Food-related rhinorrhea (gustatory)
Rhinitis in elderly subjects
Differential diagnosis is possible, such as:
CRS or nasal polyps
Aspirin-related CRS, nasal polyps, or asthma
Acute infectious rhinitis or rhinosinusitis (eg, viral upper respiratory tract infections, bacterial/fungal rhinosinusitis, bacterial rhinitis)
Anatomic abnormalities
Cerebrospinal fluid leak
Atrophic rhinitis (primary and secondary)
Granulomatous rhinitis (sarcoid and Wegener syndrome)
Ciliary dyskinesia

Adapted with permission from Scarupa and Kaliner.⁷

OCCUPATIONAL SCUAD

The workplace environment contributes significantly to the general burden of asthma, AR, and NAR because of occupational sensitizing agents and irritants (reactive airway dysfunction syndrome). These conditions can be caused or exacerbated by work and are often associated and tightly interrelated, leading to the concept of work-related airway diseases.

Many patients with work-related airway diseases are exposed to several occupational and nonoccupational risk factors, and it might not be easy to demonstrate the occupational origin of the disease.²³

Work-related airway diseases can have long latency periods. Once these conditions have developed, they are usually chronic, although they might improve with occupational avoidance. However, once established, they often persist despite avoidance of the responsible risk factors. Early recognition of work-related airway diseases (rhinitis or mild asthma) is an essential step in preventing the onset of severe persistent asthma and SCUADs by the early removal of patients from exposure to the causative agent.

SCUAD IN CHILDREN

In children, AR and NAR are common, but SCUADs are poorly defined in preschool children. There is anecdotal evidence that SCUADs are common in preschool children, but data are lacking. The relationship between SCUADs and infectious diseases and cystic fibrosis needs more clarification in both preschool children and schoolchildren.

Unmet needs

- Assessment of prevalence and risk factors (especially early viral infections) for chronic upper airway diseases (eg, AR, NAR, and CRS) and SCUADs in children, including genome-wide characterization in population-based studies, with special attention to NAR.
- Longitudinal evaluation of the effect of early detection, prevention, and management of chronic upper airway diseases on the development of lower airway diseases.
- Large-scale cooperative cohorts with a focus on the upper airways to better understand SCUAD in children.

SCUAD IN DEVELOPING COUNTRIES

Reports on the frequency of chronic upper airway diseases in developing countries are scarce. The prevalence of rhinitis is generally lower in low- and middle-income countries than in affluent societies, but it is increasing steadily.²⁴ However, in some urban centers of low- and middle-income countries, a high prevalence of asthma and rhinitis has been reported that is comparable with that of high-income countries.²⁴ A possible explanation for the contradictory observations is that atopy might not be the most important risk factor for rhinitis in developing countries.¹² In developing countries presenting a high prevalence of rhinitis, susceptibility to exposure of the respiratory tract to inhalable hazards, including indoor and outdoor air pollution, cold dry air, viral infections, and bacterial products, could promote inflammation and damage on the respiratory mucosa.

Unmet needs

- Assessment of prevalence and risk factors for chronic upper airway diseases (eg, AR, NAR, and CRS) and SCUADs, including genome-wide characterization in population-based studies, with special attention to NAR.
- Longitudinal evaluation of the effect of early detection, prevention, and management of chronic upper airway diseases on the development of lower airway diseases.

SCUAD AND COMORBIDITIES

The relationships between upper airways and asthma or some diseases, such as gastroesophageal reflux, bronchiectasis, or sleep apnea syndrome, have been largely studied, but relationships with COPD need further analysis.

AR and NAR and severity and control of asthma

Both AR and asthma are systemic inflammatory conditions and often comorbidities. AR is frequently associated with ocular

TABLE II. Priorities for research in SCUADs

Definition of genotypes/phenotypes in relation to disease heterogeneity, immune responses (innate and specific), and inflammation
Assessment of prevalence, burden, and costs of different causes of SCUADs
Assessment of SCUAD comorbidities
Development of new forms of treatment
Longitudinal evaluation of SCUADs to find preventive strategies

symptoms and other comorbidities, including asthma.² Asthma is also common in patients with NAR.

Rhinitis, even in the absence of atopy, is a powerful predictor of adult-onset asthma.²⁵ However, the severity of the asthma in relation to rhinitis is not known.

Rhinitis can lead to a poorer control of asthma. Adults and children with asthma and documented concomitant AR experience more asthma-related hospitalizations and physician visits and incur higher asthma drug costs than adults with asthma alone.² These patients also experience a more frequent absence from work and decreased productivity. However, some studies have not shown such an association. In developing countries a strong association was found between the severity of rhinitis and the control of asthma.

The treatment of rhinitis might have an effect on asthma and its severity, but definite results are lacking. In particular, intranasal corticosteroids do not improve seasonal asthma, but in *post hoc* studies they were suggested to reduce asthma hospitalizations.²

CRS and severity and control of asthma

The coexistence of asthma and CRS has been noted for a long time. The debate remains as to whether CRS is a precipitating factor for asthma.²⁶ It seems that CRS and asthma are linked by a common inflammatory pathway among which eosinophils and airway epithelium play an important role. Many asthmatic patients, whatever their severity, have CRS, at least demonstrated on CT scans.²⁷ However, patients with severe asthma, uncontrolled asthma, or both have more severe CT scan abnormalities than other patients.²⁷ In many patients with severe asthma, nasal polyposis is common. Surgical treatment of CRS or nasal polyposis might improve asthma symptoms, but studies with an appropriate methodology are needed.

Unmet needs

- To assess the severity/control of asthma in patients with AR and NAR with new-onset asthma, particularly in developing countries.
- To confirm in prospective studies that rhinitis and asthma severity are linked.
- To prospectively study the effect of rhinitis treatment in outcomes of severe/uncontrolled asthma.
- To confirm the link of CRS and nasal polyps with asthma and other lower chronic airway diseases, such as COPD and bronchiectasis, in epidemiology, mechanism of action, and severity.

CONCLUSIONS

SCUADs represent an underestimated medical problem. They define those patients whose symptoms are inadequately controlled despite adequate (ie, effective, safe, and acceptable)

pharmacologic treatment based on guidelines. They are present in various upper airway diseases, such as AR, NAR, CRS, aspirin hypersensitivity, and occupational airway diseases. A list of priorities has been set (Table II). Because of their severity and socioeconomic consequences, SCUADs need special attention to better define their prevalence, risk factors, severity, mechanisms, and novel treatments.

The members of the Allergic Rhinitis and its Impact on Asthma Study Group were as follows: C. A. Akdis, MD,* Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland; C. Baena-Cagnani, MD,† Catholic University of Cordoba, Cordoba, Argentina; E. D. Bateman, MD, Health Sciences Faculty, University of Cape Town, Cape Town, South Africa; S. Bonini, MD,* Second University of Naples, INMM-CNR, Rome, Italy; L. P. Boulet, MD, Institut de cardiologie et de pneumologie de l'Université Laval, Laval, Quebec, Canada; P. J. Bousquet, MD,* BESPI, University Hospital, Nîmes, France; P. G. Burney, MD,* National Heart and Lung Institute, Imperial College, Respiratory Epidemiology and Public Health, London, United Kingdom; L. O. Cardell, MD,* the Department of ENT, CLINTEC, Karolinska Institutet, Stockholm, Sweden; K. H. Carlsen, MD,* University of Oslo, Faculty of Medicine, Oslo, Norway; B. Carsten-Jensens, MD,* Odense University Hospital, Odense, Denmark; Y. Chen, MD, the Center for Asthma Research and Education, Beijing, China; E. Chkhartishvili, MD, Children's Clinical Hospital, Tbilisi, and Highest Medical School "AIETI"; A. Chuchalin, MD,* Pulmonology Research Institute, Moscow, Russia; L. Cox, MD, Nova Southeastern University Osteopathic College of Medicine, Davie, Fla; A. Custovic, MD,* University of Manchester, Manchester, United Kingdom; R. Dahl, MD, Aarhus University Hospital, Aarhus, Denmark; L. Delgado, MD,* Faculdade de Medicina da Universidade do Porto, Hospital de S. João, Porto, Portugal; P. Demoly, MD,* University Hospital of Montpellier, France; J. Denburg, MD, AllerGen NCE and McMaster University, Hamilton, Ontario, Canada; W. K. Dolen, MD, the Medical College of Georgia, Augusta, Ga; R. Dubakienė, MD,* Vilnius University Antakalnis Hospital, Vilnius, Lithuania; Y. El-Gamal, MD,† the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University, Cairo, Egypt; W. J. Fokkens, MD,* the Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, The Netherlands; T. Fukuda, MD,† Dokkyo University School of Medicine, Tochigi, Japan; R. Gerth van Wijk, MD, the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands; M. Gjomarkaj, MD,* IBIM-CNR, Palermo, Italy; T. Haahtela, MD, Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland; E. Hamelmann, MD, the Department for Paediatrics, Ruhr-University Bochum, Bochum, Germany; S. T. Holgate, MD,* Southampton General Hospital, Southampton, United Kingdom; P. Howarth, MD,* the University of Southampton, Southampton, United Kingdom; J. C. Ivancevich, MD,† Immunology School of Medicine, del Salvador University, Buenos Aires, Argentina; E. Jensen-Jarolim, MD,* the Department of Pathophysiology, Center of Physiology, Pathophysiology and Immunology, Medical University of Vienna, Vienna, Austria; O. Kalayci, MD, Hacettepe University School of Medicine, Pediatric Allergy and Asthma Unit, Hacettepe, Ankara, Turkey; M. Kaliner, MD,† George Washington University School of Medicine, Washington, DC, and the Institute for Asthma and Allergy, Chevy Chase, Md; Y. Y. Kim, MD, Seoul National University Hospital, Seoul, Korea; M. L. Kowalski, MD, Medical University of Lodz, Lodz, Poland; L. Le, MD, the University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam; B. W. Lee, MD,† the Department of Pediatrics, Yong Loo Lin School of Medicine, National University of Singapore; B. Leynaert, PhD, INSERM, U700 Université Paris 7, Faculté de Médecine Denis Diderot, Paris, France; K. Lodrup-Carlsen, MD, the Department of Paediatrics, Oslo University Hospital, Ullevål, and the Faculty of Medicine, University of Oslo, Oslo, Norway; E. O. Meltzer, MD, Allergy and Asthma Medical

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†Members of the Board of the World Allergy Organization.

Group and Research Center, San Diego, Calif; Y. Mohammad, MD, Tishreen University School of Medicine, Lattakia, Syria; M. Morais-Almeida, MD, the Immunoallergy Department, CUF-Descobertas Hospital, Lisbon, Portugal; J. Mullol, MD,* Hospital Clínic-IDIBAPS, Barcelona, Spain; R. Naclerio, MD, the University of Chicago, Ill; E. Nizankowska-Mogilnicka, MD,* Jagiellonian University School of Medicine, Krakow, Poland; R. E. O'Hehir, MD, Alfred Hospital and Monash University, Melbourne, Australia; K. Ohta, MD, Teikyo University School of Medicine, Tokyo, Japan; Y. Okamoto, MD, the Department of Otorhinolaryngology, Chiba University Hospital, Chiba, Japan; N. Papadopoulos, MD,* the University of Athens, Athens, Greece; H. S. Park, MD,† Aju University School of Medicine, Suwon, Korea; G. Passalacqua, MD,* Allergy and Respiratory Diseases Clinic, University of Genova, Genova, Italy; R. Pawankar, MD,‡ Nippon Medical School, Bunkyo-ku, Tokyo, Japan; T. Popov, MD, the Clinic of Allergy and Asthma, Alexander's University Hospital, Sofia, Bulgaria; P. Potter, MD,‡ Groote Schuur Hospital and the University of Cape Town Lung Institute, Cape Town, South Africa; D. Price, MD,* the University of Aberdeen, United Kingdom; K. F. Rabe, MD,* Leiden University Medical Center, Leiden, The Netherlands; N. Rodriguez Perez, MD,‡ State University of Tamaulipas, Matamoros, Mexico; A. Romano, MD,* the Department of Internal Medicine and Geriatrics, UCSC-Allergy Unit, Complesso Integrato Columbus, Rome, Italy; L. Rosenwasser, MD,‡ Children's Mercy Hospital, and the University of Missouri-Kansas City School of Medicine, Kansas City, Mo; D. Ryan, MD,* Woodbrook Medical Centre, Loughborough, and the University of Aberdeen, Aberdeen, United Kingdom; M. Salapatas, MD,* the European Federation of Allergy and Airway Diseases Patients' Associations, Brussels, Belgium; M. Sanchez-Borges, MD,‡ the Department of Allergy and Clinical Immunology, Centro Medico-Doctore La Trinidad, Caracas, Venezuela; G. Scadding, MD, Royal National TNE, London, United Kingdom; P. D. Schmid-Grendelmeier, MD,* University Hospital, Zurich, Switzerland; F. E. R. Simons, MD, the University of Manitoba, Winnipeg, Manitoba, Canada; A. Todo-Bom, MD,* Coimbra University Hospital, Coimbra, Portugal; E. Toskala, MD,* the Finnish Institute of Occupational Health, Helsinki, Finland; E. Valovirta, MD,* Suomen Terveystalo Allergy Clinic Turku, Turku, Finland; P. van Cauwenberge, MD,* UZG, University Hospital Ghent, Ghent, Belgium; C. van Weel, MD, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; O. Vandenplas, MD, Cliniques universitaires UCL de Mont-Godinne, Yvoir, Belgium; P. Vichyanond, MD,‡ Siriraj Hospital, Faculty of Medicine, Department of Paediatrics, Bangkok, Thailand; D. Y. Wang, MD, Yong Loo Lin School of Medicine, National University of Singapore; M. Wickman, MD,* Sachs' Children's Hospital, Karolinska Institutet, Stockholm, Sweden; A. Yorgancioglu, MD, Celal Bayar University, Medical Faculty, Department of Pulmonology, Manisa, Turkey; O. Yusuf, MD, the Allergy and Asthma Institute, Islamabad, Pakistan; H. Zar, MD, Red Cross Children's Hospital, University of Cape Town, Cape Town, South Africa; N. Zhong, MD, Guangzhou Institute of Respiratory Diseases, Guangzhou, China; M. Zitt, MD,‡ Medicine State University of New York, Stony Brook, NY; and J. P. Zock, MD, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.

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