Managing severe asthma in adults: lessons from the ERS/ATS guidelines

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Purpose of review
To review the latest guidelines on severe asthma.

Recent findings
An updated definition of severe asthma is provided together with the evaluation steps necessary to reach a diagnosis of severe asthma. The importance of phenotyping is emphasized, and recommendations are provided for therapies specifically directed for severe asthma.

Summary
Severe asthma is widely recognized as a major unmet need. It is defined as asthma that requires treatment with high-dose inhaled corticosteroids and a second controller and/or systemic corticosteroid to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy. Severe asthma is a heterogeneous condition that consists of phenotypes such as eosinophilic asthma. More phenotypes need to be defined. Evaluation of the patient referred to as having severe or difficult-to-control asthma must take into account adherence to treatment, comorbidities and associated factors including side effects from therapies. These need to be addressed. Recommendations on the use of sputum eosinophil count and exhaled nitric oxide to guide therapy are presented. Treatment with anti-IgE antibody, methotrexate, macrolide antibiotics, antifungal agents and bronchial thermoplasty is reviewed and recommendations made. Research efforts into phenotyping of severe asthma will provide both biomarker-driven approaches and newer effective therapies to severe asthma management.

Keywords
asthma phenotypes, guidelines for asthma, severe asthma

INTRODUCTION
Asthma can be considered a complex disease because it is likely to be caused by multi-factorial components and can present in different ways with varied long-term outcomes. The basis for this likely rests on the lack of a diagnostic marker of disease and the current diagnosis resting mostly on a history of intermittent wheeze. Another paradox is that although most patients with a diagnosis of asthma can be adequately treated with a combination therapy of inhaled corticosteroids (ICS) and a bronchodilator, usually long-acting β-agonists (LABAs), there is a core of patients whose asthma remains uncontrolled despite being on these treatments. These patients are generally termed having severe asthma or refractory asthma, particularly if addition of other controller medications on top of combination therapy does not lead to any improvement in asthma control. Such patients taking high-level treatments as exemplified by the steps 4 and 5 of the Global Initiative for Asthma (GINA) guidelines indeed experience the most morbidity, and although consisting of only 5–10% of the asthma population, consume the majority of the healthcare costs for asthma. In a recent study of patients with persistent asthma taken from 10 countries in Europe, the estimated costs for patients with uncontrolled asthma as defined in GINA that included expenses for drugs, doctor visits, tests and hospital admissions and costs linked to loss of productivity and days lost amounted to 2281 Euros compared to 509 Euros in a controlled asthma patient [1]. Clearly, there is an unmet need in this group of patients

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KEY POINTS

- When the diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids and a second controller and/or systemic corticosteroid to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy.

- The evaluation of the patient referred with ‘difficult-to-treat’ asthma should include: an assessment of whether the patient with ‘difficult asthma’ has asthma, an appropriate assessment of confounding factors and comorbidities and the initial determination of phenotypes which may be useful in optimizing therapy.

- Recommendations have been made that clinicians do not use methotrexate or macrolide antibiotics in adults with severe asthma, that a therapeutic trial of omalizumab is used in severe allergic asthma, that antifungal agents is tried in severe asthma with recurrent exacerbations of allergic bronchopulmonary aspergillosis and that bronchial thermoplasty is performed only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study.

- Research into improving our understanding of the pathobiology of severe asthma, of potential biologic targets and of inflammatory and molecular phenotypes will lead to better effective therapies for specific phenotypes.

called severe. Not only do these patients need to benefit from more efficacious therapies, the whole condition called severe asthma needs to be understood more.

ERS/ATS TASK FORCE ON SEVERE ASTHMA

For this reason, the European Respiratory Society and American Thoracic Society (ERS/ATS) Task Force was set up with the aims of updating the previous definitions, identifying potential mechanisms/phenotypes of severe asthma, outlining its evaluation and providing guidance on treatment, with respect to both adults and children. The Task Force was made up of adult and paediatric-trained specialists and scientists with extensive experience of managing and investigating patients with asthma, particularly severe asthma. The target audience of these guidelines was defined as specialists in respiratory medicine and allergy who manage adults and children with severe asthma. The approach taken was to establish a list of questions that the Task Force felt was important to be addressed. Evidence summaries for each question were prepared following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [3], and these were based on existing up-to-date well executed systematic reviews and more recent randomized controlled trials, and with the unavailability of systematic reviews, relevant studies were searched for. It must be emphasized that the Task Force reviewed studies that were available in the public domain until September 2013. This is an important point because there may have been studies published after that date that could have an important bearing on recommendations, but these have not been included yet.

It is clear that although there have been hundreds of randomized controlled trial studies in asthma, there have been relatively few in severe asthma, mostly dealing with clinical trials of treatments for severe asthma. The Task Force therefore reached an agreement on recommendations mostly on the basis of such data, but in many instances, these were made on the combination of available data and on the basis of best opinion or best practice. It is also to be noted that not all the questions identified by the Task Force as being important have been addressed mainly because of time constraints. The output from the Task Force represents the first International Guidelines on Severe Asthma [2**].

DEFINITION OF SEVERE ASTHMA

The Task Force took a practical approach to the definition of severe asthma [2**]. Patients presenting to the specialist would come from various sources and they would be considered as ‘difficult-to-treat’ asthma patients, and such patients would be considered as such. The question then is whether the patient has asthma and the first stage of the definition is a recommendation that patients presenting with ‘difficult asthma’ have their asthma diagnosis confirmed and be evaluated and managed by an asthma specialist for more than 3 months. Thus, severe asthma according to the ATS/ERS definition only includes patients with refractory asthma and those in whom treatment of comorbidities such as severe sinus disease or obesity has been considered.

In the second stage of the definition, the question posed is what makes the asthma severe as compared to mild asthma. The definition rests mainly on the level of treatment requirements of the patient, with severe asthma being defined as ‘asthma which requires treatment with high-dose ICS and a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy. This definition includes patients who received an adequate trial of these therapies in whom treatment was stopped due to lack of
response. Therefore, this definition includes patients at steps 4 and 5 of the GINA guidelines. This definition is similar to the Innovative Medicine Initiative [3], but does not include the group of patients identified by the World Health Organisation (WHO) with untreated severe asthma [4], which is an important problem in many areas where asthma therapies are not widely available or affordable. The ATS/ERS Task Force focuses solely on severe asthma refractory or insensitive to currently available medications, including corticosteroids.

At the third stage, the recommendation is to determine whether the severe asthma is controlled or uncontrolled, with all asthma at this stage being considered as severe asthma. Any one of the following four criteria would define uncontrolled asthma: poor symptom control, that is Asthma Control Questionnaire (ACQ) consistently above 1.5 or Asthma Control Test (ACT) below 20 (or ‘not well controlled’ by National Asthma Education and Prevention Program or Global Initiative for Asthma guidelines over the 3 months of evaluation [5]); frequent severe exacerbations, defined as two or more bursts of systemic corticosteroids (>3 days each) in the previous year; serious exacerbations, defined as at least one hospitalization, ICU stay or mechanical ventilation in the previous year; airflow limitation, that is forced expiratory volume in 1 s (FEV1) below 80% predicted [in the presence of reduced FEV1/forced vital capacity (FVC) defined as less than the lower limit of normal] following a withhold of both short and long-acting bronchodilators [2**].

It should be mentioned that the reason why controlled asthma on high-dose medication is considered severe is because of the concept of future risks, both in terms of future exacerbations and of side effects from maintenance asthma medications.

**EVALUATION OF THE PATIENT PRESENTING WITH DIFFICULT-TO-TREAT ASTHMA**

In the evaluation of adults with difficult-to-control asthma, it was emphasized that first the evaluation needed to address the question as to whether the patient with ‘difficult asthma’ has asthma. A high degree of suspicion of potential diseases or factors that can masquerade as asthma should be a clinician’s attitude at this stage. In the evaluation of the difficult-to-treat asthma, the Task Force recommended that in adults with severe asthma without specific indications for chest high-resolution computed tomography (HRCT) based on history, symptoms and/or results of prior investigations, a chest HRCT only be done when the presentation is atypical (conditional recommendation, very low quality evidence). An atypical presentation of severe asthma could include excessive mucus production, rapid decline in lung function, reduced carbon monoxide transfer factor coefficient and the absence of atopy in a child with difficult asthma. Assessment of spirometry with a bronchodilator test and measurement of diffusing capacity, and bronchoprovocation testing, such as methacholine or exercise challenges, in the patient with relatively preserved lung function, can be considered on a case-by-case basis. Referral to an asthma centre where patients can undergo a systematic evaluation is advisable as previous studies have shown that 30–50% of patients previously called severe were classed as difficult to control after such an evaluation [6].

Co-existing conditions need to be determined and addressed [7]. Non-adherence to treatment should be considered in all difficult-to-control patients, as well as poor inhaler technique. Detecting poor adherence can be challenging and patients need to be confronted to this issue. Atopy and allergy, rhinosinusitis, nasal polyps, gastro-oesophageal reflux, obesity, concurrent smoking, anxiety and depression are important co-existing conditions that may contribute to the severity of asthma. Atopy to moulds, particularly to *Aspergillus fumigatus*, is of particular interest as they are related to asthma severity [8]. In addition, side effects of medications, particularly corticosteroids, need to be taken into account.

In the third step of evaluation, approaches to phenotyping should be considered. This is a novel approach to asthma evaluation, given the realization that severe asthma in particular is increasingly being recognized as heterogeneous processes, not all of which have the same clinical course nor respond similarly to current therapies [9*,10*]. Despite the fact that there are no widely accepted definitions of specific asthma phenotypes, identifying certain characteristics may lead to more effective targeted therapies as well as predict different natural histories [11*]. Eosinophilic inflammation, allergic/Th2 processes, corticosteroid insensitivity and obesity are potential characteristics or phenotypes which may be helpful when considering specific therapies [9*,12,13].

**Use of sputum eosinophil counts to guide treatment in patients with severe asthma**

The recommendation is that in adults with severe asthma, treatment guided by clinical criteria and sputum eosinophil counts is performed in centres experienced in using this technique rather than by clinical criteria alone. This places a higher value on
possible clinical benefits from adjusting the treatment in selected patients and on avoidance of inappropriate escalation of treatment and a lower value on increased use of resources. The usefulness of this recommendation is that it will identify patients with severe asthma for Th2-directed therapies. However, this recommendation was reached without consideration of the value of the blood eosinophil count or of the more recently introduced biomarker, serum periostin, as a biomarker of Th2 activation. The value of sputum eosinophils as a marker of response to anti-IgE therapy with omalizumab is not known, although blood eosinophil count can be a good marker to define responders to this treatment [14].

Use of exhaled nitric oxide levels to guide treatment in patients with severe asthma

The recommendation is that clinicians do not use exhaled nitric oxide (FeNO) to guide therapy in adults or children with severe asthma. A higher value is placed on avoiding additional resource expenditure and a lower value on uncertain benefit from monitoring FeNO. This recommendation was based on the limited amount of data available in patients with severe asthma. Recent studies of the efficacy of interleukin (IL)-13 antibody and anti-IgE therapy would indicate that FeNO may be a reasonable biomarker predictive of therapeutic response to these therapies [14*,15].

THERAPY OF SEVERE ASTHMA: CURRENTLY EXISTING THERAPIES

The Task Force reviewed the use of currently existing therapies for severe asthma.

Inhaled and oral corticosteroids

The benefits of ICS in asthma are well known, with improvement in asthma control, lung function and reduction in exacerbations, and in terms of exacerbation rates. Yet, the fact that there is variability in the response to ICS is less well known. It has been known for a while that blood eosinophilia is a good marker of a therapeutic response to corticosteroids [16], and more recently, it was shown that in mild-to-moderate asthmatic patients, those who responded well in terms of an improvement in FEV1 to a medium dose of ICS, were characterized by high expression of Th2 biomarkers in airway epithelial brushings, and those who did not, by a low level of Th2 biomarkers [17]. It is conceivable that some of the patients with severe asthma have inherent corticosteroid insensitivity.

Despite the large amount of information existing on these medications on patients with mild-to-moderate asthma, very little information exists on their benefits in severe asthma. What is clear is that in the case of corticosteroid therapy, these are likely to be less effective in severe asthma compared to milder non-severe asthma. Corticosteroid insensitivity has been associated with different comorbid conditions such as obesity, smoking, low vitamin D levels and non-eosinophilic (low-Th2 inflammation) mainly in adults [18]. In adults, a non-eosinophilic phenotype appears to form a large subgroup of asthma, with data from a mild-to-moderate cohort showing relatively poor corticosteroid sensitivity [19,20]. Several agents with immunosuppressive properties, such as methotrexate, cyclosporin A and gold salts, were studied as corticosteroid-sparing agents. However, the Task Force recommended that clinicians do not use methotrexate in adults or children with severe asthma, with this preference placing a relatively higher value on avoiding adverse effects of methotrexate and a relatively lower value on possible benefits from reducing the dose of systemic corticosteroids (Table 1).

About one-third of the patients with defined severe asthma are on regular oral corticosteroids (OCS), with over half needing more than three bursts of OCS in the previous year [21,22]. The optimal timing for the initiation of OCS therapy has also not been defined. Intramuscular triamcinolone in severe asthma improves eosinophilic inflammation and airflow obstruction, and prevents exacerbations [23,24], but with a significant side-effect profile of an increased risk of fractures, cataracts, adrenal suppression and growth retardation.

Long-acting β-agonists

Increased use of β-agonists may lead to worsening of asthma control, and the association between the use of inhaled β-agonists and asthma mortality was confined to the excessive use of β-agonists [25,26]. In clinical practice, doses and treatment duration in both adult and paediatric severe asthma frequently exceeded those recommended by expert guidelines, making it difficult to decide on a 'well tolerated' upper dose limit. One should be cautious in going above the recommended doses.

Leukotriene pathway modifiers

A leukotriene receptor antagonist or synthesis inhibitor has shown some efficacy on lung function when added to ICS in adults with moderate-to-severe asthma not taking LABAs [27,28].
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<th>Context: treatment</th>
<th>Recommendation</th>
<th>Strength</th>
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| **Anti-IgE antibody**
  (omalizumab) | In patients with severe allergic asthma, we suggest a therapeutic trial of omalizumab both in adults and in children. | Conditional Low (adults) very low (children) | This recommendation places higher value on the clinical benefits from omalizumab in some patients with severe allergic asthma and lower value on increased resource use. | Those adults and children aged 6 years and above, with severe asthma, who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance if their total serum IgE level is 30–700 IU/ml (in three studies the range was wider: 30–1300 IU/ml). Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilization, and improvement in quality of life. If a patient does not respond within 4 months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial. |
| **Methotrexate** | We suggest that clinicians do not use methotrexate in adults or children with severe asthma. | Conditional Low | This recommendation places a relatively higher value on avoiding adverse effects of methotrexate and a relatively lower value on possible benefits from reducing the dose of systemic corticosteroids. | Evidence from randomized trials is only available for adults. Because of the probable adverse effects of methotrexate and need for monitoring therapy, we suggest that any use of methotrexate is limited to specialized centres and only in patients who require daily OCS. If a decision to use methotrexate is made, a chest radiograph, complete blood count with differential and platelets, liver function tests, serum creatinine and transfer factor to carbon monoxide (DLCO), are recommended prior to and after commencing therapy. |
| **Macrolide antibiotics** | We suggest that clinicians do not use macrolide antibiotics in adults and children with severe asthma for the treatment of asthma. | Conditional Very low | This recommendation places a relatively higher value on prevention of development of resistance to macrolide antibiotics, and relatively lower value on uncertain clinical benefits. | This recommendation applies only to the treatment of asthma; it does not apply to the use of macrolide antibiotics for other indications, for example, treatment of bronchitis, sinusitis or other bacterial infections as indicated. |
| **Antifungal agents** | We suggest antifungal agents in adults with severe asthma and recurrent exacerbations of allergic bronchopulmonary aspergillosis (ABPA). | Conditional Very low | The recommendation to use antifungal agents in patients with severe asthma and ABPA places a higher value on possible reduction of the risk of exacerbations and improved symptoms, and a lower value on avoiding possible adverse effects, drug interactions and increased use of resources. | In children, the evidence is limited to isolated case reports. Children should be treated with antifungals only after the most detailed evaluation in a specialist severe asthma referral centre. As antifungal therapies are associated with significant and sometimes severe side effects, including hepatotoxicity, clinicians should be familiar with these drugs and follow relevant precautions in monitoring for these, observing the limits to the duration of treatment recommended for each. |
B We suggest that clinicians do not use antifungal agents for the treatment of asthma in adults and children with severe asthma without ABPA irrespective of sensitization to fungi (i.e., positive skin prick test or fungus-specific IgE in serum). The recommendation not to use antifungal agents in patients with severe asthma without confirmed ABPA (irrespective of sensitization) places a higher value on avoiding possible adverse effects, interactions of antifungal agents with other medications and increased use of resources, and a lower value on uncertain possible benefits.

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<th>Condition</th>
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<tr>
<td>Strong</td>
<td>Bronchial thermoplasty</td>
<td>This recommendation places a higher value on avoiding adverse effects, on an increased use of resources, and on a lack of understanding of which patients may benefit and a lower value on the uncertain improvement in symptoms and quality of life.</td>
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<td>Very low</td>
<td>The recommendation not to use antifungal agents in patients with severe asthma without confirmed ABPA applies only to the treatment of asthma; it does not apply to the use of antifungal agents for other indications, for example, treatment of invasive fungal infections.</td>
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<td>Conditional</td>
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This is a strong recommendation, because of the very low confidence in the currently available estimates of effects of bronchial thermoplasty in patients with severe asthma. Both potential benefits and harms may be large and the long-term consequences of this new approach to asthma therapy utilizing an invasive physical intervention are unknown. Specifically designed studies are needed to define its effects on relevant objective primary outcomes such as exacerbation rates, and on long-term effects on lung function. Studies are also needed to better understand the phenotypes of responding patients, its effects in patients with severe obstructive asthma (FEV₁ < 60% of predicted value) or in whom systemic corticosteroids are used, and its long-term benefits and safety. Further research is likely to have an important impact on this recommendation.
**Long-acting muscarinic antagonists**

Tiotropium bromide improved lung function and symptoms in moderate-to-severe asthma patients not controlled on moderate to high-dose ICS with or without LABAs, with also a reduced risk of severe exacerbation [29,30].

**NEWLY INTRODUCED AGENTS**

The therapeutic options evaluated in this context were the use of anti-IgE therapy, the use of macrolide therapy, the role of antifungal treatments and the newer treatment of bronchial thermoplasty, which are treatments that have been introduced and considered for the treatment of severe asthma. The recommendations based on analysis of available studies until September 2013 are summarized below and more comments regarding these are provided in Table 1.

**Anti-IgE therapy**

A therapeutic trial of omalizumab both in adults and in children is recommended based on the clinical benefits from omalizumab in some patients with severe allergic asthma and lower value on increased resource use.

**Macrolide antibiotics**

Clinicians are recommended not to use macrolide antibiotics in adults with severe asthma for the treatment of asthma based on the higher value on prevention of development of resistance to macrolide antibiotics, and relatively lower value on uncertain clinical benefits.

**Antifungal agents**

The recommendation is that antifungal agents are used in adults with severe asthma and recurrent exacerbations of allergic bronchopulmonary aspergillosis (ABPA), but that antifungal agents are not used for the treatment of asthma in adults with severe asthma without ABPA, irrespective of sensitization to fungi (i.e. positive skin prick test or fungus-specific IgE in serum).

**Bronchial thermoplasty**

It is recommended that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study. This recommendation was based on avoiding adverse effects and on increased use of resources, and on a lack of understanding of which patients may benefit, and a lower value on the uncertain improvement in symptoms and quality of life.

**NOVEL THERAPIES FOR SEVERE ASTHMA**

Novel therapies for severe asthma that may be of benefit for patients with severe asthma [11] include anti-Th2 targets such as anti-IL-5 antibody, mepolizumab [31]; anti-IL5Rα antibody, benralizumab [32]; anti-IL-13 antibody, lebrikizumab [15] and anti-IL-4Rα antibody, dupilumab [33]. These treatments will likely be targeted towards patients with an eosinophilia, and in some cases towards patients who express high levels of Th2 biomarkers, such as serum periostin. The situation is less clear with the patients who do not have evidence of Th2-high expression. More validated markers are indeed needed for non-eosinophilic asthma, together with the identification of targets for treatments.

**CONCLUSION**

The Task Force has defined severe asthma, and made recommendations on five treatments for severe asthma. Not only does it help the clinician in evaluating these patients, it has also taken an important step in recommending initial steps towards characterization and phenotyping patients with severe asthma so that patients can receive the appropriate targeted therapies. However, more needs to be done in characterizing severe asthma. The availability of high-throughput biological data has now opened up an important avenue for an unbiased discovery of biomarkers useful to delineate phenotypes and to predict therapeutic response, and also for determining targets for treatment. Biologic processes involved in inflammation, immunity, cell cycle, apoptosis or metabolism will need to be linked to the clinical and phenotypic expression of asthma. Analysis of clinical, physiologic and genomic, transcriptomic, lipidomic and proteomic data will provide a more complex but more definitive phenotypic/endotypic representation of the patient’s disease which combines clinical characteristics with identifiable mechanistic pathways. This represents an important step towards a more personalized care of severe asthma [34]. Future guidelines for severe asthma will need to take into account these foreseeable advances, as well as the newly published data since September 2013.

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Conflicts of interest

K.F.C. is a co-leader of an IMI-funded project on Severe Asthma: IMI is a private public partnership between the EU and EFPIA. K.F.C. does not have any conflict of interest to declare with respect to this article.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

3. First international guidelines on severe asthma.
11. Review that scores the importance of phenotyping for therapeutic responses to new biologic therapies for asthma.
13. Review that focuses on a systems biology approach to phenotyping of asthma.
15. Review on the new promising biologic therapies for severe asthma.