

US and European severe asthma cohorts: what can they teach us about severe asthma?

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Asthma is a global health problem affecting around 300 million patients of all ages and ethnic groups in all countries around the world. In the majority of subjects with persistent, mild-to-moderate asthma (MA), the disease can be relatively well controlled by the use of currently available medications; however, five to ten per cent of patients suffer from a particularly severe disease that is poorly controlled clinically and often refractory to usual treatment. Improved care of severe asthma (SA) is a major unmet medical need and several international consortia

aim at improving our understanding of mechanisms in SA. To manage SA better, standardized definitions and concepts of asthma severity, risk and level of control are critical. In the following sections, we present several guidelines approaches and definitions followed by an overview of US (SARP) and European (ENFUMOSA, BIOAIR, U-BIOPRED) SA networks. Key findings regarding SA phenotypes, risk factors and pathophysiology are discussed. International cooperation in the area of respiratory diseases, including SA, across the Atlantic Ocean, will lead to a better understanding of asthma pathology, especially of those severe, not well controlled or difficult-to-treat cases.

Keywords: asthma networks, asthma phenotypes, refractory asthma, severe asthma.

Introduction

Asthma is a global health problem affecting around 300 million patients of all ages and ethnic groups in all countries around the world [1]. In the majority of subjects with persistent, MA the disease can be relatively well controlled by the use of currently available medications; however, 5–10% of patients suffer from a particularly severe disease that is poorly controlled clinically and often refractory to usual treatment [2–4]. Severe asthmatics impose a significant burden on healthcare utilization through unscheduled visits to general practitioners, emergency visits, hospitalizations, days off work/school and a requirement for multiple asthma medications. In comparison with mild or moderate asthma, severe asthmatics are 15 times more likely to use emergency services and 20 times more likely to be admitted to hospital [5].

Improved care of severe asthma (SA) is a major unmet medical need and several international consortia aim at improving our understanding of mechanisms in SA [6–8]. Studying large numbers of these patients is critical as it is now accepted that asthma is not a

single disease entity. Rather, the different subgroups (called phenotypes) can have different clinical manifestations, be driven by a variety of pathophysiological mechanisms and associate with a range of different biomarkers (Fig. 1). Thus, the effectiveness of a given pharmacotherapy may be dependent on asthma phenotype with this heterogeneity likely impacting the variable responses to medications observed in SA [4]. In the following sections, we present an overview of concluded and ongoing trials with the main goal to improve our understanding of SA.

Defining severe asthma

To understand and treat SA better, standardized definitions and concepts of asthma severity, risk and level of control are critical [1, 6–8]. Commonality in approaches to defining severe, ‘difficult-to-treat’ or ‘therapy-resistant’ asthma, with accompanying characterization, should improve our understanding of phenotypes. This should enhance our ability to personalize management, decrease the burden of symptoms and risk of exacerbations and improve the level of asthma control.

Guidelines definitions and approaches

In the first edition of the Global Initiative for Asthma (GINA), overall asthma severity was based on the patient's clinical characteristics, including lung function measurements, prior to commencing the treatment. Over the years, it became increasingly recognized that categorizing asthma severity should also involve responsiveness to treatment. In the latest GINA guidelines [2], optimal asthma control is the main goal of asthma management, together with improving patients' quality of life, reducing exacerbations and decreasing the cost of the health care. Measuring level of control includes monitoring several clinical parameters as follows: daytime and nighttime symptoms, limitation of activity, impairment of lung function and use of rescue medication. Using this approach to optimize control, guidelines recommend a step-up/step-down approach. In those patients in whom asthma is not well controlled an increase in dose of the currently used controller medication or adding another drug is the recommended action. On the other hand, in well-controlled cases, the dose or the number of controller medications should be decreased to limit the possibility of side effects and decrease the costs. This approach gives us a valuable tool to improve the quality of asthma care in the majority of patients. Unfortunately, the latest edition of GINA guidelines does not give a clear and helpful definition of how to identify or treat those 10% of patients with asthma who do not achieve control of their asthma and thus likely represent the majority of SA.

Societal and programmatic definitions

European. In 1999, a European Respiratory Society (ERS) Task Force [9] defined difficult, therapy-resistant asthma as poorly controlled disease with continuous requirement for rescue medications (short acting β_2 agonists) despite treatment with reasonable doses of inhaled corticosteroids (ICS) and with at least 6 month of follow-up by a specialist in lung diseases. The *European Network for Understanding Mechanisms of Severe Asthma* (ENFUMOSA) [6] and later BIOAIR, defined the severe stage of the disease as lack of good control of asthma (manifested by occurrence of one or more exacerbations during one year of follow-up) despite oral corticosteroids or high-dose ICS ($\geq 1600 \mu\text{g}$ of budesonide or beclomethasone daily, or $\geq 800 \mu\text{g}$ of fluticasone daily).

To meet criteria for SA, the diagnosis of asthma must first be confirmed by typical symptoms in the face of reversibility in FEV_1 or airway hyperresponsiveness, as masqueraders of asthma, including paroxysmal vocal fold motion disorder, bronchiectasis and others may also not respond well to typical asthma therapies. Once the diagnosis is confirmed, these patients are often given additional controller medications such as long acting β_2 agonists or oral theophylline. Good quality education regarding inhalation techniques, adherence to treatment and management plans are mandatory. One year of follow-up under specialist treatment was suggested to guarantee exclusion of comorbidities and misdiagnoses that could impact the severity of the disease.

North American. In 2000, an American Thoracic Society (ATS) Workshop [10] developed a definition of refractory asthma which required at least one major criteria (treatment with continuous or near continuous ($\geq 50\%$ of year) oral corticosteroids and/or treatment with high-dose inhaled corticosteroids ($>880 \text{ mcg}$ fluticasone or equivalent), and two of seven minor criteria. Minor criteria included the following: requirement for additional treatment with a controller medication, for example, long acting β_2 agonist, theophylline, or leukotriene antagonist, asthma symptoms requiring short acting β_2 agonists use on a daily or near daily basis, persistent airway obstruction ($\text{FEV}_1 < 80\%$ predicted, diurnal peak expiratory flow variability $> 20\%$), one or more urgent care visits for asthma per year, three or more steroid bursts per year, prompt deterioration with $\leq 25\%$ reduction in oral or inhaled corticosteroid dose and a near-fatal event in the past (Table 1). This definition was incorporated into all studies carried out in con-

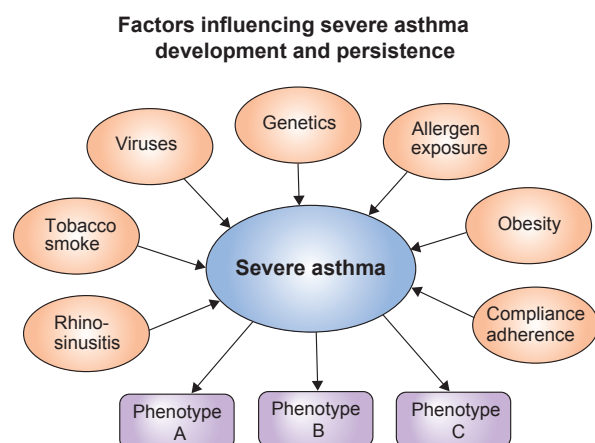


Fig. 1 Factors influencing severe asthma, development and persistence.

Table 1 Overview of severe asthma definitions [1, 2, 6, 8]

Definitions of severe asthma		
ERS/ENFUMOSA/BIOAIR	ATS/SARP network	WHO
One or more exacerbations during one year of follow-up (lack of good control of the disease)	Requires 1 or both major and at least two minor criteria Major criteria: Treatment with continuous or near continuous ($\geq 50\%$ of year) oral corticosteroids	Uncontrolled disease which can result in: Risk of frequent severe exacerbations (or death) and/or
Oral corticosteroids or high-dose ICS ($\geq 1600 \mu\text{g}$ of budesonide or beclomethazone daily or $\geq 800 \mu\text{g}$ of flutikazone daily).	Requirement for treatment with high-dose inhaled corticosteroids) and 2 minor criteria. Minor criteria: Requirement for additional daily treatment with a controller medication, eg. long acting β_2 agonist, theophylline, or leukotriene antagonist,	Adverse reactions to medications and/or Chronic morbidity (including impaired lung function or reduced growth in children).
Additional controller medications (long acting β_2 agonist or oral theophylline)	Asthma symptoms requiring short acting β_2 agonists use on a daily or near daily basis,	Severe asthma can be divided into:
Diagnosis of asthma confirmed by typical symptoms, reversibility in FEV ₁ or airway hyper-responsiveness	Persistent airway obstruction (FEV ₁ $< 80\%$ predicted, diurnal peak expiratory flow variability $> 20\%$), One or more urgent care visits for asthma per year, Three or more steroid bursts per year,	Untreated severe asthma, difficult-to-treat severe asthma Treatment-resistant severe
One-year follow-up under specialist treatment (to exclude comorbidities, misdiagnoses, provide education regarding inhalation techniques, management plans and evaluate adherence to treatment.	Prompt deterioration with $\leq 25\%$ reduction in oral or inhaled corticosteroid dose Near-fatal event in the past	asthma (including both asthma for which control cannot be achieved despite the highest level of recommended treatment – refractory and corticosteroid-resistant asthma, and asthma for which control can be maintained only with the highest level of recommended treatment)

junction with the *National Heart, Lung and Blood Institute's Severe Asthma Research Programme* (SARP) with Sally Wenzel as one of initiators of this network [8].

Global. In 2010, a uniform definition of asthma severity, control and exacerbations from the World Health Organization (WHO) was published [1]. In this document, it was underlined that concepts of asthma severity, control and responsiveness (and availability) to treatment are linked. The level of asthma control includes current clinical control (frequency and intensity of day and night symptoms, functional and activity limitations, use of rescue medications, impairment of lung function) and number (severity) of exacerbations. Additional factors contributing to

asthma severity include level of current controller medications, inhalation technique and adherence to treatment, as well as responsiveness to treatment. Asthma severity and control also intertwine to increase disease burden and asthma risk, which includes the likelihood of exacerbations, development of chronic morbidity (progressive decline in lung function) and risk of adverse reactions from asthma medications (Table 2). Thus, WHO suggested that SA be defined by level of current clinical control and risk. Uncontrolled severe disease can result in frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced growth in children). When applying this definition to a global population, SA is divided into three groups: untreated

Table 2 *Components of asthma severity (based on [1])*

Components of asthma severity	
Level of control	Current clinical control (frequency and intensity of day and night symptoms, functional and activity limitations, use of rescue medications and impairment of lung function) Number and severity of exacerbations (last 6–12 months) and number of bursts of systemic corticosteroids
Level of treatment	Including prescribed medications, inhalation technique and compliance with treatment
Responsiveness to treatment	Relative insensitivity to corticosteroids Corticosteroid dependent cases
Risk	Likelihood of exacerbations, Development of chronic morbidity (progressive decline in lung function) Risk of adverse reactions from asthma medications

SA, difficult-to-treat SA and treatment-resistant SA (including both asthma for which control cannot be achieved despite the highest level of recommended treatment – refractory and corticosteroid-resistant asthma, and asthma for which control can be maintained only with the highest level of recommended treatment. This uniform global definition is important for the public health and makes it applicable in all countries independent of the level of health resources, socio-economic or racial differences. Simultaneous with the release of this definition, WHO called for wider availability of essential medicines for asthma and chronic obstructive pulmonary disease (COPD) (beclomethasone, salbutamol and ipratropium), as it has been clearly shown that good asthma care, with the introduction of inhaled steroid and bronchodilators, leads to a considerable reduction in hospitalizations and deaths, and in longer time-lines, decreases the costs of the health care [11, 12].

Commonalities across definitions. Before making the final diagnosis of SA, all definitions recommend ruling out other diseases and addressing confounders

Table 3 *Major factors possibly influencing effectiveness of therapeutic intervention in asthma in every-day clinical practice*

Factors	Comments
Comorbidities	Allergic rhinitis, nasal polyps, sinusitis, cardiovascular diseases
Socio-economic status	Education and income impact healthcare accessibility
Smoking status	Lung function is lower in smokers and exacerbations are more frequent
Obesity	Exacerbations are more frequent and lung function is lower in obese patients
Compliance	With medications may be dependent on formulation (tablets versus inhalers) and patients' preferences
Adherence	With treatment plan (action in case of exacerbation) may be variable
Follow-up	Frequent and intense follow-up especially first months after diagnosis is made may improve compliance with treatment
Inhalation techniques	Differences between different inhalers: MDI, DPI
Steroid phobia	Not only for systemic but also corticosteroids in inhalations
Age	Compliance with treatment may be lower in adolescents
Expertise of practitioner	May be different in those trained in allergic and lung diseases and those who are not trained
Healthcare system	Accessibility to specialist and medication
Allergen exposures	Animal dander, house dust mites
Indoor environment	Damp housing

and comorbidities, including poor adherence to treatment, lack of compliance with management plans, poor inhalation techniques, reduction or elimination of several environmental factors (allergen exposure, recurrent infections and tobacco smoke) and psychological or social issues (Table 3). Several possible comorbidities that can masquerade and aggravate asthma must be carefully excluded or appropriately

treated (Table 4). Finally, SA is also generally associated with poor asthma control (defined by symptoms, exacerbations and lung function changes) despite intensive inflammatory treatment, although the WHO definition also allows achievement of control but only on high doses of medications. It is important to recognize there are no current biomarkers or even distinct physiological parameters that define SA (or its phenotypes).

Networks to increase understanding of severe asthma

European networks

To increase our knowledge of pathophysiological and clinical characteristics of chronic SA, a *European Network for Understanding Mechanisms of Severe Asthma* (ENFUMOSA) was established in the mid-1990s. ENFUMOSA was a multicentre, cross-sectional study which provided the first, comprehensive assessment of the SA phenotype [6]. A total of 163 subjects with

Table 4 Comorbidities that may masquerade and/or aggravate asthma in children and adults (based on [1])

Adults	Children
COPD	Vocal cord dysfunction
Chronic rhinosinusitis and nasal polyps	Obliterative bronchiolitis
Aspirin hypersensitivity	Developmental abnormalities of the upper airways
Vocal cord dysfunction	Congenital malformations
Gastroesophageal reflux disease (GERD)	Tuberculosis
Tuberculosis	Cystic fibrosis
Bronchiectasis	Primary ciliary dyskinesia
Cystic fibrosis	Tracheobronchomalacia
Hyperventilation syndrome	Recurrent aspirations
Tracheobronchomalacia	Tumours (carcinoid)
Sleep apnoea syndrome	Inhaled foreign bodies
Recurrent aspirations	Pulmonary eosinophilic syndromes
Congestive heart failure	
Tumours	
Inhaled foreign bodies	
Pulmonary eosinophilic syndromes	

COPD, chronic obstructive pulmonary disease.

SA were compared with 158 patients whose asthma was controlled with low doses of inhaled corticosteroids. In this SA cohort, persistent symptoms and abnormal lung function, despite regular use of high-dose controller and reliever medications, were accompanied by a component of irreversible airflow obstruction, neutrophilic inflammation, ongoing pro-inflammatory mediator release and less atopy. Risk factors and characteristics associated with severe and difficult-to-treat asthma phenotype were further studied [4], as were the risk factors for near-fatal asthma (NFA) cases characterized by SA attacks usually regarding intensive care unit admission. These 24 patients with NFA were characterized by less corticosteroid use and less compliance/adherence with the prescribed asthma medications. Lung function, blood gases, atopic status, sputum and blood inflammatory cell count were similar to mild-to-moderate, but not to the patients with SA [13]. Thus, it was not clear whether the NFA with SA differed from those SA patients without NFA on the basis of a different, more atopic phenotype predisposed to near-fatal attacks, or whether the differences were more likely due to differences in treatment and the compliance with it. Thus, the ENFUMOSA cross-sectional study generated several interesting hypotheses, but at the same time left many questions unanswered. For these reasons, the ENFUMOSA group launched the BIOAIR (*Longitudinal Assessment of Clinical Course and BIOMarkers in Severe Chronic AIRway Disease*) study to prolong and expand on the data collection and subsequent findings from ENFUMOSA.

The BIOAIR study was based at the Karolinska Institutet with Sven-Erik Dahlem as primary investigator. The trial began with cross-sectionally comparing patients with severe, MA and (COPD). These patients had their treatment optimized, then began a two week double-blind oral steroid intervention and were followed up in a longitudinal (1 year) manner. The primary goal of the BIOAIR consortium was to build a cohort of carefully phenotyped patients with (SA), who could be compared to patients with mild-to-moderate asthma (MA) and COPD. The longitudinal year-long follow-up provided insight into lung function variability, medication use and exacerbations. A total of 233 patients, from 12 European centres, were screened and included into the BIOAIR study: 93 with severe, 76 with MA and 64 with COPD. Severe asthmatics, in comparison with MA, were older (50 vs. 42.2 years), had higher BMI (28.5 vs. 25.0), lower lung function (FEV₁% of predicted: 70.4 vs. 88.7%), worse quality of life (SGRQ score 44.8 vs. 23.2) and worse asthma

control (Juniper ACQ score 2.03 vs. 1.03). Patients with SA were also significantly older when their asthma developed (29.2 vs. 22.2 years, SA vs. MA). A particular strength of the BIOAIR study is the repeated measures and a longitudinal, 1-year follow-up design. Although the clinical part of the study was concluded years ago, several projects are ongoing. The BIOAIR dataset and the biobank of samples represent a unique resource and a real 'gold mine' for further cooperation and studies (Table 5).

Finally, the pan-European project *Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED)* was launched as a public-private collaboration funded by the European Commission and the Innovative Medicine Initiative (IMI) of the European Union. The Karolinska Institutet is an active part of this trial as well. The main goal of the consortium is to subphenotype patients with severe, refractory asthma using an innovative systems biology approach. Integration of high-dimensional data from invasive (bronchial biopsies), noninvasive (blood, sputum, urine and exhaled air) and patient reported outcomes will enable identification of distinct phenotypic handprints with the aim to predict therapeutic (including innovative and new molecules) efficacy in view of personalized management. More than 40 organizations including 20 academic centres and nine pharmaceutical companies are actively involved in this project. The clinical part of the study has already started, with a targeted enrolment of up to 500 adult patients with SA and several control groups including up to 75 nonsevere asthma patients, 100

patients with COPD and 50 nonsmoking healthy persons.

AirPROM (Airway Disease Predicting Outcomes through Patients Specific Computational Modelling) brings together existing clinical consortia (including U-BIOPRED) with expertise in physiology, radiology, image analysis, data harmonization, computation modelling and systems biology. The goal of this project is not to screen and create new cohorts of patients, but using existing experience and clinical databases to work on processing facilities to develop an integrated multiscale airways model. This model should increase our understanding of physiological and pathological mechanism underlying chronic airway diseases and finally should help to develop new diagnostic or treatment methods.

North American cohorts

In 2000, the American Thoracic Society sponsored a workshop on severe asthma, which developed a definition of refractory asthma noted previously and which proposed directions for future investigations [10]. In response to this, and the ongoing European efforts, the National Heart Lung and Blood Institutes (NHLBI) launched the *Severe Asthma Research Programme (SARP)* in seven sites in the United States and one in the United Kingdom. The goal of the SARP was to identify and characterize patients with SA, as defined by the 2000 ATS workshop definition, to understand the pathophysiology of the disease, improve care and develop new treatments. Another aim was to

Table 5 Ongoing projects and new studies resulting from the BIOAIR trial

Goal of the project	Comments
Steroid sensitivity in SA	Oral steroid intervention with lung function as a main outcome
Phenotypic predictors of steroid sensitivity	Based on clinical characteristic and biomarkers
Detection of exacerbations	Based on daily measurements of lung function and symptoms variability
Risk factors for exacerbations	Based on clinical characteristics and biomarkers
Stability of phenotypes	Based on the longitudinal, one-year follow-up data
Fluctuation analysis	Based on the longitudinal, one-year follow-up data
New biomarkers of SA	Chitinases, periostin, lipid mediators and other. Based on biobank of samples
Genetic and epigenetic studies	In severe and mild-to-moderate asthma
Health economy data	To decrease costs of asthma care
Infections and pathogens in SA	Viral load and <i>Staphylococcus aureus</i> sIgE – association with severity of the disease and exacerbations
Integration of data in system biology approach	As a step towards personalized medicine in severe asthma

determine factors that differentiate patients with SA from those with milder disease. Initially, the SARP reported data from 438 patients with asthma including 204 with severe disease [8]. Subjects with SA were older, had longer disease duration, a significant burden of daily symptoms, frequent and severe exacerbations and had more comorbid conditions, including sinusitis and pneumonia, particularly in those with later onset asthma. Similar to the ENFUMOSA data, the patients with SA were less likely to be atopic and had lower lung function, usually with sustained bronchodilator reversibility. There were no differences in blood eosinophils, IgE and exhaled nitric oxide levels when compared with milder cases. These studies also are ongoing with 1644 asthmatic including 583 individuals with SA screened [14]. A comparison of the characteristics of the SA cohorts collected by SARP, ENFUMOSA and the BIOAIR consortia are presented in Table 6, showing a great deal of similarity. However, it must be kept in mind that there are some significant differences in socio-economic status, national healthcare differences and in race between included populations.

Severe asthma phenotypes

The increased awareness of SA and the evolution of the asthma networks has increased the understanding that asthma, and SA in particular, is a heterogeneous disease. Characterization of patients by a single clinical or physiological characteristic

Table 6 Clinical characteristics of the severe asthma cohorts as compared with mild-to-moderate asthmatics in SARP, ENFUMOSA and BIOAIR networks

Variable	SARP	ENFUMOSA	BIOAIR
Age	Older	No difference	Older
Sex	No difference	Females 4 : 1	No difference
BMI	No difference	Females increased BMI	Increased
Atopy	Decreased	Decreased	No difference
Aspirin hypersensitivity	Increased	Increased	Not studied
Sinusitis	Increased	Increased in females	Not studied
GERD	Increased	Not reported	Not studied

(i.e. reversible airflow limitation) or biomarker is inadequate. In 1999, Rosi *et al.* [15] evaluated 99 clinically stable patients with asthma and concluded that airway function, baseline BHR, and airway inflammation were separate dimensions of 'asthma'. In the same year, severe asthmatics were divided into those with and without tissue eosinophils, revealing that those with eosinophils had a thicker subepithelial basement membrane, more transforming growth factor beta and more SA exacerbations than those without eosinophils [16], supporting different inflammatory-based phenotypes. A follow-up study in 2004, suggested the additional importance of age at onset to the clinical course and eosinophilic inflammation [17]. Similarly, using sputum analysis, Hastie *et al.* [18] from the SARP group stratified subjects by percentages of eosinophils (<2% or ≥2%) and neutrophils (<40% and ≥40%). The group with high eosinophils and neutrophils appeared to be the most severe inflammatory group, with more frequent and SA exacerbations. The question arises as to whether eosinophilic inflammation is associated with a Th2 immune process. Woodruff *et al.* [19] divided mild asthmatics into two groups on the basis of their epithelial expression of IL-13 inducible genes. Interestingly, those with elevations in Th2 signature genes, including a pro-fibrotic factor, periostin, had more blood and lung eosinophils, higher IgE levels and a thicker SBM as compared to those without a Th2 signature. Preliminary studies of moderate to severe asthmatics with higher serum periostin levels suggest that identifying a Th2-Hi group using this approach predicted a better response to therapy with a monoclonal antibody to IL-13 (improvements in lung function), than those without evidence for Th2 inflammation (low periostin levels) [20].

In 2006, it was proposed that for phenotypes to become meaningful, pathobiology must be linked to clinical features, genetics, physiology and natural history [21] (Table 7). Early approaches to this were generally performed in a biased/clinically based manner. More recently, less biased, statistical approaches to defining phenotypes have been reported. A study by Brasier *et al.* [22] identified a pattern of cytokine expression in bronchoalveolar lavage fluid (BAL) that characterized a distinct subset of methacholine hyperresponders. Halder *et al.* [23] were the first to apply a multivariate mathematical technique – cluster analysis – to identify distinct phenotypic groups, incorporating lung inflammation (sputum eosinophils) into the clinical data (but not including physiological data). Two clusters characterized by marked discordance between symptom expression

Clinical and physiological phenotypes	Phenotypes related to triggering factors	Phenotypes defined by underlying pathobiology
Defined by severity	Aspirin or other nonsteroida	Eosinophilic
Frequent exacerbators	anti-inflammatory	Neutrophilic
Defined by chronic/irreversible obstruction	drugs induced	Pauci-granulocytic
Treatment-resistant	Allergens	
Defined by age of onset	Occupational factors (allergens and irritants)	
	Menses exercise	

Table 7 Phenotypic categories of asthma (based on [21])

and eosinophilic airway inflammation (early-onset symptom predominant and late-onset inflammation predominant) were specific to refractory asthma, whereas another two clusters (early-onset atopic and obese, noneosinophilic) were common in both mild-to-moderate and refractory asthmatics. Similar clustering analyses were used to identify asthma phenotypes in the SARP cohort [24]. A total of 720 patients were evaluated and from the initial 628 available descriptive variables, 34 variables were included into the clusters analysis. Five main cohorts were identified. Subjects in Cluster 1 were characterized by early-onset atopic asthma with normal lung function, Cluster 2 included more severe early-onset atopic asthmatics with preserved lung function and increased health care utilization. Cluster 3 grouped mostly older, obese women with late-onset, nonatopic asthma, a moderate reduction in FEV₁ and frequent systemic corticosteroid bursts owing to exacerbations. Cluster 4 represented the most severe early-onset/allergic asthmatics, whilst Cluster 5 consisted of patients with severe airflow obstruction which did not reverse to normal. A practical algorithm based on lung function, reversibility and age of onset of the disease was proposed to easily allocate patients to most probable cluster.

In conclusion, improved understanding of different phenotypes and endotypes falling under a general definition of asthma is likely to improve our understanding of underlying pathological processes, to develop new, specific and sensitive biomarkers and to better target personalized treatment.

Risk factors for severe asthma

Risk factors for the development of SA remain largely unknown. Low prebronchodilator FEV_{1%} of predicted increases the risk of being classified as SA (36%

increase for every 5% fall in FEV₁) [24]. Thus, from a genetics perspective, abnormalities in genes related to lung function are likely to play a role. Genes in the hedgehog pathway have recently been linked to lower lung function in asthmatics, but it is likely that there are other unknown genetic factors as well [25]. In addition, African racial background, male sex, sputum eosinophilia and personal smoking are risk factors for lower FEV₁ in SA [26, 27]. Interestingly, total IgE and family history of asthma were only risk factors for SA in African Americans in the SARP cohort [28]. Whilst gastroesophageal reflux disease (GERD) (41% of patients with SA), history of sinusitis and nasal polyps (54%) and pneumonia (63%) are common comorbidities, it is not clear whether these contribute to the development of SA or are secondary to SA [8]. A history of pneumonia (OR 3.3) increased the odds of having SA [8]. Second hand smoke exposure is also associated with greater airflow obstruction and hyperresponsiveness and has been suggested to be a risk factor for more SA [29]. Recurrent respiratory infections requiring antibiotics have also been shown to be a risk factor for SA exacerbations (OR 6.9) [8]. Nonetheless, much remains unknown regarding the factors which lead to the development of SA. Longitudinal follow-up of large cohorts of patients with asthma are clearly needed.

Exacerbations of asthma

Frequent and severe exacerbations are a major source of morbidity and mortality in SA and exacerbations are a prominent feature of poorly controlled and SA [7]. It has been shown that in children costs of asthma care are three times higher in exacerbators as compared to those patients who did not experience these attacks [30]. Recent ATS/ERS guidelines [31] pointed out that exacerbations constitute significant risk to patients, are the major cause of stress and anxiety to patients

and their families, and generate the greatest cost to the healthcare system. Implications of those flare-ups include risk of mortality, low health status, decreased quality of life and extensive utilization of healthcare resources. Respiratory tract viruses are the most frequent triggers for asthma exacerbations both in children and in adults followed by other pathogens, aeroallergens and pollutants. Most of infections are induced by rhinoviruses (including groups RV-A, RV-B and RV-C), influenza viruses and respiratory syncytial viruses (RSV) [32]. Viral infections have typical seasonal pattern with peak in autumn/winter and early spring. This has important practical implications as most of exacerbations have an annual cycle with peaks of hospitalizations in periods of epidemics typical for given region. Several therapeutic strategies are studied to alter the natural history of virus-induced asthma exacerbations including: vaccines, antiviral agents, anti-inflammatory and interferon treatments [33]. Some cases of asthma exacerbations are associated with bacteria (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae*). Other exacerbations triggers include allergens (indoor and outdoor exposure) and pollutants, in particular nitrogen dioxide (NO₂), particulate matter and ozone [32].

A high rate of exacerbations is inherent in the definition of severe, poorly controlled asthma and has been incorporated in most definitions [6, 8]. It has been hypothesized that baseline disease control and mechanisms underlying exacerbations may be driven by different factors [7]. Recent exacerbations represent an important independent predictor of future exacerbations in patients with severe or difficult-to-treat asthma [34]. Ten Brinke *et al.* [35] found that frequent exacerbators are younger, have positive family history of asthma, higher reversibility rate and higher bronchial hyperreactivity as compared to nonfrequent exacerbators. In the GOAL (Gaining Optimal Asthma control) study, it was shown that exacerbations could be reduced in the majority of patients by increasing the daily dose of inhaled corticosteroid and LABA. However, a proportion of patients could not achieve good control despite doses of corticosteroids reaching 1000 µg of fluticasone [36]. This suggests that even guidelines recommended treatment may not be efficacious in reducing the risk of the exacerbation prone phenotype.

Understanding severe asthma pathophysiology

The pathophysiology of SA is complex and likely differs by phenotypes. Several physiological and pathological studies have supported the importance of

small airway disease and increased air trapping. This field has been enhanced by the use of multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) techniques to better define structure in relation to function and biology. SA is associated with CT defined air trapping as well as airway wall thickening [14, 37]. Airway biopsy studies have suggested that the epithelium and lamina reticularis are thicker in some severe asthmatics, often in association with an eosinophilic inflammation. A mast cell phenotype (chymase expressing 'MCTC') is present in higher numbers, particularly in epithelium and associates with lower lung function, exacerbations and symptoms [38]. In the ENFUMOSA study, the persistence of eosinophils in induced sputum contributed to the hypothesis that SA might be characterized by a diminished or sub-optimal sensitivity to glucocorticosteroids [6]. The presence of increased neutrophils in the circulation and the sputum was found as well. This phenomenon has been associated with virus-induced exacerbations of asthma, sudden onset fatal asthma and prolonged corticosteroid treatment (which protects neutrophils from apoptosis). It has been concluded that neutrophils may be important in pathology of severe chronic airway disease because of their capability of causing tissue destruction similar to what can be found in COPD [6]. A particular role of interleukin-17 (IL-17) produced by a subset of CD4 cells, named Th17 cells could also play a role in recruiting and activating neutrophils and eosinophils in airway diseases [39]. To further analyse chronic inflammation underlying pathophysiology of SA, cytokines levels in bronchoalveolar lavage (BAL) fluid were studied. Brasier *et al.* [22] found that amongst several studies molecules IL-1Ra, MIP-1a, MIG, IL-15, IL-2R, IP-10, IL-4, IL-6, MCP-1 and IL-2 were the most informative to enable differentiation in between different clusters and severity levels. In patients with SA, IL-4 and IL-6 were slightly increased, whereas levels of IL-1Ra, MIP-1a, MIG, IL-15, IL-2R, IP-10 and IL-6 were decreased as compared with nonsevere asthmatics. No significant differences were found between patients taking inhaled corticosteroids versus those not taking corticosteroids. Fitzpatrick *et al.* [40] analysing BAL from 53 children found that IL-13 and IL-6 differentiated subjects with asthma from controls, whereas growth-related oncogene (CXCL1), RANTES (CCL5), IL-12, IFN-gamma, and IL-10 best characterized severe versus moderate asthma. However, in another study in children, Bossley *et al.* [41] could not find any differences in BAL fluid IL-4, IL-5 or IL-13 levels in patients with SA compared with control subjects.

Thus, a clear handprint of cytokines typical for severe asthma has not been clearly established yet. Further studies are needed, probably in better pre-defined phenotypes of the disease.

Oxidative stress is also likely to play a role in SA, as fraction of exhaled nitric oxide (FeNO), arginase, superoxide dismutase (SOD) and urinary bromotyrosine (as a marker of eosinophil peroxidase activity) have all been associated with SA, airflow obstruction, risk of exacerbations and importantly an eosinophilic phenotype [14]. Tobacco smoke exposure and elevated oxidant burden have been associated with corticosteroid insensitivity [42]. In mechanistic experiments, corticosteroid insensitivity in blood mononuclear cells and lung macrophages was linked to extensive activation of mitogen-activated protein kinases and decreased activity of nuclear histone deacetylase and histone acetyltransferase [14]. Dysregulation of lipid mediators, including reduced lipoxin A₄ and receptor expression [43], as well as prostaglandin D₂ [38] have also been reported in SA, each of which may offer additional therapeutic options.

Understanding the critical elements of the pathobiology of SA will be determined by the response of these patients or specific phenotypes to biologically targeted therapies. One example of such therapy is omalizumab, a monoclonal antibody to IgE. This treatment has shown efficacy in a phenotype of atopic, SA [44] by decreasing the circulating IgE and thus downregulating expression of its high affinity receptor (FcεRI) on mast cells involved in allergic reactions [45]. Recent trials showed that use of the anti-interleukin (IL)-5 monoclonal antibody (mepolizumab) could decrease exacerbations [46], systemic steroid use [47] and increase quality of life in asthmatic subjects [46]. This approach is particularly targeted to those asthmatics with remaining eosinophilic inflammation. A study with a targeted, Th2-focused therapeutic approach with a monoclonal antibody to IL-13 as mentioned previously, improved lung function and tended to decrease exacerbations in those fitting a Th2 phenotype [20]. Thus, these effective therapies are beginning to tease out the biological pathways of relevance to phenotypes of SA. Data from additional targeted interventions will continue to dissect the critical pathobiology pathways in SA and its phenotypes.

Severe asthma in children

Severe asthma in children has also been confounded by the difficulty in determining whether the asthma is truly severe or whether it is just diffi-

cult to treat because of confounding issues. Problematic SA has been proposed to describe children with any combination of chronic symptoms, severe exacerbations and persistent airflow limitation despite prescribed therapy [48]. Three steps are needed to approach problematic asthma in children: confirmation that the problem is really caused by asthma (often requiring a complete diagnostic re-evaluation), treatment of comorbidities and personal or family psychological disorders, and re-evaluation of medication adherence, inhaler technique and environmental factors, all of which may impact the level of asthma control. Large scale cohort studies of SA in children are still lacking. In a national Swedish cross-sectional, multicentre study [49] of children with persistent asthma, 54 patients with problematic disease were identified. Most of them (61%) had therapy-resistant asthma, and the rest were difficult to treat because of several identified aggravating factors. Children with problematic asthma more often had parents with asthma, came from families with a lower socio-economic status, were less physically active and had more comorbidity including rhinoconjunctivitis. Although SA in children has not been studied in a network-wide approach in Europe, studies have suggested that much of the SA described in children is actually poorly controlled asthma [50]. However, a portion of these patients remain severe and poorly controlled despite management of confounding factors, including evidence for ongoing eosinophilic inflammation despite high-dose systemic steroids. Little is understood regarding the underlying pathogenesis of these severe asthmatic children [51].

In the United States, an analysis of nearly 300 children participating in the SARP study revealed that children with SA were defined by lower lung function and higher healthcare utilization than milder asthmatic children. Although not defined by these additional characteristics, severe asthmatic children also more atopic/allergic had peripheral blood eosinophilia, elevated serum IgE levels and sustained increases in FeNO [14, 52]. They also were more likely to be younger at diagnosis of asthma.

New direction in research on asthma

Several new directions have been evaluated recently to improve our understanding of asthma. Thamrin *et al.* [53] reported associations between fluctuations in lung function and asthma control in two asthma cohorts with different severity of the disease. They took advantage of a new and interesting

mathematical tool, namely detrended fluctuation analysis [54], to evaluate the hypothesis that past history of fluctuations in lung function provides additional information for the assessment of asthma control. It has been found that α , as a variable representing the strength of correlation with past lung function and asthma stability and PEF, both evaluated over six months of follow up, were significantly associated with GINA-defined control level. The authors concluded that fluctuation analysis may provide further insight into the future risk of an individual patient to have exacerbations of the disease. Defining new outcomes, including this lung function fluctuation analysis, as well as other clinical and biological (genomic, transcriptomic, proteomic and metabolomic) data may allow for better classification and phenotyping of asthma by the use of mathematical modelling in a systems biology approach [55].

How can we use this expertise to increase our understanding of severe asthma?

Asthma remains a major health problem and severe asthmatics require a disproportional amount of healthcare resources. What seems to be clear is that medical science is changing from single site, small studies into international, collaborative trials including huge numbers of cooperating centres. Those trials are often not industry sponsored but mostly investigator or government initiated studies, managed by academia. Combining expertise in different fields (clinical medicine, basic studies, computing methods, data management, biostatistics and systems biology) may trigger further advances. In contrast with a single-centre approach, collaborative trials allows enrolment of greater number of subjects, greater diversity and lower possible bias. We are hoped that international cooperation in the area of respiratory diseases, including severe asthma, across the Atlantic Ocean, will lead to a better understanding of asthma pathology, especially of those severe, not well controlled or difficult-to-treat cases.

Conflict of interest statement

No conflict of interest to declare.

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