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Severe Chronic Allergic (and Related) Diseases: A Uniform Approach - A MeDALL - GA2LEN - ARIA Position Paper

Bousquet, J ; et al

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

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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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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 FEV₁ (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.

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 (GA²LEN)-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].

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 H₁-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 gran-

ulomatosis 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. Mucocoeles 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

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

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.

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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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