

INVITED REVIEW

Current treatment of severe asthma

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Summary

Severe asthma is considered a heterogeneous disease in which a variety of clinical, physiological and inflammatory markers determine disease severity. Pivotal studies in the last 5 years have led to substantial progress in many areas, ranging from a more accurate definition of truly severe, refractory asthma, to classification of the disease into distinct clinical phenotypes, and introduction of new therapies. This review focuses on three common clinical phenotypes of severe asthma in adults (early onset severe allergic asthma, late onset non-atopic eosinophilic asthma, late onset non-eosinophilic asthma with obesity), and provides an overview of recent developments regarding treatment options that are best suited for each of these phenotypes.

Introduction

Severe asthma is a term that encompasses all forms of asthma that do not respond to standard therapy comprising of high doses of inhaled corticosteroids in combination with other medications including long-acting beta-2-agonists and leukotriene-receptor antagonists [1]. It is considered a heterogeneous disease in which a variety of clinical, physiological and inflammatory markers determine disease severity [2]. Pivotal studies in the last 5 years have led to substantial progress in various areas, including a more accurate definition of truly severe refractory asthma [3, 4], and classification of the disease into distinct clinical phenotypes. An accurate definition of severe asthma is important to exclude patients with a wrong diagnosis or those who have uncontrolled asthma because of unaddressed or untreated aggravating factors. Furthermore, clinical phenotyping is mandatory to predict asthma outcome, to better understand the mechanisms of disease and to target specific treatment. This article aims to provide directions on how to make a correct diagnosis of truly severe refractory asthma, how to better recognize and address the pathogenetic factors that are operative in a given clinical phenotype, and how to identify the best treatment for patients with severe, refractory asthma taking into account the specific phenotypes.

Diagnostic workup: wrong diagnosis and aggravating factors

The first step towards adequate treatment of a patient with severe asthma is to establish a secure diagnosis and to address and remove factors that may aggravate or complicate the disease [3].

Wrong diagnosis

There are many conditions that may mimic severe asthma and some patients may not have asthma at all. In a case study where difficult-to-treat adult asthma patients were systemically assessed, 12% of the patients were judged to have a diagnosis other than asthma, such as chronic obstructive pulmonary disease (COPD), alpha-1 antitrypsin deficiency, cystic fibrosis, cardiomyopathy, obliterative bronchiolitis, dysfunctional breathing and vocal cord dysfunction [5]. Another study showed that such additional diagnoses could even be detected in more than half of the patients with therapy resistant asthma [6]. Therefore, every patient with asthma who does not seem to respond to high-intensity asthma treatment should undergo objective tests to exclude other diseases and confirm the diagnosis of asthma.

Non-adherence to therapy

Adherence to anti-inflammatory treatment is low in patients with chronic diseases such as asthma [7–10], and is an important cause for loss of asthma control [10]. In a recent pragmatic trial evaluating the real-world effectiveness of a leukotriene-receptor antagonist in uncontrolled moderately severe asthma, the median adherence of patients to the use of inhaled steroids was as low as 40% [11]. Non-adherence is also a major issue in patients at the more severe spectrum of the disease. In a study by Robinson and colleagues, 50% of subjects with 15 mg prednisolone prescribed per day had either non-detectable serum prednisolone or normal cortisol levels [5], and a study by Gamble and colleagues showed that 45% of patients with prescribed oral steroids were found to be non-adherent using objective measures [8].

Adherence to asthma medication can be improved. Self-reporting is usually unreliable and it has been described that patients only admitted low adherence when confronted with objective measurements such as medication adherence questionnaires (Medication Adherence Rating Scale (MARS) [12], assessment of prescription refill record [8, 13] or measurement of serum or urinary cortisol levels [5, 8, 14]. Confronting the problem in a medical concordance interview can lead to sustained behavioural changes as has been shown in a randomized controlled pilot study in patients referred to a specialized centre with low adherence as the primary cause of difficult-to control asthma [15]. Since many patients do not take their medication because they perceive it to be unnecessary or because they are concerned about potential adverse effects [16, 17], these issues should be addressed systematically in every patient with severe asthma.

Exposure to occupational agents

There are more than 200 high and low molecular agents identified which can induce work-related asthma or aggravate pre-existing mild to moderate asthma [18, 19]. The diagnosis of occupational asthma requires objective measures [20]. Removal from exposure and reducing exposure have been shown to improve asthma symptoms and lung function, although the evidence is variable [20, 21]. Therefore, the clinical benefit of removal from exposure should be balanced against the increased risk of unemployment. Since the incidence of work-related asthma is highest in the first 2–3 years of exposure [22] and young adults have the best career opportunities, early detection and removal from exposure should be considered in particular in this category of patients with work aggravated asthma [23].

Exposure to indoor-allergens

Another important issue contributing to aggravated asthma is the continuous exposure to indoor-allergens, of which house dust mites, cockroach and fungal spores are the most important contributors. Exposure to house dust mites undoubtedly contributes to the severity of asthma symptoms in sensitized patients [24, 25]. Also exposure to cockroach [26], *Aspergillus* [27], *Trichophyton* [28] and *Alternaria* [29] has been associated with increased asthma morbidity in patients sensitized to these agents.

Despite the harms associated with exposure to indoor-allergens, the effectiveness of allergen avoidance measures is not unequivocal and continues to generate controversy [30–32]. Complete avoidance of house dust mite allergen exposure at high altitude (>1600 m) has shown striking improvements in asthma control, lung function and airway inflammation in sensitized children [33, 34], but measures to improve asthma control by reducing mite allergen levels at sea level have been rather disappointing [31]. Even with a major reduction in allergen levels, it may take many months before the beneficial effect on symptoms, medication use, pulmonary function, airway responsiveness and immunological parameters become fully apparent [35]. Still, current guidelines and experts in the field continue to recommend environmental control as an integral part of the overall management of sensitized patients with severe asthma [36–38].

Environmental pollutants

Smoking of cigarettes and exposure to second hand smoke [39] as well as environmental pollutants, including traffic related pollutants [40–43], nitrogen dioxide [41, 44], ozone [44, 45] and fine particles [46] are well documented environmental factors that increase asthma severity and promote exacerbations.

Cigarette smoke is probably the strongest known environmental factor influencing asthma severity [47]. Patients with asthma who smoke have more severe symptoms [48], and reduced sensitivity to inhaled corticosteroids [49, 50], and are more likely to be admitted to hospital for asthma than non-smokers with asthma [51]. Smoking cessation programmes are extremely important for these patients and have been shown to improve lung function and asthma control [52].

Also exposure to environmental tobacco smoke in non-smoking patients with asthma is associated with worse lung function, higher risk of exacerbations, more health care utilization, and greater bronchial reactivity [47]. Remarkably, the implementation of a smoke free public places law was associated with significant fewer asthma emergency department visits among both adults [53] and children [54].

Short- and long-term exposures to outdoor pollution, in particular traffic exhausts have adverse effects on asthma symptoms [44], lung function [43] and airway inflammation [43, 55], whereas reduction of air pollution exposure contributes to improved respiratory health [56–58]. Therefore, reduction of indoor pollution, in particular second hand smoke, and avoidance of outdoor pollution, for example by moving house to less polluted areas, might become part of the integral management of patients with severe asthma.

Pharmacological treatment options for severe refractory asthma

After separating all true severe asthma by revisiting the diagnosis, ongoing exposures and treatment adherence [3], optimization of therapy is the major objective. There are rapid developments in the pharmacological as well as non-pharmacological treatment of severe asthma.

High or ultra high doses of inhaled corticosteroids?

In severe asthma, doses of inhaled corticosteroids higher than that recommended in international guidelines (>2000 mcg of fluticasone equivalent) are sometimes prescribed but there are many reasons not to do so. Firstly, there is no evidence that such high doses would give better control of asthma, improve lung function or asthma-related quality of life [59, 60]. More importantly, there are strong data indicating that the incidence of local adverse effects increases with increasing doses [59, 61] and cause adrenal suppression [62–66]. High doses of inhaled corticosteroids are associated with substantial systemic bioavailability leading to adverse effects comparable to those of oral corticosteroids. A meta-analysis of 13 studies evaluating dose-related adrenal suppression showed that oral prednisolone and inhaled fluticasone were systematically equivalent on a 10:1 mg base [62]. Therefore, the prescription of ultra high doses of inhaled corticosteroids should not be encouraged.

Short-acting beta-2-agonists

Short-acting beta-2-agonists form a fundamental part of asthma treatment. Nevertheless excessive doses of these short-acting bronchodilators may be associated with unfavourable asthma outcomes [67, 68], including higher asthma morbidity and mortality [69, 70]. Regular use of short-acting beta-2-agonists has been shown to lead to partial loss of effectiveness [71] and increases in airway responsiveness [72], whereas sudden cessation of regular beta-2-agonists may lead to rebound bronchoconstriction, and thereby pharmacological dependence. The basis for the unfavourable effects of

short-acting beta-2-agonists is still unclear, but could be related to a pharmacogenetic-related adverse effect [73, 74]. Fortunately, careful gradual reduction of beta-2-agonist overuse can result in substantial improvements in asthma control, as was elegantly described in a case report by Taylor and Hannah [75]. Recently, even beta blockers have been proposed for the treatment of asthma, and trials investigating potentially beneficial effects of these drugs in chronic asthma are now underway [76–78]. Altogether current evidence suggests that short-acting beta-2-agonists should preferably not be prescribed on a regular basis, but only as needed, and overuse should be controlled and avoided.

Long-acting beta-2-agonists

The benefits of adding long-acting beta-2-agonists to inhaled corticosteroids in patients with moderately severe asthma have been convincingly demonstrated in many controlled studies, and include a better control of asthma with a significant reduction in the rate of exacerbations [79–81].

On the other hand, in large epidemiological and post marketing studies [82, 83] the use of long acting beta-2-agonists has been associated with an increased risk of severe exacerbations, leading to hospitalizations as well as asthma deaths, in particular if not combined with inhaled corticosteroids [84–87].

In February 2010, the FDA required the manufacturers of long-acting beta-2-agonists to revise their drug labels because of these undesirable effects [88, 89]. Currently, several large multicentre trials requested by the FDA are underway to clarify the safety risk associated with long-acting beta-2-agonists when used concurrently with inhaled corticosteroids [89].

Thus, although in severe asthma it is hard to imagine how to treat patients adequately without long-acting beta-2-agonists, caution is warranted about potential serious adverse effects in susceptible individuals [90]. Instruction about the safe-use of long-acting beta-2-agonists and close monitoring are needed to identify when the risk of adverse events has become greater than the potential benefit [84].

Anticholinergic agents

Anticholinergic agents may be used as alternative bronchodilators for asthmatic patients who experience adverse effects from beta-2-agonists [91], or who use beta-2-agonists in too large amounts. Recently, anticholinergic agents have also shown to have beneficial effects on lung function when given on top of maximal recommended treatment with inhaled corticosteroids and long-acting beta-2-agonists [92]. Whether or not anticholinergic agents could be as effective in severe

asthma as in COPD, especially in the subgroup with fixed airflow limitation has still to be investigated.

Targeted, phenotype-driven treatment

Apart from specific considerations regarding standard inhaled medications, there are exciting new possibilities for a more targeted, phenotype-driven approach. Severe refractory asthma is a heterogeneous condition, and over the last few years several clinical phenotypes have been defined by the use of unsupervised cluster analysis [93, 94]. These phenotypes appear to have different clinical, physiological and inflammatory markers of severity, which may be used to target treatment.

The severe asthma research program (SARP) investigators [93] defined five phenotypes of asthma, of which three with severe asthma. One cluster of severe asthma constituted mainly of patients with early onset severe allergic asthma with very low FEV₁, a second cluster of patients with late onset non-atopic steroid dependent asthma with fixed airways obstruction and a third cluster of mainly older, obese women with late onset asthma and reduced lung function.

Halder and colleagues [94] used sputum eosinophil data in their model, which led to slightly different clusters. Also in their analysis there was a cluster of patients with early onset severe atopic asthma, a second cluster of mainly male patients with late onset asthma, characterized by severe persistent eosinophilic airway inflammation and a cluster of obese women with late onset asthma, who did not show eosinophilia in sputum.

Although these studies were performed in different settings and used different dimensions to define the phenotypes, it is interesting to notice that the three subtypes of severe asthma in each study have many characteristics in common. In the following paragraphs we will discuss targeted treatment approaches that could be applied to each of these three adult phenotypes of severe, refractory asthma.

Early onset severe atopic asthma

In this phenotype of severe asthma, immune globulin E (IgE) plays an important role. The relevance of IgE in severe atopic asthma has been recognized for many decades in epidemiological studies [95–97]. High levels of IgE increase the surface expression of the high-affinity IgE receptor on mast cells and basophils, and recently it has been shown that airway tissue from patients who died in an asthmatic attack shows a high expression of this receptor [98], indicating that patients with severe atopic asthma have an increased capacity to mount IgE-mediated reactions and exacerbations.

Monoclonal antibodies against IgE are the optimal targeted treatment for patients with this phenotype of

severe asthma. Many studies have confirmed the beneficial effects of anti-IgE therapy in patients with severe allergic asthma despite treatment with inhaled corticosteroids and rescue medication [99]. Omalizumab reduces the frequency and occurrence of exacerbations [100, 101] and improves symptom control while allowing for a reduction in the use of corticosteroids and beta-2-agonists [100–102].

Another targeted treatment, which might become commercially available in the near future, is the monoclonal antibody against interleukin-13. Interleukin-13 is found in the airways of patients with asthma and is thought to mediate several features of asthma, including airway hyperresponsiveness, inflammation, mucous metaplasia, and activation and proliferation of airway fibroblasts, which contribute to adverse airway remodelling [103, 104]. In a recent randomized, placebo-controlled trial including patients with moderate to severe uncontrolled asthma, lebrikizumab treatment was associated with improved lung function, particularly in patients with high pre-treatment levels of serum periostin. These findings suggest that the prespecified marker, serum periostin, could potentially be used to identify patients with asthma who may have an increased response to lebrikizumab treatment. [105]

Patients with the early onset severe allergic asthma phenotype are often sensitized to fungi [27, 106–108], which has been shown to be associated with reduced lung function, increased sputum neutrophils and bronchiectasis [109], even in those who do not fulfil all the criteria for allergic bronchopulmonary aspergillosis (ABPA) [110].

Antifungal therapy has shown some beneficial effects in patients who are sensitized to fungi of the genus *Trichophyton* or *Aspergillus*. In a small pilot study Ward and colleagues showed a beneficial effect of 5 months treatment with fluconazole in patients sensitized to *Trichophyton* [111], whereas Denning and colleagues showed an improvement in asthma-related quality of life after 8 months treatment with itraconazole in a randomized controlled trial [112]. They also demonstrated a fall in IgE levels and a modest improvement in rhinitis and morning peak flow, but no improvement in FEV₁ [112]. More studies are necessary to address the questions of patient selection, optimum duration of therapy and prediction and management of azole-corticosteroid drug interactions before recommending this treatment to all sensitized patients with colonized airways [113].

Late onset non-atopic, inflammation predominant phenotype with fixed airflow limitation

Late onset, non-atopic asthma has been regarded as a separate phenotype for many decades and was called

'intrinsic asthma' by Rackemann in 1947 [114]. He described 'intrinsic asthma' as a disease characterized by later onset in life, female predominance, higher degree of severity, and more frequent association with rhinosinusitis and nasal polyposis. Later it became clear that this phenotype was also frequently associated with aspirin sensitivity [115–117], distal airway inflammation [115, 118, 119] and persistent eosinophilia [120].

Chronic rhinosinusitis with nasal polyposis is strongly associated with asthma severity [121, 122] and represents a risk factor for loss of asthma control [123] and frequent severe asthma exacerbations [124]. Very often patients with severe asthma who do not report nasal symptoms appear to have chronic rhinosinusitis on CT-scanning or after nasal endoscopy [125, 126]. This implies that in patients with severe refractory asthma investigation of the sinuses should be part of the routine assessment.

Treatment of chronic rhinosinusitis and nasal polyposis, either surgical or medical, has been shown to improve asthma control, airway inflammation and lung function [123, 127]. In patients with nasal polyposis, medical treatment appeared to be superior to surgical treatment [127].

Chronic rhinosinusitis with nasal polyposis is often associated with aspirin sensitivity [116], but many patients with nasal polyposis have severe disease without exposure [115] or sensitivity to these drugs and in about half of the patients, adequate control of asthma can only be achieved with oral corticosteroids [128].

Proposed targeted therapies for patients with aspirin-induced asthma include aspirin desensitization [129–131] and leukotriene modifiers [132, 133]. Aspirin desensitization has been shown efficacious in several controlled and uncontrolled studies [129–131], although there are still unresolved questions with respect to optimal dosing and length of treatment. Leukotriene-receptor antagonists [133] and synthesis inhibitors [134] have been demonstrated to improve control of asthma [133] and sinonasal symptoms [134] in aspirin sensitive patients with moderately severe asthma.

Remarkably, patients with severe asthma, chronic rhinosinusitis and nasal polyposis are also prone to inflammation and narrowing of the distal airways [118, 119], resulting in air trapping and hyperinflation [115, 135], which has been shown to be associated with more severe asthma, hospitalizations and ICU admissions [136].

Small airways inflammation can be targeted with ultrafine ICS, which have been shown to decrease the number of eosinophils in biopsies taken from the distal airways [137] reduce the number of asthma exacerbations as well as the need for oral corticosteroids in patients with severe, refractory asthma [138]. However, the superiority of ultrafine ICS over regular ICS has yet to be proven.

The most important marker of disease severity in patients with the adult onset non-atopic asthma phenotype is persistent airway eosinophilia [120]. Persistent eosinophilia has been associated with frequent asthma exacerbations [139], fixed airflow limitation [140] more intubations [141] and many patients require continuous systemic corticosteroid treatment to keep their asthma under control [142, 143]. Unfortunately the chronic use of oral corticosteroids is associated with serious side effects such as osteoporosis, diabetes, hypertension, cataract formation and myopathy [144] and since these adverse effects are dose and time dependent, all efforts should be taken to taper the oral corticosteroid to the lowest effective dose in each patient [145].

Steroid sparing drugs such as methotrexate [146], cyclosporine [147], Troleandomycin [148] and oral gold [149] have been applied in patients with prednisone-dependent asthma, but unfortunately none of these drugs has gained complete acceptance in clinical practice, because of either limited efficacy or unacceptable side effects [150, 151].

Theophylline might be a useful option in the management of patients with severe corticosteroid dependent asthma. This drug may potentiate the anti-inflammatory actions of corticosteroids resulting in the use of lower doses of oral corticosteroids and less side effects of these drugs [152].

A novel promising strategy to treat patients with persistent eosinophilic inflammation is to target the eosinophil itself. The anti IL-5 humanized monoclonal antibody mepolizumab has been demonstrated to be very efficacious in reducing the circulating eosinophils [153] and preventing eosinophil recruitment into the airways after allergen challenge [154]. In clinical trials, anti-IL5 significantly reduced the occurrence of induced [155] and spontaneous [156] asthma exacerbations in patients with persistent eosinophils in sputum. Mepolizumab treatment was also associated with improved symptom control [155] and quality of life in these patients [156]. Large multicentre clinical trials with anti-IL5 agents are now ongoing and will hopefully lead to FDA approval of this important drug in the near future.

Late onset obese female preponderant asthma

This asthma phenotype has become increasingly prevalent during the last decade, which is probably due to the steady increase in subjects with morbid obesity [157, 158]. The major marker of severity in this phenotype is the excess weight and large waist circumference of the patients [159]. Obesity is associated with more severe asthma symptoms [160, 161], poor asthma-related quality of life [160, 162], and more asthma-related unscheduled medical visits and hospitalizations [160] despite high doses of asthma treatment.

The association between obesity and severe asthma can be explained by several mechanisms [158] including flow limitation secondary to mechanical factors [163], pro-inflammatory effects of adipose tissue on the lungs [164] and a high prevalence of co-morbidities that may affect lung function, in particular sleep disordered breathing and gastro-oesophageal reflux disease [165].

The primary treatment of patients with the obese phenotype of severe refractory asthma is weight reduction. In a randomized controlled trial it was demonstrated that weight reduction led to an improvement in lung function and asthma symptoms and quality of life [166] and a decrease in asthma exacerbations [166]. Similar results were obtained with gastric surgery [167, 168].

Obstructive sleep apnoea is extremely prevalent in obese patients with severe asthma [169] and has been shown to be associated with frequent asthma exacerbations [124]. Since treatment with continuous positive airway pressure has been shown to improve asthma control [170–172] sleep-related symptoms should be routinely assessed, and a polysomnography should be performed.

Patients with morbid obesity often suffer from gastro-oesophageal reflux [173], which has been suggested to contribute to asthma severity [174]. Unfortunately, improvement with treatment is not clear-cut [175–178]. Therefore, the current recommendation for patients with uncontrolled moderately severe asthma is that treatment with proton pump inhibitors is indicated only if the patient presents with clinical symptoms of gastro-oesophageal reflux, but not in patients without symptoms. Whether or not the same recommendation applies to patients with severe refractory asthma requires further investigation.

Other proposed phenotypes of (severe) asthma and targeted therapies

An asthma phenotype that did not emerge from the cluster analyses is neutrophilic asthma. In this subtype of severe asthma, airway eosinophils are either absent or suppressed by treatment in the presence of a high level of asthma symptoms [179, 180], while neutrophils [181] and IL-8 levels in the airways [182] are increased. As compared to the eosinophilic subtype of severe chronic asthma, the neutrophilic subtype has been reported to show less evidence of small airways involvement and to be less often associated with a history of respiratory failure requiring intubation [141]. Neutrophilic asthma is more prevalent in older patients than in younger patients [183], and a relationship between sputum neutrophilia, asthma duration and persistent airflow limitation has been observed [184]. Two studies have shown an association of neutrophilia with

air trapping on CT scans.[136, 185] Conventional therapies such as inhaled corticosteroids, although very effective in those with eosinophilic inflammation, have limited efficacy in neutrophilic asthma [186].

Accumulating evidence suggests that neutrophilic asthma might be associated with infections with *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, or both [187]. A high titre of antibodies to *Chlamydia pneumoniae* is associated with bronchial hyperresponsiveness, more severe asthma [188, 189] and accelerated decline in lung function [190]. A proposed targeted therapy for the neutrophilic asthma phenotype is macrolide antibiotics [191]. Clarithromycin has been reported to decrease the neutrophil chemo-attractant Interleukin-8 in induced sputum in patients with neutrophilic asthma, even though insignificant against placebo, with a simultaneous improvement in asthma symptoms [191]. Thus, for patients with neutrophilic asthma, a trial of macrolide antibiotics might be a good choice.

Another potentially related phenotype of severe refractory asthma is the up-regulated tumour necrosis factor (TNF)-alpha phenotype, proposed by Berry and colleagues [192]. Because of the role of TNF in promoting sputum neutrophilia and airway hyperresponsiveness [193] anti-TNF monoclonal antibody seemed a good candidate for the treatment of this type of severe asthma [194, 195]. Unfortunately the enthusiasm of the first results [192] was followed by disappointment and concern about the serious adverse events of the drug [196]. Consequently, this treatment is no longer considered an option in patients with severe asthma.

Non-pharmacological treatments for severe asthma

Bronchial thermoplasty

Thermoplasty has been proposed as a promising new option in the treatment of severe asthma [197]. The first studies suggested that this intervention could improve lung function (FEV₁ and morning peak flow), airways hyperresponsiveness, asthma-related quality of life and symptom scores [198, 199]. Unfortunately, subsequent multicentre controlled trials in patients with moderate and severe asthma failed to show an effect on FEV₁ and airway responsiveness, but suggested a favourable effect on exacerbations and hospitalizations [200]. The results of a 5 years follow-up of these patients have confirmed the long-term safety of the procedure, without long-term complications and maintenance of stable lung function [201]. Therefore, thermoplasty might be an option for some patients who do not respond to pharmacological treatment but it is still not clear which asthma phenotypes and which clinical outcomes benefit most of it.

High altitude treatment

Prolonged hospitalization of patients with severe asthma at high altitude might be of benefit to patients with allergic and non allergic phenotypes of severe refractory asthma [34, 202]. The high altitude climate offers more than decreased levels of HDM allergens. It also offers decreased exposure to pollens, fungal spores and air pollution, as well as lower work of breathing, relief from stress and high UV-light exposure with a potential immunomodulatory effect [203]. A rehabilitation programme at high altitude might be a good treatment option for patients who remain uncontrolled despite maximal recommended treatment, irrespective of the asthma phenotype.

General conclusions and future perspectives

The evaluation of difficult-to-treat severe asthma patients should ideally take place in a specialized asthma centre with expertise in dealing with these patients. This includes a multidisciplinary team of physicians, nurses and respiratory therapists. In every patient with severe asthma the diagnosis of asthma should be confirmed, adherence with therapy and inhalation technique checked, aggravating factors eliminated, and the clinical phenotype with its specific markers of severity defined. When keeping the three most common clinical phenotypes of severe asthma in

mind (early onset severe allergic asthma, late onset non-atopic eosinophilic asthma, and late onset obese female asthma), clinicians will be able to recognize the markers of asthma severity, and attune the treatment to it.

Current treatment of severe asthma is based on clinical markers of severity, but in the near future the focus will be on finding composite genetic and molecular markers that will be coupled to specific asthma phenotypes. Ongoing studies in patients with severe asthma using systems biology will certainly reveal new molecular targets that will be used to develop highly specific therapies [204]. Hopefully, such personalized medicine will improve the lives of patients with the most severe disease.

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