Severe chronic allergic (and related) diseases: a uniform approach — a MeDALL-GA²LEN-ARIA Position Paper

In collaboration with the WHO Collaborating Center for Asthma and Rhinitis

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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^{2}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 Organiztion
WHO: World Health Organization

INTRODUCTION

Allergic diseases represent the world's most common diseases. Several mechanisms are involved, but many patients suffer from IgE-mediated reactions [1]. Over 400 million people suffer from allergic rhinitis and 300 from asthma [2]. Up to 50% of the population in certain age groups and countries are sensitized to allergens. Not all sensitized patients are symptomatic [3] and symptom severity varies widely from mild to severe and from intermittent to persistent. Most patients have an early onset of symptoms but the clinical phenotypes of allergic diseases vary with age [4].

Acute, IgE-mediated, severe reactions (e.g. anaphylaxis [5]) occurring in patients sensitized to drugs [6], foods [7] or hymenoptera venoms [8] may be life-threatening. Many types of acute non-IgE-mediated allergic diseases or non-allergic diseases [1] such as aspirin hypersensitivity, hereditary angioedema [9], cold urticaria [10] or skin reactions such as DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) or Lyell syndrome [11] 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) [12], asthma [2], atopic dermatitis [13] and gastro-intestinal diseases. However, allergy is not always involved [14–17]. Diseases such as contact dermatitis are linked with other immune reactions. The present document will propose the definition of the severity of allergic and related (non-allergic origin) diseases: asthma, rhinitis (conjunctivitis), rhinosinusitis [18, 19], atopic dermatitis and chronic urticaria [20, 21]. However, the list will be expanded later.

Co-morbidities play a major role in severity adding to the complexity of the disease and its management [12]. However, in the current document, each disease will be considered separately since there may be patients with a severe disease (e.g. rhinitis) associated to 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 opposite.

These concepts have evolved over time for asthma in guidelines [23, 24], task forces [25] or consensus meetings [26]. Up to 2006, asthma was classified by severity alone [22–25]. 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] used 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]

to allergic and related diseases in order to have a uniform definition of severity, control and risk usable in most situations. This uniform definition will allow to better define phenotypes of severe allergic (and related) diseases for clinical practice, research (including epidemiology), public health purposes, education and discovery of novel therapies (Table 1).

1. SEVERITY, CONTROL, RESPONSE TO TREATMENT AND RISK IN ASTHMA

The stratification/grading of asthma severity includes several components (Table 2). The most useful concept of asthma severity is based on the intensity of 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 [29] and has been used in guidelines (22, 2008 #27059, 23) (Table 3).

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

- The Royal College of Physicians three questions [32].
- The Juniper's Asthma Control Questionnaire (ACQ) of Juniper based on 6 questions (ACQ6) and FEV1 (ACQ7) [33], but 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 assess appropriately **exacerbations** that are of importance in the assessment of control of asthma and deserve further attention.

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 [23, 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 corticosteroid)
2	Level of current treatment prescribed
3	Inhalation technique and compliance to treatment
4	Responsiveness to treatment
5	Exposure to aggravating factors
6	Risk

Biomarkers hold promise to capture complementary information, 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. oral corticosteroid-treated patient). Patients achieving control with treatment have a lower risk of exacerbation than those who are uncontrolled [39].

Table 3. Level of asthma control in patients ⩾ 5 years of age [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_2-agonists in the past 2–4 weeks	⩽ 2 days per week	> 2 days per week	Several times a day
Lung function FEV_1 or PEFR* FEV_1/FVC (< 11 yrs of age)	⩾ 80% predicted or personal best ⩾ 80%	60–79% predicted or personal best 75–80%	< 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_1 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.

1.2. Response to treatment

Responsiveness to treatment has been demonstrated in studies assessing risk reduction during treatment. Studies at the community level reveal 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 deprived populations [43]. The concept is therefore applicable to all populations and all countries. In the NAEPP-EPR3 guidelines [22], **resistance to therapy** is defined as uncontrolled asthma despite high dose inhaled corticosteroid. For the INNOVATE trial (omalizumab), the European Medical Agency requested the assessment of asthma control in patients treated by inhaled corticosteroids and long-acting β-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.

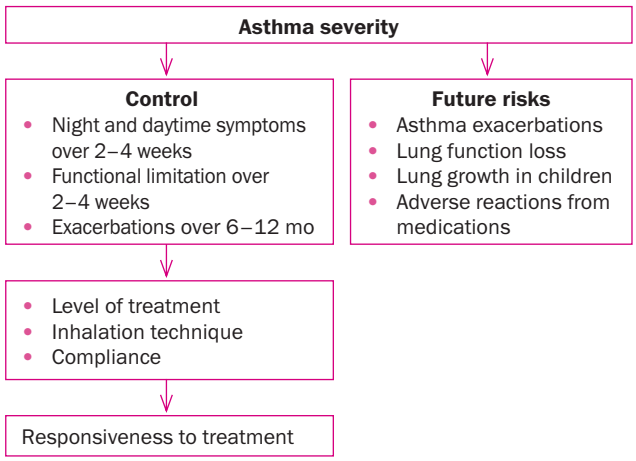
1.4. Definition of asthma severity and control

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 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 was proposed [48], but the conclusions are still under discussion.

Figure. 1. Evaluation of asthma severity [23]



2. UNIFORM APPROACH TO THE SEVERITY OF CHRONIC ALLERGIC (AND RELATED) DISEASES

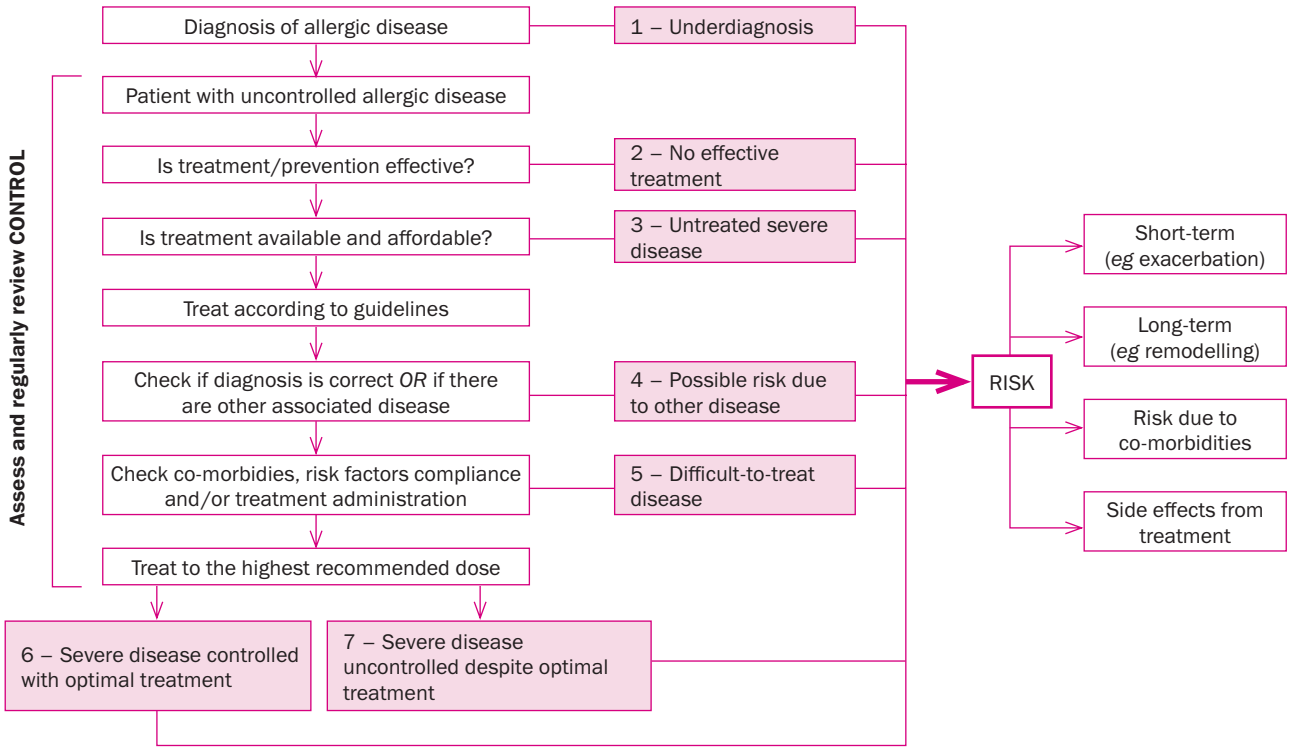
Severe allergic (and related) diseases include 7 groups, each carrying different public health messages and challenges (Figure 2):

- **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.
- **Diagnosis** is the first step, but it is not always easy as certain diseases may overlap (e.g. wheezing in preschool children).
- **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, 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, they are affordable. However, in many LMICs and in some deprived areas of high-income countries, essential medicines may be available but are rarely affordable [50]. Even if medications are affordable, health professional knowledge concerning their use is fragmented needing training, and health system often lacks infrastructure for early diagnosis, follow up, education as well as legislation for 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 for 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

Figure. 2. Uniform approach to the definition of severe allergic (and related) diseases (adapted from [47])



to guidelines existing in the country (or if guidelines do not exist, the highest controller medications available in the country). This insensitivity may not 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 patient's 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]. Vernal conjunctivitis is not considered in this document.

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 bothered by their symptoms. The GA^{2}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 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 in patients with allergic rhinitis may be increased by using H_1-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 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 controling 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, 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. Mucoceles develop slowly as long-term complications after surgery, but also develop spontaneously.

About 10–15% of the CRSsNP and up to 45% of the CRSwNP patients will develop co-morbid 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 daily number of wheals and intensity of 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 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 H1-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 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

3.4.1. 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].

3.4.2. 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].

3.4.3. 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].

3.4.4. 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 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 21st 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 need, define phenotypic heterogeneity to inform the design of research studies and to improve overall clinical care [28]. Registries will help for the surveillance of severe allergic diseases. Data from the registries may provide evidence of inadequacies in 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 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 appropriate assessment of severity and control. Thus, the definition will facilitate epidemiological research, understand modifiable risk factors and 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 for medications in a country.

5.10. Developed and developing countries

A uniform definition of severe allergic (and related) diseases should be applicable to 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-population of patients based on the concept of distinct phenotypes and endotypes.

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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