



# Severe refractory asthma: an update

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**ABSTRACT** Asthma is a heterogeneous disease in which adequate asthma control cannot be achieved in a substantial proportion despite currently available treatment possibilities. This subgroup has been defined as “severe refractory” asthma. Over the past years considerable progress has been made regarding a more exact definition of severe refractory asthma. A systematic approach to evaluate the asthma patient has been postulated. Further detailed classification into distinct phenotypes is ongoing to target the right treatment to the right patient. And, new therapeutic targeted treatment options are currently in development to provide possible new targets to improve disease state, symptoms and quality of life. This review will provide an update on the latest advancements with regard to all these domains.



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Phenotyping the severe asthma patient is essential to ensure the right treatment is given to the right patient <http://ow.ly/mOQrQ>

## Introduction

The majority of patients with asthma can be treated effectively with the currently available medications. However, a significant proportion of patients labelled as “severe refractory asthma” remain a challenge for the treating clinician. Severe refractory asthma encompasses a variety of subphenotypes of asthma that do not respond to current standard therapy, *i.e.* high doses of inhaled glucocorticosteroids in combination with long-acting  $\beta_2$ -agonists (LABA) [1, 2]. Management of severe asthma is associated with a high and disproportional consumption of healthcare resources [3, 4]. In addition, there exists a substantial unmet clinical need. Therefore, much research is currently ongoing on topics such as assessment and evaluation, subphenotyping and novel treatment modalities for severe asthma. This review will focus on the most recent research developments regarding severe refractory asthma.

## Defining severe refractory asthma

Over the past decade, much effort has been directed towards defining severe refractory asthma. The most important progress encompassed the distinction between uncontrolled asthma, difficult-to-control asthma and severe refractory asthma [5–7].

It started in 1999 when a European Respiratory Society (ERS) Task Force defined difficult asthma as “asthma remaining uncontrolled despite high dose inhaled glucocorticosteroids with or without systemic glucocorticosteroids”, and uncontrolled asthma as “persistent asthma symptoms or recurrent exacerbations” (table 1) [2]. A year later, the American Thoracic Society (ATS) definition of severe refractory asthma was very similar, and included six criteria that specified asthma control [1]. In 2010, the World Health Organization (WHO) added responsiveness to treatment to the definition, as well as future risk as an indicator for asthma control [8]. The WHO distinguished three subtypes of severe asthma: 1) severe untreated asthma, 2) difficult-to-control severe asthma, and 3) severe refractory asthma. In 2011, the Innovative Medicines Initiative introduced the term “problematic” asthma to cover all patients with

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TABLE 1 Evolution of the definition of “severe” asthma

Organisation, year	Term	Definition
ERS, 1999	Difficult asthma	Asthma remaining uncontrolled despite high-dose inhaled glucocorticosteroids with or without systemic glucocorticosteroids
ATS, 2000	Uncontrolled asthma Severe refractory asthma	Persistent asthma symptoms or recurrent exacerbations According to an ERS Task Force including criteria that specifies asthma control
WHO, 2010		Addition of responsiveness to treatment and future risk as a marker for asthma control
IMI, 2011	Poorly controlled asthma	Algorithm to distinguish difficult-to-control asthma from severe refractory asthma
ATS/ERS, 2013		Latest recommendations on the identification, evaluation and treatment of patients with severe refractory asthma

ERS: European Respiratory Society; ATS: American Thoracic Society; WHO: World Health Organization; IMI: Innovative Medicines Initiative.

“poorly controlled” asthma [7] and published an algorithm on how to distinguish difficult-to-control asthma from severe refractory asthma. This algorithm addressed all factors that can make asthma difficult to control, including non-adherence to treatment, inadequate inhalation technique, continuous exposure to environmental triggers and comorbidities. A joint Task Force of the ERS and the ATS will publish the latest recommendations on the identification, evaluation and treatment of patients with severe refractory asthma in the near future.

### Aggravating factors and comorbidities

Distinguishing severe refractory asthma from difficult-to-control asthma is critically important because it identifies the patients who may benefit from novel and, sometimes, expensive treatments. A high percentage of patients who are labelled with severe or difficult-to-control asthma actually do not have severe refractory asthma. Early studies already emphasised that comorbid conditions or inadequate treatments may interfere with asthma control and severity of symptoms [9]. Clearly, a systematic evaluation is of great value, as has been shown by several research groups [10, 11]. Such an approach can reveal an incorrect diagnosis and comorbid conditions that aggravate asthma, such as gastro-oesophageal reflux, obstructive sleep apnoea, sinonasal disease, recurrent respiratory infections and obesity. Also, non-adherence with inhaled glucocorticosteroid treatment and incorrect inhalation technique are frequently encountered factors that perpetuate poorly controlled asthma [12–16]. Addressing and treating these factors has been shown to result in better clinical outcomes [10, 11]. A systematic evaluation of patients with difficult-to-control asthma should include the confirmation of the diagnosis of asthma, assessment of disease severity, evaluation of risk factors, comorbid conditions and other factors that prohibit asthma control [17]. A standard protocol for evaluating difficult-to-control asthma has never been agreed upon but a comprehensive overview of investigations that these patients could or should undergo has recently been published [17]. In that review, the authors emphasise to perform such investigations in a dedicated multidisciplinary centre with special interest and experience in managing these patients [17].

### Subphenotypes of severe refractory asthma

Severe refractory asthma is a heterogeneous condition, and over the past few years several clinical phenotypes have been identified by the use of supervised and unsupervised cluster analysis [18–21]. These phenotypes are characterised by different clinical and physiological features, probably reflecting separate immuno-pathologies [22]. Thus, characterisation of sub-phenotypes of severe asthma may be very helpful in understanding the underlying pathophysiology and may be used to target treatment.

In the Severe Asthma Research Program (SARP) five subphenotypes were identified by unsupervised cluster analysis of which three were severe asthma [19]. One cluster of severe asthma constituted mainly of patients with early onset severe allergic asthma with very low forced expiratory volume in 1 s (FEV<sub>1</sub>), a second cluster of patients mainly had late onset non-atopic, steroid dependent asthma with fixed airways obstruction and a third cluster was characterised by mainly older, obese females with late onset asthma and reduced lung function [19]. In another landmark study that used cluster analysis to identify asthma phenotypes, sputum eosinophilia was also incorporated. This led to slightly different clustering of patients with severe asthma, including a cluster of early onset severe atopic asthma, a cluster of predominantly male patients with late onset asthma with severe persistent eosinophilic airway inflammation, and a cluster of obese females with late onset asthma without eosinophilia (table 2) [18].

TABLE 2 Identified phenotypes of severe refractory asthma

Early onset severe allergic asthma
Late onset non-atopic, inflammation predominant asthma with fixed airflow limitation
Late onset obese female preponderant asthma

Currently, a pan-European project (U-BIOPRED) is being conducted to further fingerprint the distinct phenotypes of severe asthma by integrating high dimensional data from invasive (bronchial biopsies), noninvasive (blood, sputum and exhaled air) and patient-reported outcomes, and using an innovative systems biology approach [7].

### Current treatment of severe asthma

According to current guidelines (Global Initiative for Asthma, National Asthma Education and Prevention Programme and the British Thoracic Society) the treatment of patients with severe asthma constitutes of high-dose inhaled or oral glucocorticosteroids in combination with LABAs and/or additional controller medications [1].

#### *Inhaled glucocorticosteroids*

High-dose inhaled glucocorticosteroids, sometimes even in higher dosages than maximally recommended, are used to treat patients with severe asthma. There is, however, no evidence that these ultra-high doses lead to better control of asthma, improve lung function or ameliorate asthma-related quality of life [23, 24]. Care givers need to realise that such high doses of inhaled steroids may be associated with systemic side-effects in the long run including adrenal suppression, skin thinning, ecchymoses, reduced bone mineral density, glaucoma and cataract [25, 26]. Therefore, dosages higher than recommended should not routinely be prescribed to patients with severe asthma. In many cases, however, systemic anti-inflammatory treatment with low doses of systemic glucocorticosteroids is required to maintain some degree of asthma control.

#### *$\beta_2$ -agonists*

There is no doubt that both short-acting  $\beta_2$ -agonists (SABAs) and LABAs improve asthma control and reduce asthma exacerbations [27, 28]. However, (unintended) overuse of SABAs may paradoxically lead to unfavourable asthma outcomes [29], with loss of effectiveness and increased airway hyperresponsiveness [30]. Furthermore, sudden cessation of regular  $\beta_2$ -agonists may lead to rebound bronchoconstriction as a result of pharmacological dependence [31, 32]. Fortunately, careful tapering of  $\beta_2$ -agonist overuse can result in improved asthma control [33]. Therefore, SABAs should be prescribed only as needed.

Also the use of LABAs has been associated with unfavourable adverse effects, including an increased risk of serious exacerbations and asthma-related deaths, in particular if not combined with inhaled glucocorticosteroids [34, 35]. Although inhaled glucocorticosteroids are often prescribed in a (fixed) combination with a LABA, careful instruction and monitoring are needed to prevent potential negative side-effects in selected patients [36]. Several once daily  $\beta_2$ -agonists (ultra-LABAs) such as indacaterol, carmoterol, olodaterol, vilanterol and LAS100977 are currently under investigation [37]. Because of the earlier described side-effects, once daily  $\beta_2$ -agonists should also be prescribed in fixed dose combinations. Results of these trials will be available in the near future.

#### *Anti-cholinergic agents*

Anti-cholinergic agents can be used as an alternative for  $\beta_2$ -agonists in the treatment of patients with severe asthma. The long-acting anti-cholinergic agent tiotropium has been shown to be beneficial in patients with moderate-to-severe uncontrolled asthma with improvement of symptoms, pulmonary function [38, 39], and time to first exacerbation [40]. However, increased mortality rates from cardiovascular causes have been reported in patients with chronic obstructive pulmonary disease who used tiotropium *via* a mist inhaler. Therefore, caution should be exercised in prescribing long-acting anti-cholinergic agents to patients with severe asthma and an increased cardiovascular risk [41].

#### *New classes of bronchodilator therapy*

Because the long-term safety of  $\beta_2$ -agonist therapy in asthma has been a controversial and unresolved issue for more than two decades [34, 35, 42, 43], alternative classes of bronchodilator therapy have been developed. Vasoactive intestinal peptide analogues and potassium channel openers, *i.e.* agonists of bitter taste receptors (TAS2Rs), have shown bronchodilator effects [44–46]. Unfortunately, these drugs have had more potent vasodilator than bronchodilator effects. In addition, it remains unclear which mechanism

provides bronchodilation in these potassium channel openers [47]. Furthermore, combined phosphodiesterase 3/4 inhibitors are currently under development as bronchodilator therapy [48]. However, in the near future it is not to be expected that these drugs will be available for patients with severe persistent asthma.

### Phenotype-specific treatment

It is increasingly recognised that different asthma phenotypes respond differently to asthma treatments. Phenotyping the severe asthma patient is therefore essential to ensure the right treatment is given to the right patient.

#### *Early onset severe allergic asthma*

Allergic, T-helper type-2 driven asthma is the most common and best understood subphenotype of severe refractory asthma. In this phenotype, IgE plays an important role [49, 50]. Airways from patients who died during a severe asthma attack have shown a high expression of the high-affinity IgE surface receptor on mast cells and basophils, indicating that these patients were at high risk of IgE mediated reactions and exacerbations [51]. Anti-IgE therapy has been designed as a targeted therapy for this asthma subphenotype, although predicting the response to this therapy on the basis of elevated plasma IgE levels has been disappointing [52]. Studies have shown that the anti-IgE agent omalizumab is a safe and effective treatment in severe allergic asthma. It reduces the exacerbation rate and improves asthma control allowing a reduction of inhaled glucocorticosteroid dosage and use of rescue medication [53–56].

#### *Late onset non-atopic, inflammation predominant asthma with fixed airflow limitation*

This severe refractory asthma phenotype is characterised by later onset in life (after the age of 12 years), more severe (eosinophilic) airway inflammation and more frequent association with rhino sinusitis and nasal polyposis. There is also an association with aspirin sensitivity [57], small airways inflammation [57, 58] and persistent eosinophilia [59]. Chronic rhino-sinusitis and nasal polyps, as well as persistent airway eosinophilia, are risk factors for uncontrolled asthma and asthma exacerbations [14, 60]. Clinicians should be aware that many patients with severe asthma have an asymptomatic chronic rhino-sinusitis on detailed examination [61]. Since treatment of chronic rhino-sinusitis has been shown to lead to improved asthma control and an increase in pulmonary function [62], the presence of this comorbid condition should be routinely checked and treated if necessary.

Persistent eosinophilia is the most important characteristic of this subphenotype of severe refractory asthma [59]. It correlates with disease severity and is associated with fixed airflow limitation [60], frequent asthma exacerbations and hospitalisations [63], and a higher frequency of intubations [64]. Because of the proposed association of persistent eosinophilia with small airway inflammation [58] there might be a role for ultrafine inhaled glucocorticosteroids in these patients. These drugs have been shown to reduce the number of eosinophils in small airway biopsies and to decrease the rate of asthma exacerbations [65, 66]. Still, many patients with the persistent eosinophilic phenotype need low dose systemic glucocorticosteroids to maintain acceptable asthma control [67, 68]. Unfortunately, chronic systemic glucocorticosteroid use has serious dose- and time-dependent side-effects, such as osteoporosis, diabetes, hypertension, cataract formation and myopathy [69, 70]. Therefore, tapering oral glucocorticosteroids to the lowest effective dose is of high priority [69]. Classical steroid sparing treatments including oral gold [71], methotrexate [72] and ciclosporin [73] have not gained acceptance because of limited effects and significant side-effects.

Because of its important role in propagating airway inflammation, targeting the eosinophil itself has been shown to be an effective treatment strategy for patients with severe eosinophilic asthma. Studies with the anti-interleukin (IL)-5 agent mepolizumab showed a significant reduction of the rate of asthma exacerbations in patients who had eosinophils in sputum despite high-dose inhaled or oral glucocorticosteroids. The treatment appeared to be safe and well tolerated. Mepolizumab treatment was also associated with improved symptom control and quality of life in these patients [74–76]. In addition, a small study in oral steroid-dependent asthma showed that mepolizumab was also effective in preventing exacerbations when tapering the oral glucocorticosteroid dose [74]. Large scale studies are now ongoing to confirm that this treatment can be used as a steroid-sparing agent or even as an alternative for oral glucocorticosteroids.

#### *Late onset obese female preponderant asthma*

This phenotype has increasingly been recognised over the past years, probably due to the rapidly increasing prevalence of morbid obesity [15, 77]. The association between obesity and severe asthma is complex and poorly understood. Proposed mechanisms include expiratory flow limitation secondary to mechanical factors [78], pro-inflammatory effects of adipose tissue on the airways [79], and a high prevalence of

comorbidities that may aggravate existing asthma, in particular sleep-disordered breathing and gastro-oesophageal reflux disease [80].

Obesity is associated with loss of asthma control, poor quality of life, more asthma-related unscheduled visits and hospitalisations, and blunted response to glucocorticosteroid treatment [81]. Weight reduction is the only effective treatment for these patients. It has been shown that drastic weight reduction improves pulmonary function, airway hyperresponsiveness, asthma control and asthma-related quality of life [82]. Similar results can be obtained with bariatric surgery [77].

Sleep-disordered breathing, which is a major problem in obese patients, is more prevalent in severe asthma [83], and is also associated with poorly controlled asthma [84]. Therapy with continuous positive airway pressure has been shown to improve asthma control and quality of life [85, 86], although no change in pulmonary function or airway hyperresponsiveness has been observed [86]. Therefore, sleep-disordered symptoms should be routinely assessed and polysomnography should be performed if necessary.

Gastro-oesophageal reflux disease is also highly prevalent in severe asthma [87]. However, the majority of patients are asymptomatic, and in patients with uncontrolled moderate-to-severe asthma treatment with proton-pump inhibitors has not been shown to improve asthma control [87]. Therefore, such treatment is only recommended in patient suffering from symptoms of gastro-oesophageal reflux.

### Other targeted treatments

Several biological pathways have been shown to play a role in asthma pathogenesis, and these pathways do not always overlap with the clinical phenotypes described above. Therefore, phenotyping at multiple levels is important to acquire the responder to targeted therapy. Several targets for treatment have been identified and multiple drugs are now under investigation (table 3).

Whereas anti-IL-5 therapy (mepolizumab and reslizumab) has been shown to be effective in reducing exacerbation rates in eosinophilic asthma [74–76, 88], no effect was observed on lung function or airway hyperresponsiveness. Other targeted treatments, such as tumour necrosis factor (TNF)- $\alpha$  blocking agents (golimumab [89] and etanercept [90, 91]) have shown beneficial effects on exacerbation rate, but not on lung function in the subgroups of adults with severe asthma with  $\geq 12\%$  reversibility in baseline FEV<sub>1</sub>. This dissociation between asthma exacerbations and lung function is intriguing, and suggests that different mechanisms determine airway patency at rest and the occurrence of asthma exacerbations. TNF- $\alpha$  blockers have not been further developed for the treatment of severe asthma patients because of several serious adverse events, including pulmonary infections and malignancies [89]. Other novel experimental therapies include daclizumab, a humanised IgG1 monoclonal antibody against the IL-2R chain of activated lymphocytes. This agent showed improvement in asthma scores and pulmonary function [92]. Furthermore, a CXCR2 antagonist showed modest improvement in exacerbation rate without improvement in asthma control in a subgroup of asthma patients with increased sputum neutrophils [93]. Antibodies against IL-13, lebrikizumab, showed improved pulmonary function testing but no effect on exacerbation rate or symptoms [94]. Another anti-IL-13 antibody, tralokinumab, showed improved pulmonary function without improvement of asthma symptom scores, although patients seemed to need less rescue medication [95]. In an unselected group of moderate-to-severe asthma patients the use of AMG 317, an anti-IL4 receptor blocker, showed no clinical benefit at all [96]. All these monoclonal antibodies had an acceptable safety profile.

Most of these studies have been performed without appropriate phenotyping of the patients, which could have led to false-negative results. Further studies are required to detect the right patients for the target concerned.

### Nonpharmacological “targeted” treatment

#### *Bronchial thermoplasty*

Preliminary investigations with radiofrequency ablation of airway smooth muscle have offered a novel promising treatment option in severe refractory asthma [97]. Several studies showed improved pulmonary function testing, airway hyperresponsiveness, asthma-related quality of life and symptom scores [98, 99]. Other studies did not confirm these results but showed a decrease in the rate of asthma exacerbations and hospitalisations [100]. No clinical complications were observed in the long run, and pulmonary function remained stable over a period of 5 years [101]. Therefore, this approach might be a reasonable option for patients not responding to current treatment. However, it is still not clear which clinical outcome responds best to this treatment and which subgroups of patients with severe asthma benefit the most.

#### *High altitude treatment*

Most patients with severe asthma benefit from a stay at high altitude [102, 103]. The high altitude climate offers decreased levels of house dust mite allergens and decreased exposure to pollens, fungal spores and air

TABLE 3 Targeted treatment in severe refractory asthma

Treatment	Target	Summary results
<b>Omalizumab</b>	Anti-IgE	Reduced exacerbation rate Improved asthma score
<b>Mepolizumab</b>	Anti-IL5	Reduced inhaled glucocorticosteroids and rescue medication Reduced exacerbation rate Reduced eosinophilia
<b>Reslizumab</b>	Anti-IL5	Improved symptom control and quality of life Reduced oral glucocorticosteroid dose Reduced sputum eosinophils Improved pulmonary function
<b>Golimumab</b>	Anti-TNF- $\alpha$	Trend towards better asthma control No improvement in pulmonary function No reduction in exacerbation rate
<b>Etanercept</b>	Anti-TNF- $\alpha$	Serious infection risks and malignancies Inconsistent results
<b>Daclizumab</b>	Anti-IL2R chain	Improvement in pulmonary function and quality of life versus no clinical benefit/ misbalanced risk/benefit ratio Improved asthma control and pulmonary function Reduction in SABA use
<b>SCH527123</b>	Anti-CXCR2	Prolonged time to exacerbation Small reduction in mild exacerbations Reduction in sputum neutrophils
<b>Lebrikizumab</b>	Anti-IL13	Trend toward improvement in asthma control Improvement in pulmonary function
<b>Tralokinumab</b>	Anti-IL13	Improvement in pulmonary function Reduction in $\beta$ -agonist use
<b>AMG 317</b>	Anti-IL4R	No improvement in asthma control No effect on asthma control or exacerbations

IL: interleukin; TNF; tumour necrosis factor; IL2R: interleukin-2 receptor; SABA: short-acting  $\beta$ -agonist.

pollution. At high altitude patients may benefit from lower work of breathing due to reduced gas density, relief from stress and high exposure to UV light, which has a potential immunomodulatory effect [102]. A periodic rehabilitation programme at high altitude might be a good treatment option for patients with severe refractory asthma, irrespective of the asthma phenotype, who remain uncontrolled at sea level despite maximally recommended doses of asthma medications.

### Future perspectives and conclusion

Severe asthma is a heterogeneous and complex disease requiring a multidisciplinary approach. Identifying the true “severe refractory asthma” patient is the first step in management. The second step is to phenotype the patient as accurately as possible. Until now, only clinical phenotyping has been used in clinical practice to guide treatment. Unbiased cluster analysis has already revealed three to four subphenotypes of severe asthma [18, 19]. In the near future, integrated high dimensional data will probably lead to more accurate phenotyping [104]. This will certainly improve our understanding of the patho-immunobiology of the different asthma phenotypes and will help clinicians to better predict the natural history and prognosis of an individual patient with asthma. However, the most important outcome of this systems medicine approach will be the development of new and better treatment targets/strategies for this complex group of patients with severe refractory asthma.

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