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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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Immunoglobulin E · Asthma · Rhinitis · Rhinosinusitis · Urticaria · Atopic dermatitis

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 and 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 comorbidities 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.

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 nonallergic diseases [1] such as aspirin hypersensitivity, hereditary angioedema [8], cold urticaria [9] or skin reactions such as 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 (nonallergic origin) diseases: asthma, rhinitis (conjunctivitis), rhinosinusitis [18–20], atopic dermatitis (AD) 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.

Comorbidities 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] and consensus meetings [26]. Until 2006, asthma was classified by severity alone. Then, newer Global Initiative for Asthma (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 National Asthma Education Prevention Program (NAEPP)-Expert Report (EPR)3 guidelines [23] made key suggestions combining impairment, response to treatment and risks, and 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 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].

Control

The level of asthma control incorporates current clinical control and exacerbations over the past 6–12 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, 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_1 (ACQ7) [33]. ACQ6 is more predictive than ACQ7 for asthma control [34].
- The Asthma Control Test, 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 for capturing 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 and 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].

Table 1. Goals of the current paper

– The current document proposes 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 comorbidities [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, 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

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 [41, 42] and 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 corticosteroids inhaled at high doses. 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].

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.

Table 3. Level of asthma control in patients ≥5 years of age (from [28], adapted from GINA 2006 [31] and 2007 NAEPP-EPR3 [23])

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/week	>2 days/week	several times a day
Lung function FEV_1 or PEFR FEV_1/FVC (<11 years 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)[1]	0–1/year	2/year consider severity and interval since last exacerbation	frequent (>2/year)

For well-controlled asthma, all components should be present; for partially- or poorly-controlled asthma, the presence of any of the components places the patient in the category; FEV_1 or PEFR may be ≥80% predicted in patients with severe persistent asthma.

[1] At present, there are inadequate data to analyze frequencies of exacerbations with the control of asthma of different levels of severity.

Definition of Asthma Severity and Control

The definition of asthma severity, control and exacerbations proposed to WHO [28] took existing guidelines [23, 24] and the 2008 ATS/ERS Task Force report into consideration [26] (fig. 1). The recent consensus by U-BIOPRED (Unbiased Biomarkers for the Prediction of respiratory disease outcomes) from the Innovative Medicines Initiative 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 comorbidity [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 preschool 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.

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 (fig. 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 nonallergic rhinitis or urticaria) are more difficult to control [49].
- 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 low- and middle-income countries 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.

- Reassessment 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.
  - Comorbidities 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 reassessed at regular intervals as it may change over time.

Severe Allergic and Related Diseases

Allergic and Nonallergic Rhinitis (and Rhinoconjunctivitis)

Allergic rhinitis is an IgE-mediated reaction of the nasal mucosa. It is often associated with conjunctivitis (rhinoconjunctivitis) [11]. Nonallergic rhinitis represents a group of heterogeneous diseases in which no IgE-mediated reaction can be demonstrated [17]. Clinical needs that are not met are clear in both allergic and nonallergic rhinitis [51].

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 (Allergic Rhinitis and its Impact on Asthma) severity classification [54], or patients' reported outcomes such as quality of life [11, 55]. More recently, a score with several items was proposed [56]. In rhinitis, it appears that a simple measure such as VAS may be sufficient to appreciate the control of the disease [57] and is particularly relevant to primary [58] and pharmacy care [59]. The level of control of allergic rhinitis is assessed independently of the treatment step [52, 60].

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 the guidelines, up to 20% continue to be impaired by their symptoms. The Global Allergy and Asthma European Network (GA^{2}LEN)-ARIA-World Allergy Organisation (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, 61]. 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 [62].

The efficacy of the treatment of nonallergic rhinitis is variable [17]. It is heterogeneous in etiologies and inconsistently benefits from treatments which are effective in allergic rhinitis [63, 64].

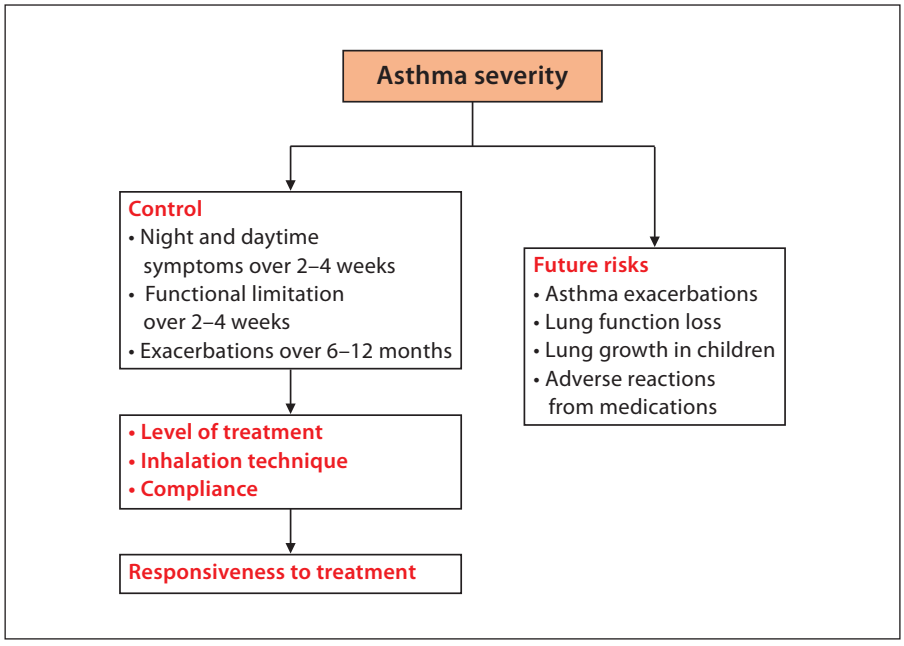

Fig. 1. Evaluation of asthma severity [from 23].

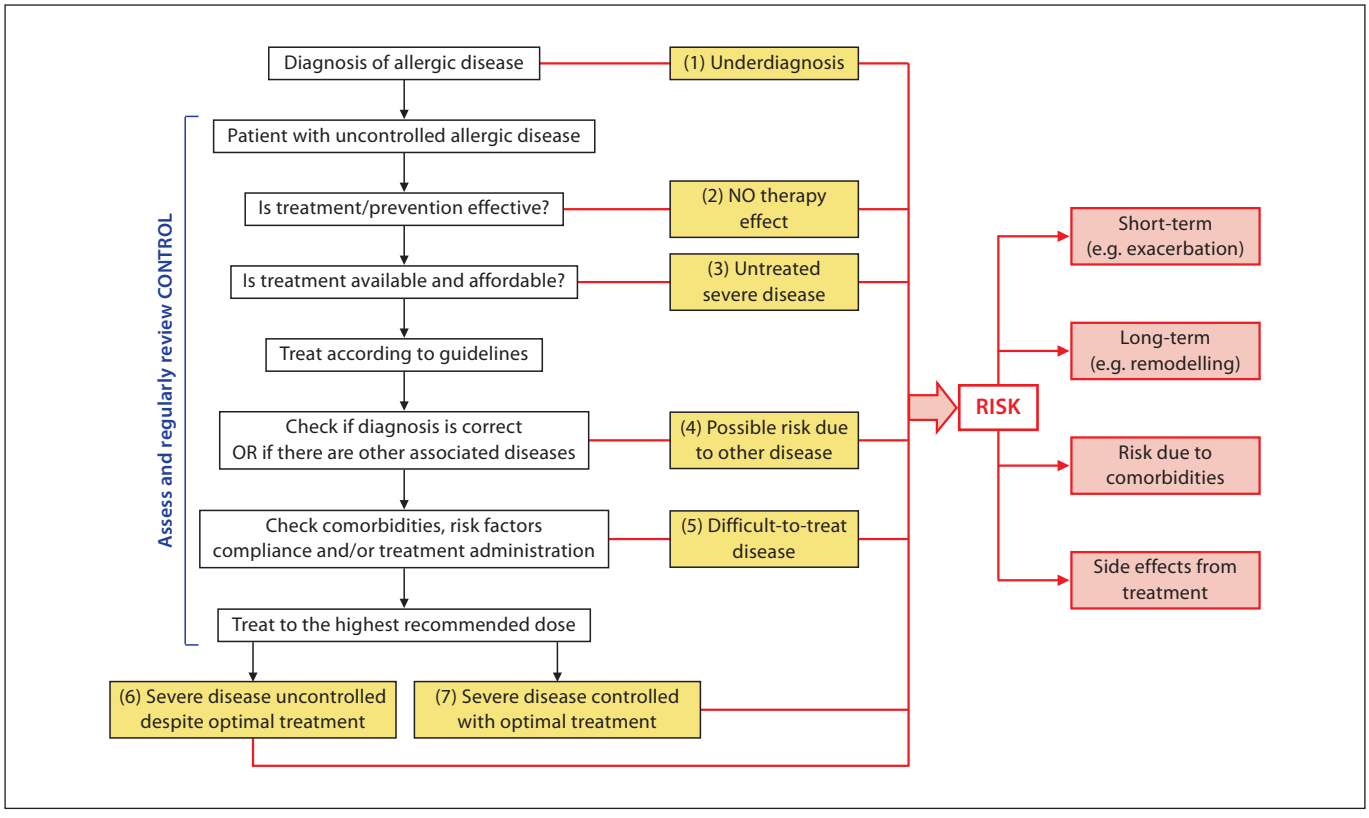

Fig. 2. Uniform approach for the definition of severe allergic (and related) diseases [from 49].

Reassessment of the Diagnosis of the Disease

Many different conditions can mimic allergic and nonallergic rhinitis [65]. Local allergic reactions with nasal but not systemic IgE antibodies [66] may be more important than initially thought. Misdiagnosis (e.g. nasal tumors, granulomas, cerebrospinal or rhinorrhea) may lead to adverse outcomes if the patient is not appropriately reassessed and reviewed.

Risk

Allergic rhinitis impairs work [67, 68] and school performance [69, 70]. Moreover, sedation may be enhanced using H_1-antihistamines with sedative properties [71]. The major long-term risk of allergic and nonallergic rhinitis is the development of asthma [72].

Chronic Rhinosinusitis

Control

Control and severity are not well delineated in chronic rhinosinusitis (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, 73] and generic health status assessment instruments [18].

Responsiveness to Treatment

Responsiveness to treatment differs between CRS without nasal polyps (CRSsNP) and in CRS with nasal polyps (CRSwNP) [74–76]. 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 cases.

In CRSwNP, symptoms may be controlled by topical corticosteroid treatment in mild to moderate localized disease [77–79]. However, in severe polyposis and asthma comorbidity, repeated courses of intranasal and/or oral corticosteroids are usually insufficient in controlling symptoms. Repeated sinus surgeries may be needed with inconsistent clinical benefits [80].

Reassessment 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, noninvasive 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 include granulomatosis with polyangiitis (Wegener's), other granuloma diseases, cocaine abuse or lymphomas. Any unilateral obstruction, pain or bleeding has to be investigated by a specialist to exclude malignancies, inverted papilloma, meningoceles and other serious conditions [81].

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 can also develop spontaneously.

About 10–15% of CRSsNP and up to 45% of CRSwNP patients present or will develop comorbid asthma, which may be severe [82]. CRSwNP may also develop into a systemic disease such as aspirin-exacerbated respiratory disease [83] or Churg-Strauss syndrome [84]. Allergic fungal sinus disease may be accompanied by allergic bronchopulmonary aspergillosis.

Repeated courses of oral corticosteroids in patients with persistent CRS may affect bone metabolism and lead to HPA-axis dysfunction [78, 85].

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, 86] with several clinical unmet needs [87]. 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.

Control

Control and severity are not well delineated in chronic urticaria [87]. 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 [88] and/or the Chronic Urticaria Quality of Life Questionnaire [89, 90]. Patient diaries and health-related quality of life instruments can be used.

Responsiveness to Treatment

In chronic urticaria, symptomatic treatment is the rule since causal treatment is rarely effective [22, 87]. 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 nonsedating oral H_1-antihistamines, the guideline-recommended first-step therapy and only in-label treatment option [91].

Reassessment of the Diagnosis of the Disease

Urticaria vasculitis and autoinflammatory disorders (e.g. cryopyrin-associated periodic syndrome [92], Schnitzler syndrome [93]), mastocytosis [94] and hereditary or other complement-associated diseases [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.

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 [95].

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) [96].

Many patients cannot be controlled using recommended doses of medications, which often causes depression and anxiety [97].

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

Atopic Dermatitis

Control

Several severity tests of current AD have been published. Three measurements (Scoring Atopic Dermatitis, SCORAD [98]; Eczema Area and Severity Index [99], and Patient-oriented Eczema Measure) have been tested sufficiently and each performed adequately [100]. Other scoring systems such as the Langeland-Rajka score have been designed to include information about the recent past (3 months) of the disease [101]. 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 to be made by the patients themselves or the caregivers of affected children [102]. These scoring systems only provide a snapshot of the current disease situation for a given patient at a defined time point [103] and should be more appropriately considered as control tests.

Impaired quality of life is common in AD, both in children (patients and caregivers) and adults, and may also be observed in infants [104]. Several quality of life measures (disease-specific and generic) have been used to determine this [105].

Responsiveness to Treatment

Most cases of patients seemingly resistant to treatment are certainly explained by the incorrect implementation of the guidelines [106, 107]. 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 closely dependent on the compliance of the patients/parents. However, truly therapy-resistant severe cases of AD 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 patients belong to this group [13].

Reassessment of the Diagnosis of the Disease

Depending on the age of onset, AD can be misdiagnosed [106, 107]. In preschool children, the spectrum of differential diagnosis is very wide, including either common diseases such as psoriasis or rather rare conditions such as Shwachman-Diamond syndrome (also named Burke syndrome), agammaglobulinemia, ataxia telangiectasia [108] and histiocytic disorders [109]. In adults, other diseases such as seborrheic dermatitis or cutaneous T cell lymphoma have to be excluded [110].

Risk

AD during infancy is a risk factor for other atopic diseases occurring later in childhood [111–113]. 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, AD is mostly related to food allergy and very often

spontaneously improves after 1–2 years. Children with early onset, a filagrin mutation and a food allergy (mainly peanut) have almost a 100% risk of developing allergic asthma [114]. 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 [115].

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 [116, 117]. The increased permeability of the skin associated with chronic inflammation may also favor sensitization to haptens, causing increasing rates of allergic contact dermatitis [118].

Application to Children

Severe Problematic Asthma

Severe problematic asthma is probably as common in children as in adults, with approximately 4–5% of children with asthma being affected [119]. Phenotypes of severe problematic asthma differ in children and in adults [120, 121]. A proposal with a 4-step procedure for the diagnosis and assessment of severe problematic asthma in childhood has recently been published [122]. 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 comorbidities; (c) an assessment of the pattern of inflammation, and (d) a documentation of the level of corticosteroid responsiveness.

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, comorbidities 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 [123]. In children, it may be difficult to distinguish between persistent nonallergic rhinitis and rhinitis associated with recurrent respiratory tract infections. It is important to rule out cystic fibrosis or primary ciliary dyskinesias in patients suspected of chronic rhinosinusitis.

Importance of a Uniform Approach

Subphenotyping Severe/Uncontrolled Diseases

Allergic diseases represent complex multidimensional 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 Severe Asthma Research Program [124, 125], U-BIOPRED [45, 126]) and allergic disease onset (MeDALL, Mechanisms of the Development of Allergy, an FP7 European Union project [49]), but more research is needed to identify allergic disease subphenotypes or endophenotypes [127] 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) [128, 129], across diseases (e.g. eosinophils in asthma and COPD) and in relation to comorbidities [130, 131]. 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 [130, 131], cluster analysis [125, 132] or free-scale networks. However, a uniform definition applied worldwide is needed, which may allow detailed subphenotyping of severe allergic diseases to be approached [28].

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 for 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 the 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.

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 [133]. The uniform approach of severity is perfectly embedded within this new paradigm.

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.

Clinical Trials

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

Registration of Medicines and Reimbursement

Controlled trials designed with a uniform approach to severity [134] will be more easily evaluated by the agencies for approval and by the Health Technology Assessment agencies (such as NICE) for reimbursement.

Research on Mechanisms and Genetics

More research into severe allergic diseases is urgently needed. Many large collaborative studies are already ongoing for severe asthma [124–126] 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].

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).

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.

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 wide-

ly around the world. Research must be planned to evaluate the phenotypes of 'severe' allergic (and related) diseases from different countries.

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 subpopulations 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 incomes, age groups and disease phenotypes.

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