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Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: http://www.tandfonline.com/loi/icmo20

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To cite this article: Daniel Colodenco, Oscar Palomares, Carlos Celis, Alan Kaplan & Christian Domingo (2017): Moving toward consensus on diagnosis and management of severe asthma in adults, Current Medical Research and Opinion, DOI: 10.1080/03007995.2017.1380617

To link to this article: http://dx.doi.org/10.1080/03007995.2017.1380617

Accepted author version posted online: 14 Sep 2017.

Moving toward consensus on diagnosis and management of severe asthma in adults

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Transparency statement

Declaration of funding
This work was funded by Novartis Pharma AG, Basel, Switzerland.

Declaration of financial/other relationships
D.C. has served on advisory boards, speaker panels, or received travel reimbursement for Altana, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck (Schering-Plough), Novartis, and Teva; he has received research, consulting, and lecturing fees from GlaxoSmithKline, Schering-Plough, Altana, AstraZeneca, Merck, Novartis, Boehringer-Ingelheim, Teva, and Phoenix.
O.P. has received research grants from Inmunotek SL; payment for lectures from Inmunotek SL, Stallergenes, Allergy Therapeutics, AstraZeneca, and Novartis; and has participated in advisory boards for Novartis, and Sanofi Genzyme.
C.C. has served on advisory boards, speaker panels or received consulting and lecturing fees from GlaxoSmithKline, AstraZeneca, and Novartis Colombia.
A.K. has served on advisory boards, speaker panels, or received travel reimbursement for AstraZeneca, Boehringer-Ingelheim, Griffols, GlaxoSmithKline, Mylan, Novartis, Sanofi, Teva, and Trudell.
C.D. has served on advisory boards, speaker panels and or received lecturing fees and travel reimbursement for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck (Schering-Plough), Novartis, Sanofi Aventis, Menarini, Chiesi, Pfizer, Teva, Esteve, Ferrer, Rovi, ALK, Stallergens, Immunotek, Allergy terapeutics, Hal Allergy, and Leti. During the last 5 years, he has conducted multicenter clinical research trials for GlaxoSmithKline, Sanofi-Aventis, TEVA, and Novartis.

CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions
All authors were involved in the conception and design, or analysis and interpretation of the data; the drafting of the manuscript, and revising it critically for intellectual content. All authors approved the final approval of the version to be published. All authors agree to be accountable for all aspects of this work.

Acknowledgments
The authors thank Rahul Lad, PhD and Praveen Kaul, PhD of Novartis for providing medical writing support, which was funded by Novartis Pharma AG in accordance with Good Publication Practice (GPP3) guidelines.

Abstract

Asthma is a considerable health problem with an increasing global prevalence. The burden of severe asthma is expected to notably increase in the following years. Some misleading concepts that sometimes appear in the literature can drive the physician responsible for the patient's management to make incorrect decisions. Furthermore, some of the concepts that appear in the literature and in the guidelines may be not be clear to understand, to follow or to adapt to the regional and local realities. This could again drive the physicians responsible of the patient's management to make incorrect clinical judgements.

In this article, we review the definition, prevalence and immunopathology of severe asthma, describe the asthma phenotypes, clinical features and comorbidities, the diagnosis of severe asthma and personalized asthma treatment. At the end, we offer a treatment approach based on the literature publications, personalized medicine and marketed biologic treatment options.

Keywords: Consensus, Diagnosis, Disease Management, Severe asthma, Treatment

Definition of severe asthma

Asthma is recognized as one of the most common chronic diseases in adults and a considerable health problem with an increasing global prevalence [1]. Approximately 334 million people have asthma, and it leads to approximately 250,000 deaths per year worldwide [2]. In order to manage asthma most effectively, an accurate evaluation of asthma severity is important. However, measures for defining severe asthma are inconsistent among different prominent guidelines (**Table 1**): the International European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines and the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) provide criteria-based definitions for severe asthma, among which corticosteroid use is a major factor in determination of severity [3]; the World Health Organization (WHO) uses the level of current clinical control and associated risks to define severe asthma [4]; according to the Global Initiative for Asthma (GINA) strategy, definition of severe asthma is based on retrospective assessment of the level of treatment required to control symptoms and exacerbations [5].

Severe asthma has been broadly categorized into three groups, according to various treatment scenario challenges: (i) untreated severe asthma: resulting from under-diagnosis, misdiagnosis or unavailability of therapy; (ii) difficult-to-treat severe asthma: associated with treatment adherence issues, inappropriate or incorrect use of therapy (appropriate use of inhalers, regular use, insufficient dose of asthma medication, etc.), and presence of environmental triggers or comorbidities; (iii) treatment-resistant severe asthma: includes asthma that is controlled or not controlled despite the highest dose of recommended treatment or asthma [6]. It is important to note that the definition of uncontrolled asthma because of poor adherence coincides with the definition of severe asthma, since the former also affects patients' quality of life (QoL) and is linked with an increased risk of exacerbations [7]. Of note, an estimated 20% of patients with severe asthma have uncontrolled disease [7], and thus it is important to distinguish between severe asthma and uncontrolled asthma. In this regard, the most practical definition of severe asthma comes from the ERS/ATS guidelines that appeared in 2014 [3]. Uncontrolled asthma is defined as at least one of the following: (i) poor symptom control: asthma control questionnaire (ACQ) score consistently >1.5; asthma control test (ACT) score <20 (or 'not well controlled' as per the national asthma education and prevention program [NAEPP]/GINA guidelines); (ii) frequent severe exacerbations: required two or more bursts of systemic corticosteroids (≥3 days each) in the previous year; (iii) serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year; (iv) airflow limitation: postbronchodilator forced expiratory volume in 1 second (FEV_1) <80% predicted (FEV_1/forced vital capacity [FVC] <70%); (v) controlled asthma that worsens on tapering of high doses of ICS or systemic corticosteroids (or additional biologics) [3].

Furthermore, increasing evidence suggests that severe asthma is not a homogeneous disease, given the variety of observable characteristics, physiological characteristics, and clinical outcomes [8,9]. It is an umbrella term that encompasses a highly heterogeneous population of patients, which has several different definitions in the literature [10,11]. Overall, at least four reasonably well-defined phenotypes/endotypes of severe asthma have been described, characterized according to the natural history of the disease, pathogenesis, clinical features, and response to treatment: severe allergic asthma, late-onset eosinophilic asthma, severe non-atopic asthma in obese adults, and adult-onset neutrophilic asthma [12]. In light of the heterogeneous nature of severe asthma consisting of different clusters, several studies have attempted to define phenotypic biomarkers, and develop targeted therapies [13–16].

There is also a tendency to include, under the definition of severe asthma, nonadherence to recommended treatment, smoking, obesity, health care resource utilization, psychological conditions, laryngeal dysfunction and gastroesophageal reflux disease, etc. These criteria may not necessarily be linked to the core cause of severity of the disease but cannot be completely ruled out as just co-morbidities or "effects" of severe asthma.

Guideline definitions of severe asthma and subsequent treatment recommendations are widely inconsistent because they have used different criteria to define suboptimal asthma control [16]. The differences in criteria are broadly centered on interpreting clinical evidence and framing recommendations [17]. This lack of agreement between different guidelines may contribute to the variations in clinical practice [16,17]. Considering the important consequences of dissimilarities among guideline definitions and recommendations, consistency on a common set of validated and clear methods across global and regional guidelines could harmonize treatment recommendations and facilitate appropriate implementation of such guidelines in the management of severe asthma.

Prevalence and burden of severe asthma

Available data regarding the prevalence of severe asthma differ across studies; overall, it is estimated that patients with severe asthma represent 5%–10% of the entire asthma population [18]. Nevertheless, this small proportion of patients is accountable for a substantially higher use of healthcare resources than other asthmatic patients [19]. A global survey on severity and control of asthma in children and adults revealed that the prevalence of severe asthma varied across different countries and regions (18% in Western Europe, 19% in the United States, 11% in Asia-Pacific, 15% in Japan, and 32% in Central Europe) [20]. Despite these variations among countries, a substantial impact was observed on patients' lives: frequent use of emergency services, admissions, high use of systemic corticosteroids, marked limitations in everyday life and sports, significant loss of school and work days, and elevated risk of death [20–22].

Data regarding the prevalence of severe asthma in Latin America are limited; however, results from a few studies provide indirect insights regarding the prevalence and burden of this disease in this particular region. In the Asthma control in Latin America (the Asthma Insights and Reality in Latin America [AIRLA]) survey conducted in 11 countries in Latin America, over half of asthma patients had been hospitalized or had used emergency care because of asthma in the past 12 months [23]. Moreover, in this survey, the rate of hospitalization in the past year (22%) was much higher than that reported in the Asia-Pacific (AIRIAP) survey (15%) [24], the European (AIRE) survey (7%) [25] and the Asthma in America national population survey (9%) [26]. In the 2011 Latin America Asthma Insight and Management (LA AIM) survey, 23% of all included patients reported hospitalizations, while 44% reported unscheduled urgent or emergency visits in the past 12 months [27]. Severe asthma had a significantly greater negative impact on patients than the non-severe form of the disease such that these patients having 15-times higher risk of emergency room visits, 20-times greater risk of hospitalization, more frequent use of systemic corticosteroids and risk of associated side effects, and greater likelihood of experiencing near fatal and fatal events [28]. Moreover, uncontrolled severe asthma is a significant health concern because it is associated with significant morbidity and healthcare resource use along with substantial indirect costs attributed to productivity losses [29]. In exacerbating patients, severity of asthma is associated with greater severity of exacerbations [30]. Furthermore, increased severity of asthma has been associated with worsening of symptoms and higher resource utilization [31]. The burden of asthma is strongly associated with disease severity, and consequently, increased asthma burden is strongly associated with reduced health-related QoL [32]. Compared with mild-to-moderate asthma, severe asthma is more likely to be associated with comorbidities such as chronic rhinosinusitis with and without nasal polyps, hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), gastroesophageal reflux disease (GERD), bronchiectasis, chronic eosinophilic pneumonia, allergic bronchopulmonary mycosis, and recurrent infectious bronchitis [33]. Therefore, a clear unmet need exists for an effective and well-tolerated treatment for inadequately controlled severe

persistent asthma. Collectively, these findings emphasize the need to consider severe asthma as a major public health concern with considerable socioeconomic implications.

Immunopathology of severe allergic asthma

Most patients with severe asthma usually show a sensitization (positive skin prick test) to ≥1 aeroallergen [19,28,34]; nevertheless, a negative association between allergy and severe asthma was found in the large European Network For Understanding Mechanisms of Severe Asthma (ENFUMOSA) survey [35]. A majority of patients with severe asthma exhibit higher levels of immunoglobulin E (IgE) [36]. In addition, the role of eosinophils has been recognized in severe asthma as eosinophilic inflammation of the airways is correlated with severity [37].

As observed in **Figure 1**, upon first allergen exposure, antigen-presenting cells such as dendritic cells (DCs) induce type 2 response to sensitize T cells (e.g. $CD4^+$ T cells) and direct their maturation into T-helper 2 (Th2) cells [38,39]. This triggers the overproduction of specific cytokines such as interleukin (IL)-4, IL-5, and IL-13 by Th2 cells. IL-4 and IL-13 increase the low-affinity FcεRII receptor expression and trigger relevant B cells to produce allergen-specific IgE [40]. During their progression to IgE-secreting plasma cells, B cells also express membrane-bound IgE, which assists in antigen processing and signal transduction. In the presence of the Th2 cytokines IL-4 and IL-13, class switching occurs in B cells, leading to production of IgE isotype antibodies specific for the trigger allergen [40,41]. On subsequent exposure to allergens, and their interaction with IgE bound to high-affinity FcεRI receptors on basophils and mast cells, the cross-linking of IgE triggers basophil and mast cell degranulation as well as release of inflammatory mediators such as histamines, tryptase, cysteinyl leukotrienes, prostaglandins, and platelet-activating factors. These mediators lead to manifestation of key symptoms of immediate allergic response, including bronchoconstriction, generation of edema in the airway walls, and increased production of mucus [42,43]. The events driven by the preformed mediators of mast cells and basophils during early allergic response lead to production and release of cytokines and chemokines such as IL-3, IL-4, IL-5, IL-13, CC chemokine ligand-5, and granulocyte-macrophage colony-stimulating factor, which recruit eosinophils, basophils, T cells, neutrophils and macrophages to the site of inflammation [44]. This process, referred as the late allergic/asthmatic response, promotes mucus hypersecretion, airway inflammation, and airway hyperresponsiveness (**Figure 1**) [45]. Of note, while allergic asthma is primarily driven by allergen-specific Th2 lymphocytes, Th17 cells are primarily involved in pathogen-induced asthma, wherein neutrophils more than eosinophils, contribute to the inflammation (**Figure 1**).

Type 2 immune responses have been implicated in the pathogenesis of viral-induced asthma exacerbations. Plasmacytoid dendritic cells (pDCs) are a subset of blood DCs that are recruited in the airways during acute viral infection [46]. The pDCs, through expression of Toll-like receptor (TLR)-7 and TLR9, induce the rapid production of large amounts of type I interferon (IFN) in response to a viral infection, thus playing a key role in viral clearance [47]. Patients with allergic asthma express increased surface FcεRI on pDCs, which is associated with reduced IFN-α secretion by pDCs in response to viruses [48]. Moreover, cross-linking of FcεRI in response to IgE is associated with decreased expression of TLR7 and TLR9 as well as with impairment of TLR7- and TLR9-mediated production of IFN-α in pDCs upon viral exposure [49,50]. This supports a key role of IgE in the pathogenesis of viral-induced asthma exacerbations whereby IgE cross-linking impairs virus recognition and IFN-α production by pDCs.

Production and release of inflammatory cytokines during the late phase and subsequent chronic inflammatory stage are associated with the induction of airway remodelling [51]. For instance, IL-4 induces synthesis and release of IgE from B cells and is suggested to be a mediator of airway remodelling by increasing synthesis of α-smooth muscle actin and collagen III [52]. The bronchial epithelial cells of asthmatics express the high-affinity receptor for IgE [53]. Moreover, human airway smooth muscle (HASM) cells express both low- and high-affinity IgE receptors [54]. Recent in vitro data suggest that IgE

might play a direct role in airway remodelling by increasing extracellular matrix and collagen deposition, proliferation and contraction in HASM cells through mechanisms depending on both high- and low-affinity IgE receptors [55,56].

As described earlier, eosinophils are known major inflammatory cells involved in the pathophysiology of asthma. These also play a role in airway remodelling through production and expression of several fibrogenic factors, particularly transforming growth factor (TGF)-β1 [57]. The cytokine IL-5 primarily drives eosinophil proliferation, maturation, activation, and survival, which are associated with severe, difficult-to-treat asthma [58]. Furthermore, IL-13 stimulates eosinophilic airway inflammation and promotes mucus metaplasia, subepithelial fibrosis, and airway remodelling [59]. While in the lung, eosinophils stimulate secretion of cytokines (IL-13 IL-5, TGF-β, and osteopontin), chemokines (CCL-11, CCL22, matrix metalloproteinases [MMPs] and granule mediators [e.g., erythropoietin and major basic protein]), and leukotrienes (LTC4 and LTB4) [60]. Recently, prostaglandin D2 (PGD2) has been shown to play a vital role in mediating eosinophilic airway inflammation in asthma through stimulation of Th2 cell migration, delayed Th2 cell apoptosis, and production of IL-4, IL-5, and IL-13 [61]. Periostin, a matricellular protein, has also been implicated in eosinophil recruitment [62].

In-depth understanding of the central roles of IgE and eosinophils along with associated cytokines in the pathophysiology of severe asthma has led to identification of several distinct underlying mechanisms for initiation and progression of the disease.

Asthma phenotypes

A phenotype is defined as an observable property of an organism that is produced by the interaction between the genotype and the environment [63]. GINA defines 'asthma phenotypes' as recognizable clusters of demographic, clinical, and/or pathophysiological characteristics; however, there is uncertainty regarding how these characteristics could correlate with specific pathological processes or treatment responses [5]. Nevertheless, asthma phenotyping is important to appropriately classify patients with a complex disease such as asthma, which includes several disease variants. Historically, asthma has been separated into two distinct phenotypes termed extrinsic (allergic) and intrinsic (non-allergic) asthma, both characterized by eosinophilic inflammation [64,65]. The concept of asthma phenotypes is still evolving, and a few prominent asthma phenotypes based on clinical characteristics, triggers, or general inflammatory processes and response to treatment have been proposed [66] and are described here: (i) Allergic asthma: this is the most recognizable phenotype, which often commences during childhood and is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergies. Examination of induced sputum of such patients before treatment often reveals eosinophilic airway inflammation [67]. Patients with this asthma phenotype usually respond well to ICS treatment [66]. (ii) Non-allergic asthma: this refers to asthma in adults that is not associated with allergies. Sputum of such patients may contain neutrophils and eosinophils or even only a few inflammatory cells. Moreover, patients with non-allergic asthma often respond poorly to ICS [5,68]. (iii) Late-onset asthma: certain adults, particularly women, present with asthma for the first time during adult life. Such patients tend to be non-allergic, and often require higher doses of ICS or are relatively refractory to corticosteroid treatment [5,69]. (iv) Asthma with fixed airflow limitation: certain patients with long-standing asthma develop fixed airflow limitation that is thought to be caused by airway remodelling [70]. (v) Obesity-related asthma: certain obese patients, primarily women, with asthma have prominent respiratory symptoms and limited eosinophilic airway inflammation. Such patients are responsive to weight loss, antioxidants, and possibly hormonal therapy.

It is imperative to consider the frequency of severe asthma in these different phenotypes in order to gauge the correlation between distinct patient characteristics and disease severity. For example, it has been observed that prevalence of severe asthma was similar in both early-onset and late-onset asthma and that there were few phenotypic differences between severe asthmatics independent of the age of onset [71,72]. Yet, a large gap exists in understanding the prevalence of severe asthma among different phenotypes and also in patients with particular demographic and clinical manifestations, e.g. smokers, obese, etc. A systematic approach to quantify the differences in prevalence of severe asthma in distinct phenotypes is expected to lead to identification of a unique target population for more focused and personalized treatment.

The concept of a phenotype has led to another concept of "endotypes", wherein a specific biological pathway is identified that explains the observable properties of a phenotype [73]. Although several endotypes of asthma have been proposed, disagreement remains on acceptance of this concept [65]. Both biased and unbiased approaches have started to connect the characteristics of asthma together to define phenotypes; however, no present system of subgrouping fulfils all the requirements for a true phenotype or endotype.

The most common approaches for identifying asthma phenotypes include the 'candidate approach' and the 'exploratory approach,' also called as the 'hypothesis-free approach' [73,74]. The 'candidate approach' defines phenotypes based on criteria selected by experts, representing one or few endotypes defined by a distinct functional and pathophysiological mechanism or components of the disease such as clinical or physiological categories, asthma triggers, pathobiology, and time course [75]. The 'exploratory approach' is based on applying unsupervised statistical methods to identify phenotypes and involves application of unsupervised statistical methods that group individuals within a population according to similarity of specified variables [73,76]. Notably, the concepts of phenotypes and endotypes are intertwined, wherein endotype is a specific biological pathway identified that explains the observable properties of a phenotype [70].

In conclusion, a true asthma phenotype should be described on the basis of consistent natural history, consistent clinical and physiological characteristics, an underlying pathophysiology with identifiable biomarkers and genetics, and a predictable response to therapy.

Clinical features of asthma and comorbidities

Asthma is a complex and heterogeneous disease characterized by recurrent episodes, varying over time and in intensity, of one or more respiratory symptoms such as wheezing, breathlessness, chest tightness, or cough [5,77]. Clinical features that increase the probability of asthma include more than one of the aforementioned common asthma respiratory symptoms, particularly if these symptoms are worse at night or early in the morning; in response to allergens, exercise, irritants (including work-related irritants), viral infections; varying over time and in intensity; worse after taking medications such as aspirin or β-blockers; a history of atopic disorder; family history of atopic disorder and/or asthma; wheezing; low FEV_1 or peak expiratory flow (PEF); and childhood asthma diagnosis [5,78,79].

The frequency and persistence of dyspnea and cough is greater in severe asthma, particularly in older patients, and has been associated with poorer lung function [80,81]. The consequences of dyspnea such as low functional status and physical inactivity have not been as thoroughly assessed in severe asthma as it has been in chronic obstructive pulmonary disease (COPD) [82]. Clinical features of asthma often overlap with other respiratory conditions; therefore, it is important to ensure that other possible diagnoses such as COPD, vocal cord dysfunction, or asthma-COPD overlap syndrome are ruled out before diagnosing a patient with asthma [79,83]. The prevalence of comorbidities is particularly high in severe asthma; cohort studies such as The Epidemiology and Natural History of Asthma: Outcomes and

Treatment Regimens (TENOR), Severe Asthma Research Program (SARP), Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome Consortium (U-BIOPRED), and Belgian Severe Asthma Registry (BSAR) have reported increased incidence of rhinitis, chronic rhinosinusitis, nasal polyps, aspirin sensitivity, smoking, gastroesophageal reflux and obesity in patients with severe asthma [80, 84–86]. In addition, dysfunctional breathing, vocal cord dysfunction, bronchiectasis, metabolic syndrome, type 2 diabetes mellitus, hypertension and cardiac diseases have emerged as significant comorbid conditions in such patients [87]. Notably, patients with asthma-associated bronchiectasis had lower FEV_1 values than did those without bronchiectasis, but the levels of Ig and subclasses of IgG were similar. Moreover, steroid-dependent asthma was associated with a greater risk of developing bronchiectasis than non-steroid-dependent asthma [88]. Moreover, severe asthma has been associated with psychological disorders such as anxiety, depression, and lack of trust toward healthcare providers [89].

Comorbidities can influence accurate diagnosis of severe asthma, assessment of disease control and efficacy (e.g., smoking and obesity), or even adherence to therapy (respiratory infections and psychological disorders) [90]. In severe asthma, the presence of comorbidities has been associated with poor asthma control, higher risk of exacerbations, decreased QoL and increased healthcare use and medical costs [91,92]. Comorbidities may also affect the choice of treatment since these may define asthma phenotypes (e.g. atopy, obesity, aspirin intolerance, and smoking) [93]. Identification of comorbidities is now recognized by ATS/ERS guidelines [3] as an integral part of management of severe asthma and a targeted approach has recently been recommended to overcome the need for several outpatient consultations, while also considering resource utilization [94]. At initial evaluation, a battery of validated screening questionnaires (allergic rhinitis/chronic rhinosinusitis, vocal cord dysfunction, dysfunctional breathing, obstructive sleep apnea, anxiety and depression, and GERD) are administrated; owing to their high negative predictive value, focused referrals (e.g. ENT, psychiatry, and speech therapy) and examinations (e.g. laryngoscopy, polysomnography, and sinus/laryngeal CT) are requested when positive scores are observed [93]. Two recent studies have reported the benefits of this approach [95,96].

It is worth noting that treatment decisions are largely driven by initial therapeutic outcomes and often involve trial and error and constant adjustment of therapy, independent of the underlying cellular pathogenic profile of asthmatics. For instance, both neutrophilic and eosinophilic asthma may present clinically similar features; thus, these patients may not be treated differently based solely on specific cellular and molecular markers [97]. Furthermore, biomarkers such as fractional exhaled nitric oxide (FeNO) and eosinophils (e.g. sputum eosinophilia) are used to determine and monitor the level of airway inflammation and severity of asthma; however, the differences in individual responses and differences in levels of these biomarkers across different asthma phenotypes make tailored interventions based on these biomarkers difficult [98,99]. Nevertheless, the promise still remains that cellular markers and associated clinical features will ultimately guide effective personalized treatment of severe asthma.

Furthermore, as evidence suggests that treatment of comorbidities improves asthma outcomes, a systematic search of asthma comorbidities and their management, ideally in the context of a severe asthma center, offers a potentially important approach toward improving control and decreasing burden of the disease on the healthcare system [95–97,100].

Diagnosis of severe asthma

Inaccurate diagnosis leads to incorrect treatment, and this issue is exemplified in a complex heterogeneous disease such as asthma, which is often incompletely or inaccurately diagnosed. Clinicians should be careful while diagnosing asthma and should clearly establish whether the patient's history and symptom evaluation represent asthma [101]. Cases of non-asthmatic conditions misdiagnosed as uncontrolled asthma have been reported to be approximately 12%–30% [102]. Clinicians should begin with careful evaluation of the patient's history, emphasizing on asthma symptoms such as dyspnea (and relation to exercise), cough, chest tightness, wheezing, and night-time awakenings [5,103]. In addition, information on risk factors, exacerbation triggers, and environmental or occupational factors that may contribute toward the presenting symptoms should be collected [5]. Adults and children should be assessed for other conditions that may resemble or be associated with asthma. Such masquerading conditions in adults include dysfunctional breathlessness/vocal cord dysfunction, COPD, bronchiectasis/cystic fibrosis, airway tumors, hypersensitivity pneumonitis, pulmonary embolism, congestive heart failure. In children: allergic bronchopulmonary aspergillosis and cystic fibrosis [104]. Spirometry measurements, following pre- and post-bronchodilator administration, should be obtained to confirm reversible airflow limitation for the diagnosis of asthma [105]. Additional assessments using pulmonary function tests and bronchoprovocation testing, such as methacholine or exercise challenges, in cases of relatively stable lung function can be considered on a case-to-case basis, particularly when patient history, physical characteristics, and spirometry measurements are inconsistent; other tests such as FeNO measurement and induced sputum cellularity can help in the diagnosis and management of patients with severe asthma [5,6].

It has been agreed that a diagnosis of severe asthma should be reserved for those patients who have refractory asthma after an extensive re-evaluation of the correct diagnosis, aggravating comorbidities and environmental factors, and an appropriate observation period of at least 6 months [106]. Moreover, poor treatment adherence should be considered in severe asthmatics [107,108]. In case of poor treatment adherence, clinicians should enable their patients to make informed choices about their medicines and also develop individualized interventions to overcome poor adherence [107,108].

In light of the association of atopy and allergy with severe asthma, assessing the relationship between specific IgE (as measured by skin prick or serum testing), allergen exposure, and symptoms may help identify factors that contribute toward asthma symptoms and exacerbations [109]. Furthermore, severe asthma should be distinguished from uncontrolled asthma. As stated earlier, severity of asthma can be characterized by pathological and physiological markers, whereas uncontrolled asthma refers to the extent to which symptoms of asthma have not been reduced or eliminated by treatment [109], as indicated by current symptoms, rescue medication use, and lung function, as well as future risks [5,110]. Nevertheless, it is noteworthy that exacerbations are a hallmark of both severe and poorly controlled asthma.

There is a substantial need to refer appropriate asthma patients to a specialist who can systematically evaluate the patients. Before referral, primary care clinicians play a pivotal role in identifying the factors behind poor asthma control (e.g., poor adherence, inhaler technique), checking for comorbidities, conducting initial tests for biomarkers including a complete blood count for blood eosinophils, and IgE levels [5]. Referrals to specialists have resulted in approximately 30%–50% of patients previously assumed to have severe asthma, being classified as having difficult-to-control asthma [111]. Several guidelines recommend referring asthma patients with co-morbidities or with severe asthma to specialist referral centers. The control achieved in such specialized units has been shown to be effective and efficient [112–114].

GINA specifically recommends that asthma treatment should be determined on the basis of the level of asthma control, and suggests referring patients in steps 4 and 5 (severe asthma) to a specialist,

so that they can be assessed for additional add-on treatment, such as anti-IgE therapy or mepolizumab, which is preferred over oral corticosteroids [5].

Overall, diagnostic assessments that aim to clearly establish the presence of asthma and appropriately identify the 'right' patients are a part of the larger precision treatment approach used for asthmatics. Precision treatment approaches have shown benefits in well-characterized patients with severe asthma and can also be valid and practically viable in other asthma patients in primary care settings.

Personalized asthma treatment

Current asthma treatment guidelines typically recommend nonspecific anti-inflammatory drugs such as ICS and oral corticosteroids as mainstays of treatment and bronchodilators as first-choice add-on therapy for a majority of patients [5]. It is noteworthy that although these guidelines discuss the management of patients with severe asthma, these were not designed with a phenotype- or endotype-driven approach toward treatment. Moreover, the current anti-inflammatory treatment paradigm with corticosteroids is not based on biological measures that may vary among different asthma phenotypes [34,112]; thus, there is marked patient-to-patient variability in the therapeutic response to corticosteroids, as seen in the GOAL study wherein patients on corticosteroids could not achieve full control [113]. The guidelines recommend an asthma severity-based stepwise approach to control asthma symptoms and minimize future risks, with stepping up treatment until control is achieved and maintained [5]. For instance, step 4 treatment comprises two or more controllers plus as-needed reliever medication and step 5 includes higher-level care and/or add-on treatment [5]. Stepping up therapy may work well for certain patients, but addressing treatment adherence, rectifying self-management deficiencies and identifying comorbidities may be helpful in others [116]. Nevertheless, certain patients require more effective treatments and more often; such patients intrinsically have the severe, therapy-resistant form of asthma [6,117]. In such patients, a greater understanding of endotypes (biological mechanisms) and phenotypes (observable characteristics) with use of biomarkers to define 'responders' would allow targeting the disease with more effective treatments [118]. In this regard, development of biologics has offered a targeted approach for the treatment of severe asthma; major biologics for treatment of severe asthma are listed in **Table 2**.

Based on the close association of allergy with asthma, and identification of IgE as a key target of treatment, the anti-IgE monoclonal antibody omalizumab was one of the first biological agents to be developed and approved for treatment of asthma, and is now a part of treatment regimen for severe, inadequately controlled asthma [5,120,121]. Initially considered to only have an anti-IgE effect, omalizumab has been shown to have a modulatory effect on the entire allergic cascade [122]. Omalizumab reduced asthma exacerbations and improved other outcomes such as QoL, symptom scores, daily rescue medication use, and oral corticosteroid use [123–125]. A major concern with the use of omalizumab, and other biologics, has been an identification of criteria/markers to more specifically select patients for treatment. Studies in this regard have shown that along with IgE levels, higher levels of FeNO, blood eosinophil counts and blood periostin levels could predict treatment responses to omalizumab, particularly in terms of reduction in asthma exacerbations with their health impact, and systemic corticosteroids use [126].

Apart from the IgE-associated allergic phenotype, patients with late-onset eosinophilic asthma phenotype have persistent eosinophilic airway inflammation despite treatment with ICS, which is associated with more severe disease [127]. Therapeutics targeting T2 cytokines, including IL-4, IL-5 and IL-13, have been developed for patients with severe eosinophilic asthma. Current anti-IL-5 monoclonal antibodies include mepolizumab and reslizumab [128,129]. In large-scale studies on patients with

persistent sputum or blood eosinophilia, mepolizumab significantly reduced asthma exacerbations with corresponding decrease in eosinophils [127,130]. On the other hand, reslizumab showed significant reductions in asthma exacerbations along with improved lung function, asthma symptom control and QoL [131]. Interestingly, the eosinophil concentrations required in the mepolizumab and reslizumab studies were different (mepolizumab: ≥300 cells/μL during previous year or ≥150 cells/μL at screening; reslizumab: ≥400 cells/μL), and patients who showed greater improvements were those with eosinophil count >500 cells/μL [128,129].

The humanized anti-IL-5 receptor antibody, benralizumab afforded reduction in exacerbations in patients with severe uncontrolled asthma, with better treatment effects in patients with more severe disease [132,133]. Benralizumab also has a direct eosinophil cytotoxic effect [134].

Another monoclonal antibody on the horizon is dupilumab, an IL-4 receptor antagonist that blocks both IL-4 and IL-13 signal transduction [135]. In a phase II study, dupilumab reduced the risk of exacerbations associated with withdrawal of pharmacological treatment in patients with moderate-to-severe eosinophilic asthma [135–137]. Taken together, clinical and immunopathological characterization of patients is essential to allow selection of patients who are more likely to respond best to these novel treatments.

In line with the GINA strategy recommendation that treatment decisions should take into account patient phenotypes that predict their response to treatment, we propose a treatment algorithm in order to provide the best-suited treatment option to patients with severe asthma, as shown in **Figure 2**.

Along with aforementioned phenotype-based approaches, add-on treatments without phenotyping are also recommended for management of severe asthma. The long-acting muscarinic antagonist, tiotropium, improved lung function and increased time to first exacerbation in patients with uncontrolled symptoms and persistent airflow limitation despite moderate-to-high dosing of ICS/LABA [138]. Other add-on controller medications such as theophylline and leukotriene receptor antagonists are also suggested for severe asthma [5]. The macrolide antibiotic azithromycin was tested in patients with exacerbations-prone severe asthma and it significantly lowered the rate of severe exacerbations in the subgroup of patients with non-eosinophilic severe asthma [139]. In addition, immunosuppressive therapy with methotrexate has also shown efficacy in GINA treatment step 5 asthma patients [140]. Among non-pharmacological interventions, bronchial thermoplasty might be helpful in selected patients with severe asthma, frequent exacerbations, hyperresponsiveness and paucigranulocytic sputum sample, although at present this technique is recommended only for research studies [141,142].

In conclusion, in light of inter-individual variability in patients' response to treatments, better understanding of asthma phenotypes and emergence of targeted therapies represent major advancements toward personalized care in patients with severe asthma.

Follow up and outcomes of severe asthma treatment

Considering the chronic and heterogeneous nature of asthma, clinicians must regularly assess whether (or not) asthma control has been maintained and should determine subsequent clinical actions (i.e., whether to maintain or adjust therapy) based on the level of control at patient's follow-up assessments. Moreover, clinicians must monitor and review patient's daily self-management and action plans, medications, and patient's inhaler techniques. Guidelines usually recommend that if asthma is uncontrolled or in case of a change in medication or clinical status, patient should be followed up in 2–6 weeks for evaluation [5,143]. A stable asthma patient should be followed up at regular intervals of 1–6 months [5]. The frequency of monitoring should be determined on the basis of the disease severity and the treatment(s) being provided. For instance, treatment response to omalizumab is routinely assessed after 16 weeks of therapy during which physicians determine whether or not the therapy should be continued [144]. A suggested tool is physician's global evaluation of treatment effectiveness, which includes essential assessments such as asthma-related QoL, control of daily asthma symptoms, and supportive assessments such as peak expiratory flow, asthma exacerbations, and unscheduled healthcare resource utilization [145]. The National Institute for health and Care Excellence (NICE) recommends that for mepolizumab, treatment response should be assessed at 12 months of treatment to discontinue the treatment if the patient has not responded adequately or to continue treatment if the patient has responded adequately, following which treatment response is assessed each year [146]. In case of reslizumab, NICE recommends that patients should be closely monitored and treatment should be discontinued after 1 year if there has not been a significant (approximately 50%) reduction in oral steroid requirement or exacerbations; moreover, patients should be continuously monitored at 6-month intervals to ensure they are still clinically benefitting from the treatment [147].

Guidelines recommend that all patients with severe persistent asthma or a history of prior severe exacerbations requiring hospitalization should be referred to an asthma specialist or a specialized asthma clinic [5,112]. Typically, the follow-up after a visit to a severe asthma clinic should include assessment of patient-reported outcomes such as ACQ and ACT, along with regular spirometry assessments. In line of the complexity of severe asthma, systematic assessment of patients with severe asthma has increasingly been taken up by severe asthma clinics, which have expertise in diagnosis, severity assessment, assessment of comorbidities, assessment of adherence and technique in using devices, and individualized treatment for such patients [100]. Such clinics also make use of the expertise of specialist doctors, nurses, psychologists, physiotherapists, as well as other healthcare providers to systematically provide these multidisciplinary services [148]. The effectiveness of such an approach has been shown to improve QoL and asthma control and to reduce health care and oral steroid use [96]. Patients referred to a severe asthma clinic may have to travel to consult with 'super-specialists' for work-up and decision of therapy, but they need to be followed up close to home. Interventions such as telephonic reminders, transportation vouchers, and monetary incentives have been shown to increase the likelihood of follow-up appointments after a visit to an emergency department or a specialty clinic [149].

It is important that noninvasive techniques are devised to quantify biomarkers of disease, determine disease phenotype, and inform treatment during follow-up visits [101]. Numerous potential biomarker strategies (e.g., IgE, FeNO, sputum/blood eosinophil counts, IL-5, and periostin) are now emerging that may predict outcomes in asthma, but the value of such strategies still needs to be assessed in the context of following up patients with severe disease [150].

Physicians should regularly assess the side effects of treatments in patients (particularly in patients who need to be treated with oral corticosteroids) and step-down of therapy should be considered in those patients who obtain and maintain good control of their asthma [5]. Asthma education should be regularly provided to patients, which should include basic facts about asthma, how medications work, inhaler technique, a written action plan including peak flow rate monitoring or a

symptom diary, environmental control measures, and emphasis on the need for regular follow-up visits [151]. Finally, regular follow-up communication between primary physicians, specialists and severe asthma clinics should lead to informed assessment of actual disease control, optimized treatment strategy, and better clinical outcomes in patients with severe asthma.

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Table 1. Definitions of severe asthma

Strategy document/Guideline	Definition
ERS/ATS	When the diagnosis of asthma is confirmed and comorbidities are addressed, severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroid (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled,' or as asthma that remains 'uncontrolled' despite this therapy
ENFUMOSA	Patients who meet at least three of the following criteria: under the care of a consultant in asthma for at least 2 years; persistent symptoms and quality of life impairment; receipt of maximal usual asthma therapy and/or medications (high doses of inhaled corticosteroids) and documented adherence to therapy; previous respiratory failure/intubation/near-fatal episodes; repeated FEV_1 <70% predicted
WHO	Uncontrolled asthma that can result in a risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidities
GINA	Asthma that requires treatment as per steps 4-5 (with high-dose ICS and a long-acting β_2-agonist [LABA] or a leukotriene modifier/theophylline) in the previous year or treatment with systemic corticosteroids for at least 6 months in the same period to prevent it from becoming 'uncontrolled,' or as asthma that remains 'uncontrolled' despite the therapy

ATS, American Thoracic Society; ENFUMOSA, European Network for Understanding Mechanisms of Severe Asthma; ERS, European Respiratory Society; GINA; Global Initiative for Asthma; WHO, World Health Organization

Table 2. Major biologics for the treatment of severe asthma

Drug	Mechanism of action	Current status	Average Annual treatment costs* (in USD)[119]
Omalizumab (Xolair®)	Binds free IgE	Approved for clinical use	10000–16000[#]
Mepolizumab (Nucala®)	Inhibits IL-5	Approved for clinical use	30000[##]
Reslizumab (Cinqair®, Cinqaero®)	Inhibits IL-5	Approved for clinical use	25000–30000[###]
Benralizumab[†]	Inhibits binding of IL-5 to IL-5Rα receptor plus a direct eosinophil cytotoxic effect	In clinical development; Phase III	-
Dupilumab[†]	Blocks IL-4Rα receptor	In clinical development; Phase III	-

*approximate costs.

[†]Not in market for asthma treatment at the time of manuscript acceptance.

[#]Subcutaneous dose regulated by body weight and serum IgE levels (maximum allowed dose: 1200 mg/month; dose range:

75–1200 mg/month [in some countries the dose range is 75–750 mg/month]).

[##]Fixed subcutaneous dose (100 mg/month).

[###]Intravenous dose regulated by patient´s body weight (recommended dose: 3 mg/kg per month).

Figure 1. Contribution of adaptive immunity to the pathogenesis of allergic asthma

IL, interleukin; IgE, immunoglobulin E; Th2, T-helper 2; Th17, T-helper 17; TSLP, thymic stromal lymphopoietin

Figure 2. Decision tree for severe asthma treatment

Modified from Domingo C.[152]

ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; SPT, skin prick test

*It should be noted that in some countries, only a high blood IgE concentration is required to prescribe omalizumab, without skin prick test or specific IgE value

¶The minimum number of eosinophils to consider an eosinophilic phenotype is 300 cells/µL; although, some studies define it as 400 cells/µL

†Alternatives: therapies not systematically recommended by the guidelines; they include azithromycin, methotrexate, and bronchial thermoplasty