International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

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ABSTRACT Severe or therapy-resistant asthma is increasingly recognised as a major unmet need. A Task Force, supported by the European Respiratory Society and American Thoracic Society, reviewed the definition and provided recommendations and guidelines on the evaluation and treatment of severe asthma in children and adults.

A literature review was performed, followed by discussion by an expert committee according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach for development of specific clinical recommendations.

When the diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy. Severe asthma is a heterogeneous condition consisting of phenotypes such as eosinophilic asthma. Specific recommendations on the use of sputum eosinophil count and exhaled nitric oxide to guide therapy, as well as treatment with anti-IgE antibody, methotrexate, macrolide antibiotics, antifungal agents and bronchial thermoplasty are provided.

Coordinated research efforts for improved phenotyping will provide safe and effective biomarker-driven approaches to severe asthma therapy.

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As a result of the corrections published in the April 2014, July 2018 and June 2022 issues of the *European Respiratory Journal*, the online version of this article has been revised.

Executive Summary

The European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force on severe asthma includes an updated definition of severe asthma, a discussion of severe asthma phenotypes in relation to genetics, natural history, pathobiology and physiology, as well as sections on evaluation and treatment of severe asthma where specific recommendations for practice are made. See the unabridged online version of the document for detailed discussion of the definition of severe asthma, phenotypes and recommendations for practice.

When a diagnosis of asthma is confirmed and comorbidities have been addressed, severe asthma is defined as ''asthma which requires treatment with high dose inhaled corticosteroids (ICS) (see table 4 for doses in adults and children) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy.''

The methods used to develop clinical recommendations in this document follow the ATS and ERS guideline methodology. The committee included clinicians and researchers with expertise in severe asthma and a methodologist who helped prepare systematic evidence summaries following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. Potential conflicts of interests were managed according to the ATS and ERS rules.

The systematic searches for evidence to support the recommendations made in these guidelines identified very few randomised controlled trials (RCTs) with low risk of bias that would provide direct, consistent and precise evidence. Therefore, many recommendations are based on indirect evidence from studies performed in patients with mild-to-moderate asthma frequently providing imprecise estimates of desirable and undesirable health effects. Moreover, few studies assessed all outcomes that the committee had identified as being critical in making the recommendations.

The committee developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach. Quality of evidence (confidence in the available estimates of treatment effects) is categorised as: high, moderate, low or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. Low and very low quality evidence indicates that the estimated effects of interventions are very uncertain and further research is very likely to have an important impact on the resulting recommendations.

The strength of recommendations is expressed as either strong (We recommend…) or conditional (We suggest…) and has explicit implications (table 2). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

Recommendations

The recommendations are detailed in table 1.

Scope and purpose

The purpose of this document is to revise the definition of severe asthma, discuss the possible phenotypes and provide guidance about the management of patients with severe asthma. The target audience of these guidelines is specialists in respiratory medicine and allergy managing adults and children with severe asthma. General internists, paediatricians, primary care physicians, other healthcare professionals and policy makers may also benefit from these guidelines. This document may also serve as the basis for development and implementation of locally adapted guidelines.

Introduction

Although the majority of asthma patients can be effectively treated with currently available medications, a substantial subset exists who remain difficult-to-treat. These patients account for a relatively large proportion of resource expenditure. Much remains unclear regarding the best approaches to the management of these patients, or concerning the underlying mechanisms driving this process. In 1999 and in 2000, the first definitions of severe/refractory asthma were published respectively in the *European*

For editorial comments see page 315.

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TABLE 1 Recommendations

Context		Recommendation	Strength	Quality of evidence	Values and preferences	Remarks
Computed tomography of chest	1	In children and adults with severe asthma without specific indications for chest HRCT based on history, symptoms and/or results of prior investigations we suggest that a chest HRCT only be done when the presentation is atypical	Conditional	Very low	This recommendation places a relatively high value on identification of alternative diagnosis and comorbidities and a relatively low value on avoiding potential complications and cost of chest HRCT	An atypical presentation of severe asthma includes such factors as, for example, 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
Sputum eosinophil counts	2A	In adults with severe asthma: we suggest treatment guided by clinical criteria and sputum eosinophil counts performed in centres experienced in using this technique rather than by clinical criteria alone	Conditional	Very low	The recommendation to use sputum eosinophil counts to guide therapy in adults 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	Because, at the present time, measurement of sputum eosinophils has not yet been sufficiently standardised and is not widely available we suggest such an approach be used only in specialised centres experienced in this technique. Patients who are likely to benefit from this approach are those who can produce sputum, demonstrate persistent or at least intermittent eosinophilia and have severe asthma with frequent exacerbations Clinicians should recognise that different choices will be appropriate for different patients
	2B	In children with severe asthma: we suggest treatment guided by clinical criteria alone rather than by clinical criteria and sputum eosinophil counts	Conditional	Very low	The recommendation not to use sputum eosinophil counts to guide therapy in children places higher value on avoiding an intervention that is not standardised and not widely available and lower value on the uncertain and possibly limited clinical benefit	
Exhaled nitric oxide	3	We suggest that clinicians do not use F_{ENO} to guide therapy in adults or children with severe asthma	Conditional	Very low	This recommendation places a higher value on avoiding additional resource expenditure and a lower value on uncertain benefit from monitoring F_{ENO}	
Anti-IgE antibody (omalizumab)	4	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 $\geqslant$6 years 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^{-1} (in three studies the range was wider: 30–1300 IU·mL^{-1}) Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilisation, 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

TABLE 1 Continued

Context		Recommendation	Strength	Quality of evidence	Values and preferences	Remarks
Methotrexate	5	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 randomised 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 specialised centres and only in patients who require daily OCS If a decision to use methotrexate is made chest radiography, complete blood count with differential and platelets, liver function tests, serum creatinine and *D*LCO are recommended prior to and after commencing therapy
Macrolide antibiotics	6	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, *e.g.* treatment of bronchitis, sinusitis or other bacterial infections as indicated
Antifungal agents	7A	We suggest antifungal agents in adults with severe asthma and recurrent exacerbations of 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 side-effects, observing the limits to the duration of treatment recommended for each
	7B	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 sensitisation to fungi (*i.e.* positive skin prick test or fungus-specific IgE in serum)	Conditional	Very low	The recommendation not to use antifungal agents in patients with severe asthma without confirmed ABPA (irrespective of sensitisation) 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	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, *e.g.* treatment of invasive fungal infections

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TABLE 1 Continued

Context		Recommendation	Strength	Quality of evidence	Values and preferences	Remarks
Bronchial thermoplasty	8	We recommend 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 (recommendation, quality evidence)	Strong	Very low	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	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 utilising 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 (FEV_1 <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

HRCT: high-resolution computed tomography; F_{ENO}: exhaled nitric oxide fraction; OCS: oral corticosteroids; D_{LCO}: transfer factor of the lung for carbon monoxide; ABPA: allergic bronchopulmonary aspergillosis; FEV_1: forced expiratory volume in 1 s.

Respiratory Journal and in the *American Journal of Respiratory and Critical Care Medicine*, with variations of these adopted by subsequent cohorts [1, 2]. In 2009, a 23 member joint Task Force from the ATS and the ERS consisting of adult- and paediatric-trained specialists and scientists with extensive experience of managing and investigating patients with asthma, particularly severe asthma, was formed to: 1) update the previous definitions, 2) identify potential mechanisms/phenotypes of severe asthma, 3) outline its evaluation and 4) provide recommendations on treatment, with respect to both adults and children. Another objective of this Task Force was to summarise the findings of the past 12 years that have elapsed since the previous reports [1, 2] and to propose directions for step-wise improvement in our understanding of severe asthma. Severe asthma is now widely accepted as a heterogeneous disease, consisting of multiple phenotypes and studies are beginning to define phenotypic biomarkers, and phenotype-targeted biological therapies are increasingly showing efficacy.

Methods

Committee composition and processes of disclosing and managing potential conflicts of interest, evidence synthesis, developing recommendations and peer review of the guidelines are described in detail in the online-only full-text document of these guidelines.

Briefly, this guideline represents a collaborative effort between the ATS and ERS. The Committee consisted of clinicians and researchers with recognised expertise in severe asthma and in the guideline development following the GRADE approach [3]. All committee members disclosed their potential conflicts of interest according to the ATS and ERS policies. During all deliberations members with perceived conflicts of interest abstained from decisions about specific recommendations related to the potential conflict of interest. The views and interests of the ATS and ERS as well as of any commercial entity that provided external funding for both professional societies had no influence on the final recommendations.

Disclosure of potential conflicts of interest

Committee members disclosed all potential conflicts of interest according to the ATS and ERS policies. The chairs (K.F.C. and S.E.W.) reviewed and resolved all potential conflicts of interest of committee members. All potential conflicts of interest (including those of the chairs) were discussed with the chair of the Ethics and Conflict of Interest Committee of the ATS. During all deliberations, members with perceived conflicts of interest abstained from decisions about specific recommendations related to the potential conflict of interest. The ATS methodologist (J.L.B.) did not participate in the vote on any of the recommendations.

The ATS and ERS provided meeting facilities during their annual conferences and financial support for conference calls. The views and interests of the ATS and ERS as well as of any commercial entity that provided external funding for both professional societies had no influence on the final recommendations.

Evidence summaries (online supplementary material 1) for each question were prepared following the GRADE approach [3] and reviewed by all committee members. We based the evidence summaries on existing up-to-date well-executed systematic reviews, if necessary supplemented with additional recent RCTs. When there was no recent valid systematic review available we did not perform rigorous systematic reviews, but we systematically searched for relevant studies (online supplementary material 2).

We labelled the recommendations as either ''strong'' or ''conditional'' according to the GRADE approach. We used the words ''we recommend'' for strong recommendations and ''we suggest'' for conditional recommendations. Table 2 provides suggested interpretation of strong and conditional recommendations by patients, clinicians and health care policy makers.

Many questions relevant to the management of patients with severe asthma have been identified by the committee as potentially important but have not yet been addressed (online supplementary material 2). The committee intends to regularly update the document up until 2015.

How to use these guidelines

The ERS/ATS guidelines about the management of severe asthma are not intended to impose a standard of care. They provide the basis for rational decisions in the management of severe asthma. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines and recommendations can take into account all of the often-compelling unique individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

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TABLE 2 Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not
Clinicians	Most individuals should receive the intervention Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Recognise that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences
Policy makers	The recommendation can be adopted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

1. Task Force definition of severe asthma

The definition of severe asthma in patients aged ⩾6 years is shown in table 3.

Stage 1: confirm an asthma diagnosis and identify difficult-to-treat asthma

Inherent in the definition of severe asthma is the exclusion of individuals who present with "difficult" asthma in whom appropriate diagnosis and/or treatment of confounders vastly improves their current condition (see the evaluation section). Therefore, it is recommended 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 remains incomplete.

Stage 2: differentiate severe asthma from milder asthma

When a diagnosis of asthma is confirmed and comorbidities addressed, severe asthma is defined as "asthma which requires treatment with high dose inhaled corticosteroids (ICS) (see table 4 for doses in adults and children) plus 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. In patients >6 years of age, "Gold Standard/International Guidelines treatment" is high dose ICS plus a long-acting β_2-agonist (LABA), leukotriene modifier or theophylline and/or continuous or near continuous systemic corticosteroids as background therapy [4–7]. This definition is similar to the recent Innovative Medicine Initiative [8], but does not address the group of patients identified by the World Health

TABLE 3 Definition of severe asthma for patients aged ⩾6 years

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS[#] and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ⩾50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently ⩾1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)
2) Frequent severe exacerbations: two or more bursts of systemic CS (⩾3 days each) in the previous year
3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

[#]: the definition of high dose inhaled corticosteroids (ICS) is age-specific (table 4). GINA: Global Initiative for Asthma; LABA: long-acting β_2-agonists; CS: corticosteroids; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; NAEPP National Asthma Education and Prevention Program.

TABLE 4 Definition of high daily dose of various inhaled corticosteroids in relation to patient age

Inhaled corticosteroid	Threshold daily dose in μg considered as high	
	Age 6–12 years	Age >12 years
Beclomethasone dipropionate	⩾800 (DPI or CFC MDI) ⩾320 (HFA MDI)	⩾2000 (DPI or CFC MDI) ⩾1000 (HFA MDI)
Budesonide	⩾800 (MDI or DPI)	⩾1600 (MDI or DPI)
Ciclesonide	⩾160 (HFA MDI)	⩾320 (HFA MDI)
Fluticasone propionate	⩾500 (HFA MDI or DPI)	⩾1000 (HFA MDI or DPI)
Mometasone furoate	⩾500 (DPI)	⩾800 (DPI)
Triamcinolone acetonide	⩾1200	⩾2000

Notes: 1) Designation of high doses is provided from manufacturers' recommendations where possible. 2) As chlorofluorocarbon (CFC) preparations are being taken from the market, medication inserts for hydrofluoroalkane (HFA) preparations should be carefully reviewed by the clinician for the equivalent correct dosage. DPI: dry powder inhaler; MDI: metered-dose inhaler.

Organization with untreated severe asthma [9]. Although untreated severe asthma is an enormous problem in many areas where current therapies are not widely available, the definition of severe asthma agreed upon by the 2013 ATS/ERS Task Force focuses on severe asthma refractory or insensitive to currently available medications, including corticosteroids, and asthma complicated by comorbidities, the types of greatest concern to the countries primarily served by the two societies [9].

Stage 3: determine whether the severe asthma is controlled or uncontrolled

The background for criteria for uncontrolled asthma is presented in the online supplementary material 3. Any one of the following four criteria qualifies a patient as having uncontrolled asthma: 1) poor symptom control, *i.e.* Asthma Control Questionnaire (ACQ) consistently ⩾1.5 or Asthma Control Test (ACT) <20 (or "not well controlled" by National Asthma Education and Prevention Program or Global Initiative for Asthma guidelines over the 3 months of evaluation [6, 10]); 2) frequent severe exacerbations, defined as two or more bursts of systemic corticosteroids (⩾3 days each) in the previous year; 3) serious exacerbations, defined as at least one hospitalisation, intensive care unit stay or mechanical ventilation in the previous year; 4) airflow limitation, *i.e.* forced expiratory volume in 1 s (FEV_1) <80% predicted (in the presence of reduced FEV_1/forced vital capacity (FVC) defined as less than the lower limit of normal) following a withhold of both short- and long-acting bronchodilators.

Evidence of any one of these four criteria while on current high-dose therapy identifies the patient as having "severe asthma" (table 3). Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering of corticosteroids, will also meet the definition of severe asthma. Fulfilment of this definition predicts a high degree of future risk both from the disease itself (exacerbations and loss of lung function), as well as from side-effects of the medications.

2. Phenotyping: epidemiology, pathogenesis, pathobiology, structure and physiology

Phenotypes and clusters of severe asthma

It is increasingly evident that severe asthma is not a single disease, as evidenced by the variety of clinical presentations, physiological characteristics and outcomes. To better understand this heterogeneity the concept of asthma phenotyping has emerged. A phenotype is defined as the composite, observable characteristics of an organism, resulting from interaction between its genetic make-up and environmental influences, which are relatively stable, but not invariable, with time. Phenotyping integrates biological and clinical features, ranging from molecular, cellular, morphological and functional to patient-oriented characteristics with the goal to improve therapy (fig. 1). Detailed efforts in this regard require organisation and integration of these defining characteristics into clinically recognisable phenotypes. Ultimately, these phenotypes should evolve into asthma "endotypes", which combine clinical characteristics with identifiable mechanistic pathways. Their identification to date remains speculative at best [11]. In general, temporal stability of phenotypes will be required to provide evidence of their clinical usefulness. The ultimate clinical usefulness of these severe asthma phenotypes will be determined by their therapeutic consequences (see the evaluation section).

There are currently two strategies to delineate phenotypes: hypothesis-based and unbiased approaches. Unbiased analyses are being applied to a broad range of clinical, physiological and biological characteristics, utilising unsupervised hierarchical clustering stepwise discriminant and other approaches [12–15]. The

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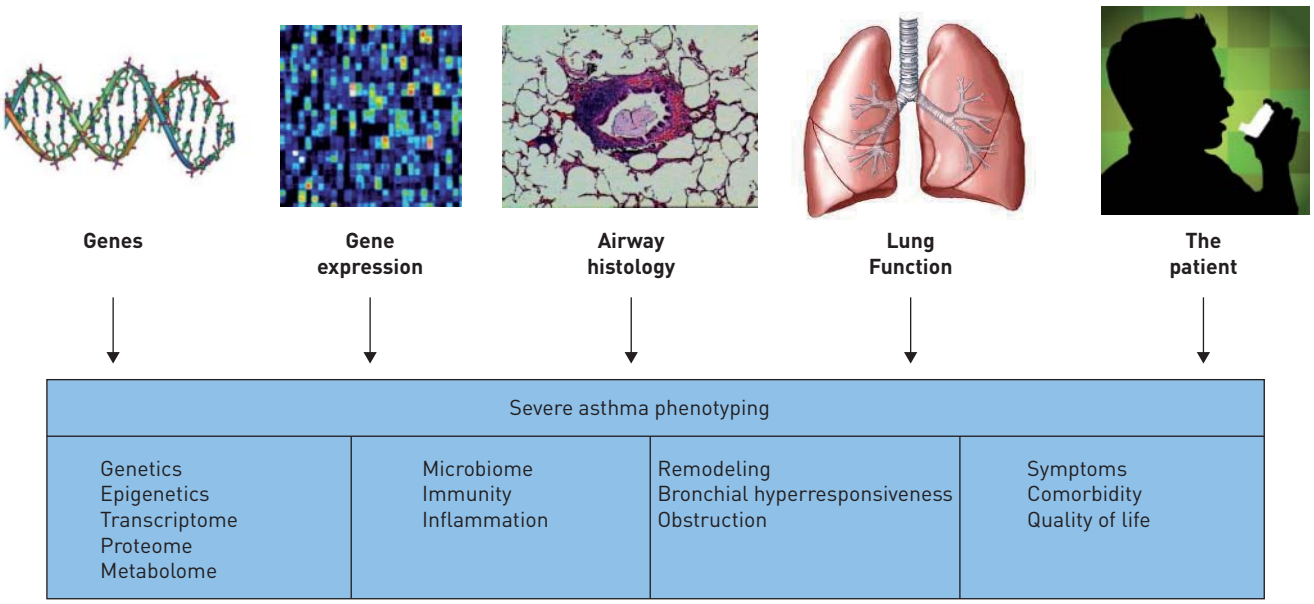

FIGURE 1 Integration of factors, beginning with genetics, which may contribute to the ultimate phenotype of the severe asthma patient.

Severe Asthma Research Program (SARP), using predominantly clinical characteristics, identified five clusters of asthma amongst adult patients with mild, moderate and severe asthma. They included three groups of mild, moderate and severe early-onset atopic asthma (based on range of lung function, medication use and frequency of exacerbations), a more severe late-onset obese group of primarily older females with moderate FEV_1 reductions and frequent oral corticosteroid use, and a later onset but long duration very severe, less atopic group, with less reversible airflow limitation [15]. Another adult asthma cohort analysis from the Leicester group included sputum eosinophil counts and identified four clusters including a similar early-onset atopic-asthma, an obese non-eosinophilic asthma, an early-onset symptom predominant-asthma, and a later onset inflammation predominant asthma [14]. In both cluster analyses, severe asthmatics were distributed among several clusters supporting the heterogeneity of severe asthma. Finally, a SARP study of children found four clusters: 1) later-onset with normal lung function, 2) early-onset atopic with normal lung function, 3) early-onset atopic with mild airflow limitation, and 4) early-onset with advanced airflow limitation [16].

These three studies derived phenotypes by less biased analysis, although the data entered into the analyses varied, as did the approaches. Whereas the SARP adult cluster classification related primarily to lung function, age at onset and level of therapy, the Leicester cluster indicated that an eosinophilic phenotype may be more common in later onset severe asthma. Interestingly, these unbiased phenotypes have substantial overlap with phenotypes previously recognised clinically (late-onset eosinophilic and early-onset atopic/allergic), supporting the identification of these phenotypes in particular [17, 18].

Natural history and risk factors

Little is understood regarding the prevalence of severe asthma in adults or children, especially when using rigorous definitions as outlined here. However, figures of 5–10% of the total asthma population are often estimated.

It is likely that some of the difficulty in estimating these figures is also due to asthma heterogeneity. This heterogeneity of severe asthma and its phenotypes and lack of long term studies limit our understanding of the natural history of severe asthma, including whether severe asthma develops early in the course of the disease, or whether it develops over time. There is increasing evidence that severe asthma phenotypes are related to genetic factors, age of asthma onset, disease duration, exacerbations, sinus disease and inflammatory characteristics [14, 16, 17, 19–21]. Early childhood-onset asthma (over a range of severity) is characterised by allergic sensitisation, a strong family history and, more recently, non-allergy/atopy related genetic factors [14, 17, 22]. Late-onset severe asthma is often associated with female sex and reduced pulmonary function despite shorter disease duration. In some subgroups, it is associated with persistent eosinophilic inflammation, nasal polyps and sinusitis and often aspirin sensitivity (aspirin-exacerbated respiratory disease) and respiratory tract infections, but less often with specific genetic factors [14, 15, 17, 23, 24].

However, at least some of these apparently late-onset cases may have been symptomatic with abnormal airway physiology early in life, but the relation to severe asthma development is less clear [25].

Occupational exposures have also been associated with late-onset, and often severe asthma [26]. Obesity is associated with both childhood and adult onset severe asthma, but the impact of obesity may differ by age at onset and degree of allergic inflammation [27, 28]. Tobacco smoke and environmental air pollution are routinely linked as risk factors for more severe asthma [29, 30]. Both personal smoking and obesity have been linked to corticosteroid insensitivity, also associated with severe asthma [31, 32]. Recurrent exacerbations in adult severe asthma are more frequent in patients with comorbid conditions such as severe sinus disease, gastro-oesophageal reflux, recurrent respiratory infections and obstructive sleep apnoea [33]. Sensitisation to fungi such as *Aspergillus* has also been associated with severe asthma development in adults [34, 35].

Genetics and epigenetics

Genetic approaches in complex diseases such as asthma can predict risk for development (susceptibility) or progression (severity). Comprehensive genetic association studies using genome-wide association approaches have identified and replicated gene variants important in determining asthma susceptibility which is often based on the loose description of a physician diagnosis of asthma rather than a comprehensive clinical characterisation [22, 36]. Other studies have compared more severe asthma with non-asthma controls or smaller cohorts with mild disease and have identified similar genes [20]. Differences in asthma susceptibility genes also appear to differ by age at onset of disease, a characteristic critical to both biased and unbiased phenotyping approaches [22, 37]. Understanding the functional biology of these gene variants may help identify biomarkers in relation to phenotypes and new pharmacotherapies. For example, single nucleotide polymorphisms in the interleukin (IL)-4 receptor-α specifically associate with persistent airways inflammation, severe asthma exacerbations and submucosal mast cells supporting functional alterations in the IL-4 pathway influencing allergic inflammation in some severe asthmatics [19]. Another recent paper showed that variation in IL-6 receptor associated with lower lung function and more severe asthma subphenotypes suggesting another therapeutic target [38]. Finally, there is evidence that genetic variation in a number of genes may interact and influence lung function, asthma susceptibility and severity [39]. Another mechanism predisposing to more severe or difficult-to-treat asthma may relate to pharmacogenetics, where responsiveness to asthma therapy is altered or reduced in some individuals. Asthmatics with reduced therapeutic responsiveness to controller therapies such as inhaled corticosteroids or even specific novel biological therapies could exhibit more difficult-to-control asthma and be classified as more severe [40, 41].

Epigenetic changes result from non-coding structural changes to DNA, such as DNA methylation or chromatin structural alterations to histones, or from the effects of small non-coding RNA, microRNA (miRNA). A role for miRNAs in regulating T-helper cell (Th)2 function, subsequent allergic airways disease and T-cell production of IL-13 has been proposed from murine studies [42, 43]. Another study reported alterations in specific miRNAs in asthmatic CD4 and CD8 T-cells [44], but the relevance for severe asthma remains to be ascertained.

Inflammation and adaptive immunity

Inflammation in severe asthma has been measured by enumerating inflammatory cells in sputum induced from the airways by inhalation of hypertonic saline, as well as through endobronchial biopsies and bronchoalveolar lavage. This inflammation has been categorised into eosinophilic, neutrophilic, and/or paucigranulocytic [14, 18, 45–47]. The concomitant presence of both eosinophils and neutrophils (mixed cellularity) has been reported to be associated with the most severe disease [48]. However, both eosinophil and neutrophil sputum numbers show wide variability in severe asthma with patients demonstrating none to very high levels of either cell, despite being on high doses of corticosteroids [48–50]. The neutrophilic and eosinophilic components of sputum can vary substantially on a monthly basis [51]. However, sputum eosinophilia appears more stable, especially in severe asthma, when examined over longer yearly periods in adults [52]. This stability appears to be less in children [53]. The mechanisms behind these diverse inflammatory profiles are likely complex, varied, and related to corticosteroid sensitivity (fig. 2) [54, 55]. Eosinophilic inflammation, for instance, is likely to have a Th2 immune component, a reflection of adaptive immunity, as evidenced by four separate studies demonstrating efficacy of a monoclonal antibody to IL-5 in eosinophilic severe asthma in adults [14, 56–58]. Whether the Th2 profile is similar to that observed in corticosteroid-naïve patients awaits further study, but would be supported by studies demonstrating efficacy of an anti-IL-13 antibody in improving FEV_1 in adult patients with moderate-to-severe asthma [59, 60]. Evidence for a Th2 pattern in severe asthmatic children remains controversial [61, 62]. Inflammation associated with high expression of Th2 cytokines has also been linked to mast cells [63]. Mast cells are

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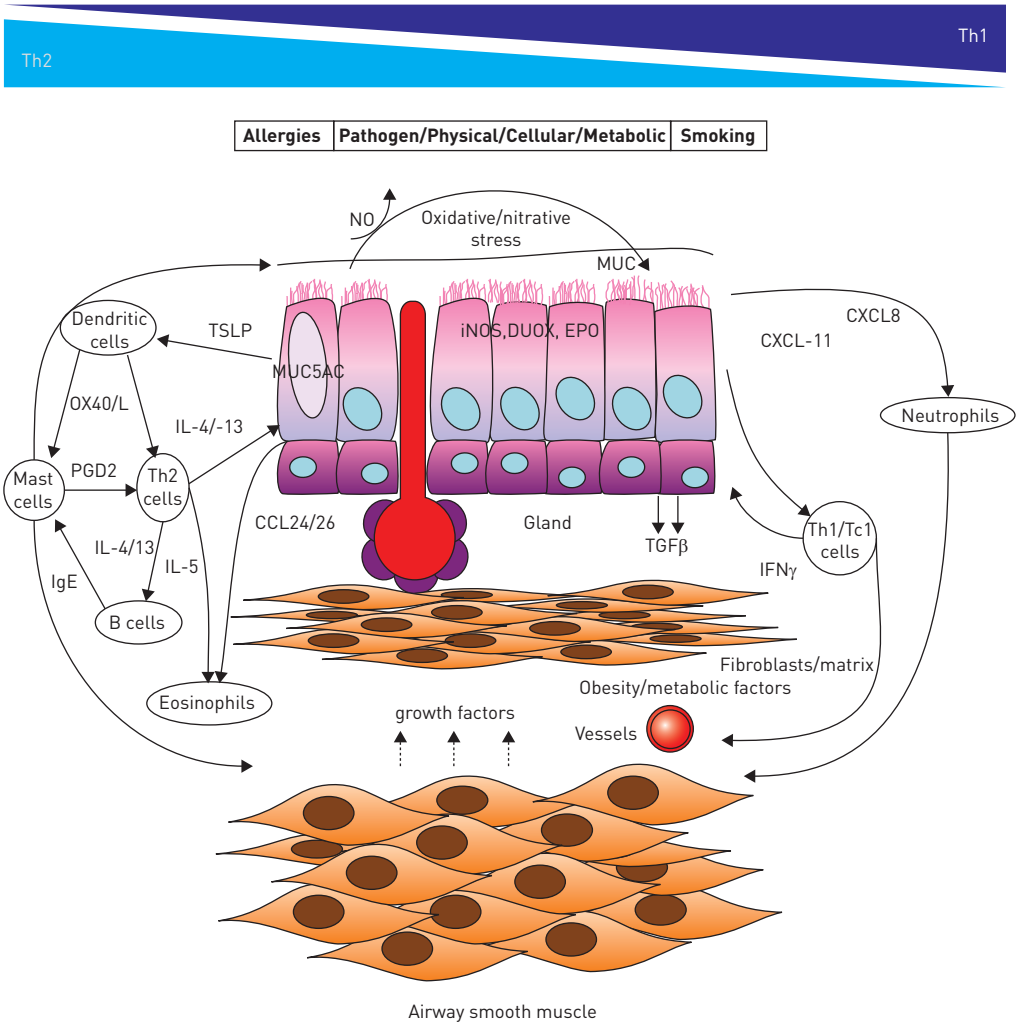

FIGURE 2 Potential immune-inflammatory and cellular interactions contributing to the pathogenesis of phenotypes of asthma. CXCL: CXC chemokine ligand; CCL24/26: CC chemokine ligand 24/26; DUOX: dual oxidase; EPO: eosinophil peroxidase; IFNγ: interferon-γ; IgE: immunoglobulin E; IL: interleukin; iNOS: inducible nitric oxide synthase; MUC5AC: mucin 5AC; NO: nitric oxide; OX40/L: CD134 ligand; PGD2: prostaglandin D2; Tc1: cytotoxic T-cell type 1; TGFβ: transforming growth factor-β; Th1: T-helper cell type 1; Th2: T-helper cell type 2; TSLP: thymic stromal lymphopoietin.

increased in airway smooth muscle and epithelial compartments in asthma where they have been linked to poor asthma control and airway hyperresponsiveness [64, 65].

The mechanisms for airway neutrophilia are less clear. Corticosteroids themselves can contribute to the neutrophilia to some degree and even Th1 factors may play a role [66, 67]. Th17 immunity has been implicated as a cause for neutrophilia, primarily in murine models of asthma, with some supporting data from severe asthma [66, 68–70].

The underlying mechanisms for severe asthma in those patients with little or no inflammation remain poorly understood, but could involve activation of resident cellular elements including smooth muscle cells, fibroblasts and neurons. Importantly, while emphasis has been placed on assessing inflammation by analysis of sputum samples, its relationship to cellular profiles in airway/lung tissues is poor and remains poorly understood [55, 71].

Molecular phenotyping approaches are also emerging with data from severe asthmatic children suggesting Th1 skewing compared to those with moderate asthma, while a recent transcriptome analysis of peripheral blood cells suggested differential activation of $CD8^+$ T-cells in severe asthma as compared to $CD4^+$ T-cells [44, 62]. Patterns of exhaled volatile organic compounds also differ between asthmatics with fixed airflow limitation and patients with chronic obstructive pulmonary disease supporting their potential in the phenotyping of severe asthma [72, 73]. Finally, exhaled nitric oxide fraction (F_{ENO}) has been extensively

evaluated in mild-to-moderate asthma and the ATS has recently published specific guidelines for *F*eNO use in these patients [74]. Cross-sectional studies of severe asthma have indicated some potential usefulness of *F*eNO as a measure of symptom frequency [75] and as an index of the most obstructed and frequent users of emergency care [76].

Respiratory infections

The role of infections, particularly viral infections, in asthma exacerbations is well-established and their contribution to asthma development and progression increasingly recognised; however, the relation to asthma severity has rarely been addressed [77–79]. There is an association between Staphylococcal superantigen-specific IgE antibodies and asthma severity and sinusitis, while fixed airflow limitation has been associated with positive serology for intracellular pathogens, such as *Chlamydia pneumoniae* [24, 80, 81]. Emerging data indicate an altered microbiome in asthma as measured by 16s rRNA, but the role of bacteria in severe asthma requires further study [82]. Positive *Haemophilus influenzae* and *Pseudomonas aeroginosa* cultures were reported in sputum samples of severe asthmatic patients without evidence of bronchiectasis and from those with a long duration of asthma and exacerbations in the past year [83]. These infection-related factors have only been evaluated in cross-sectional studies with modest regard to asthma characteristics or phenotypes, except for the relationship of Chlamydial infections with lung function in adult-onset asthma [24].

Activation of innate immune pathways

There is growing evidence for involvement of innate immune pathways, with certain aspects abnormally diminished while others may be enhanced. Thus, macrophage phagocytosis of apoptotic epithelial cells or of bacteria has been reported to be impaired, which could lead to enhanced inflammation [84, 85]. Toll-like receptor signalling may also be impaired, leading to inadequate Type I and III interferon (IFN) responses which decrease viral clearance [86]. In addition, the antimicrobial activity of airway epithelial cells and their production of β-defensins are reduced when these cells are exposed to Th2 cytokines, while allergic inflammation leads to a reduction in cathelicidin antimicrobial peptide [87, 88]. In contrast, other elements of innate immunity may be enhanced, including increased expression of thymic stromal lymphopoietin, IL-25 and IL-33 in airway cells from patients with severe asthma [70, 89, 90]. Whether these abnormalities are specific to certain phenotypes awaits further study.

Several studies suggest that oxidative and nitrative stress is also increased in severe asthma. Higher *F*eNO values, perhaps due to the higher reported inducible nitric oxide synthase expression in severe asthmatic epithelial cells, have been associated with a more exacerbation prone phenotype in severe asthma, as well as more rapid decline in FEV_1 [76, 91–93]. In addition, higher levels of oxidative stress have been associated with a reduction in superoxide dismutase and s-nitrosothiol depletion [94, 95].

The expression of tumour necrosis factor (TNF)-α has been reported to be increased in severe asthmatic airways, and recent genomic and proteomic approaches have suggested increases in IL-1β in certain asthmatics, in conjunction with neutrophilia [96–98]. Although a trial using anti-TNF-α antibody in severe asthma provided disappointing results, there were suggestions that certain phenotypes associated with late-onset reversible disease may respond better [99].

Finally, there is increasing interest in factors which contribute to resolution of inflammation. Thus, in severe asthma, it is conceivable that some of the pathobiology is related to a lack of resolution. In this regard, severe asthma has been associated with lower levels of lipoxins, with their potential anti-inflammatory qualities, than in patients with milder asthma [100–102].

Structural abnormalities

Resident airway cells such as epithelial, fibroblast and smooth muscle cells are increasingly recognised as modulators of inflammation and remodelling. Structural alterations can affect airway mechanics, while structural cells can also contribute to inflammatory processes through release of cytokines, chemokines, growth factors and extracellular matrix elements [103]. First, the epithelium in severe asthma is reported to be thicker than in mild-to-moderate asthma [104], with altered proliferation, apoptosis and release of pro-inflammatory factors [105]. Second, autopsy and biopsy studies have linked an increased amount of airway smooth muscle to asthma severity, airflow obstruction and bronchial hyperresponsiveness [71, 106–109]. Finally, fibrocytes, which can differentiate into myofibroblasts, are increased in blood and in smooth muscle bundles in asthmatics with fixed airways obstruction and/or severe asthma [110, 111].

Subepithelial thickening of the bronchial reticular layer is an early feature of severe asthma in children, and appears to be a characteristic of the eosinophilic phenotype [18, 112, 113]. Patients with severe asthma also have increased expression of transforming growth factor-β isoforms and collagen deposition as compared to

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mild asthmatics, again in association with eosinophilic asthma, with evidence for remodelling in the peripheral airways as well [18, 114]. Indeed, increased production and altered composition of extracellular matrix in the small airways is characteristic of fatal asthma [114].

High resolution computed tomographic (HRCT) studies of airway structure are providing quantitative morphometry of the airways and distal lung in adults with severe asthma, but less is known in children [115–118]. In adults, there are relationships to lung function and more severe exacerbation-prone disease. These structural changes lead to ventilatory defects that can be visualised by magnetic resonance imaging with hyperpolarised helium [119]. Initial studies suggest that neutrophilic inflammation may be linked to air trapping, while biopsy-measured epithelial thickness predicts airway wall thickness measured from HRCT scans [116, 117].

Physiology

Chronic airflow limitation which is less responsive to bronchodilators and to inhaled or oral corticosteroid therapy is observed in some severe asthma phenotypes [15, 16, 120]. Chronic airway obstruction may result in airway closure or uneven ventilation of small airways, which associates with severe exacerbations [121]. Severe asthmatics were found to exhibit air trapping (reduced FVC in relation to FEV_1/FVC) when compared with non-severe asthmatics at matched levels of airflow limitation measured by FEV_1/FVC ratio [122]. Bronchodilator use in patients with low baseline FEV_1 resulted in a marked increase in FVC, supporting a role for airway smooth muscle in the air-trapping component of airflow obstruction. Finally, severe airway obstruction is a characteristic in some phenotypes of severe asthma, with studies suggesting that eosinophilic and/or neutrophilic inflammation may contribute to greater airflow limitation [116, 123, 124]. One of the SARP clusters was characterised by severe airway obstruction, with continued β-agonist reversibility, but without reversibility into the normal range, and in association with sputum neutrophilia [15]. Day-to-day variations in lung function are also less variable in severe asthmatics [125]. Such reduced dynamic behaviour of the airways suggests that an uncontrolled clinical status in severe asthma may imply more fixed and severe obstruction than rapid changes in airway patency.

Prospective studies of lung function decline in severe asthma are limited, but suggest that male sex, smoking, increased F_{ENO} and African ancestry are contributors, while interestingly, allergic status may be protective [93, 126].

Aside from airway calibre, lung elastic recoil is also a determinant of maximal airflow, as well as a force that prevents airway closure. Patients with severe asthma and persistent airflow limitation after bronchodilation can have reduced lung elastic recoil accounting for a portion of their residual airflow limitation [127]. Whether this is related to the reported loss of alveolar attachments in asthma deaths remains to be confirmed [128].

Studies of bronchial hyperresponsiveness in terms of its sensitivity and maximal responses have not yet proven to be helpful in severe asthma, partly due to difficulties in measuring it in the face of low lung function. However, related information may be gained from the fluctuation patterns of lung function over days [125, 129]. Using new methods derived from physics, fluctuation analysis of lung function measured twice daily over weeks can provide markers for the patient's individual risk of future exacerbations. The impact of these fluctuations in patients with severe asthma is less clear, although the differences in fluctuations compared with mild-to-moderate asthma suggest these fluctuation patterns may also be a phenotypic characteristic [130].

Conclusion

The evolution of phenotyping of severe asthma over the past decade has been substantial. Given the potential of genetic, molecular, cellular, structural and physiological biomarkers in severe asthma, and their integration using systems medicine approaches, currently available clinical phenotypes will likely improve substantially. Progress in this field will not only allow better diagnosis and targeted treatment, but also provide focus to the research questions that need to be addressed, as prioritised in table 5.

3. Evaluation

This section focuses on the evaluation of adults and children with difficult-to-control asthma. It will address: 1) the evaluation required to determine that the patient with "difficult asthma" has asthma, 2) the appropriate assessment of confounding factors and comorbidities and 3) the initial determination of phenotypes which may be useful in optimising therapy.

Step 1: Determining that the patient has asthma

Clinicians should maintain a degree of scepticism regarding the diagnosis and establish whether the patient's history and evaluation truly represent asthma. Misdiagnosis of non-asthmatic conditions as

TABLE 5 Priority questions on phenotypes

1) The validation of the eosinophilic *versus* non-eosinophilic, and of the Th2 predominant *versus* non-Th2 asthma phenotype, are they persistent over time and do they predict distinct natural histories?
2) Are risk factors, comorbid factors and natural history also governed by specific immune-inflammatory phenotypes?
3) Are there genetic, epigenetic and inflammatory biomarkers of specific phenotypes or characteristics of severe asthma?
4) Is the innate immune response abnormal in severe asthma, and do these contribute to inflammation and remodelling of the airways?
5) What is the relationship between structural determinants, inflammation and airway function in severe asthma, and can imaging be used to noninvasively address these issues?
6) Is there an altered microbiome and virobiome in the airways of severe asthma?

Th: T-helper cell.

uncontrolled asthma has been reported to be as high as 12–30% [131, 132]. The evaluation should start with a careful history with emphasis on asthma symptoms including dyspnoea (and relation to exercise), cough, wheezing, chest tightness and nocturnal awakenings. In addition, information should be obtained on exacerbating triggers, and environmental or occupational factors that may be contributing. Respiratory symptoms related to obesity have also been mistaken for asthma, especially when the patient is seen in an urgent care setting [133]. Children and adults should be evaluated for other conditions that may mimic or be associated with asthma (table 6). As confirmation of reversible airflow limitation is part of the diagnosis of asthma, spirometry with both inspiratory and expiratory loops, assessed following pre- and post-bronchodilator administration should be obtained [134]. Appropriate withholding of medication is required to best assess reversibility. Further testing with complete pulmonary function tests, including diffusing capacity, and bronchoprovocation testing, such as methacholine or exercise challenges, in the case of relatively preserved lung function can be considered on a case-by-case basis, particularly when there are

TABLE 6 Diseases which can masquerade as severe asthma

Children
- Dysfunctional breathing/vocal cord dysfunction
- Bronchiolitis
- Recurrent (micro)aspiration, reflux, swallowing dysfunction
- Prematurity and related lung disease
- Cystic fibrosis
- Congenital or acquired immune deficiency
- Primary ciliary dyskinesia
- Central airways obstruction/compression
- Foreign body
- Congenital malformations including vascular ring
- Tracheobronchomalacia
- Carcinoid or other tumour
- Mediastinal mass/enlarged lymph node
- Congenital heart disease
- Interstitial lung disease
- Connective tissue disease

Adults
- Dysfunctional breathlessness/vocal cord dysfunction
- Chronic obstructive pulmonary disease
- Hyperventilation with panic attacks
- Bronchiolitis obliterans
- Congestive heart failure
- Adverse drug reaction (*e.g.* angiotensin-converting enzyme inhibitors)
- Bronchiectasis/cystic fibrosis
- Hypersensitivity pneumonitis
- Hypereosinophilic syndromes
- Pulmonary embolus
- Herpetic tracheobronchitis
- Endobronchial lesion/foreign body (*e.g.* amyloid, carcinoid, tracheal stricture)
- Allergic bronchopulmonary aspergillosis
- Acquired tracheobronchomalacia
- Churg–Strauss syndrome

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inconsistencies between history, physical features and spirometry. This should heighten suspicion of an alternative diagnosis (online supplementary material 3, table S1).

It is important to confirm whether children with suspected asthma have variable airflow obstruction, but this is difficult in practice. Children with severe asthma often have normal lung function and no acute response to bronchodilators [135]. Children with a normal FEV_1 both before and after a short-acting β-agonist may show a bronchodilator response in terms of forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) [136]. However, the utility of $FEF_{25–75\%}$ in the assessment or treatment of severe asthma is currently unknown. Bronchial provocation testing with exercise or methacholine bronchial challenge may be indicated in difficult cases.

Referral to a specialised centre where patients can undergo a systematic evaluation, resulted in 30–50% of patients previously called severe, being classed as difficult-to-control [131, 137, 138]. Many children with asthma will also be found not to have severe, treatment-refractory asthma after a thorough evaluation [139] and approximately 50% of children referred for severe asthma have persistent symptoms and poor control because of inadequate disease management [138].

Question 1

Should chest HRCT scans be routinely ordered in patients with symptoms of severe asthma without known specific indications for performing this test (based on history, symptoms and/or results of other investigations)?

Recommendation 1

In children and adults with severe asthma without specific indications for chest HRCT based on history, symptoms and/or results of prior investigations we suggest that a chest HRCT only be done when the presentation is atypical (conditional recommendation, very low quality evidence).

Values and preferences

This recommendation places a relatively high value on identification of alternative diagnosis and comorbidities and a relatively low value on avoiding potential complications and cost of chest HRCT.

Remarks

An atypical presentation of severe asthma includes such factors as, for example, 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.

Step 2: assessing comorbidities and contributory factors

Difficult-to-control and severe asthma are often associated with coexisting conditions (table 7 and supplementary material 3, table S2). Non-adherence to treatment should be considered in all difficult-to-control patients, as reports show that non-adherence can be as high as 32–56% [131, 137, 140]. Poor inhaler technique is also common and should be addressed [138]. Detecting poor adherence can be challenging. Measuring serum prednisolone, theophylline, systemic corticosteroid (CS) side effects and suppression of serum cortisol levels can be used to evaluate adherence to oral medications, but methods for measuring inhaled CS compliance, such as canister weight, pressure-actuated or electronic counters, are not widely available in clinical practice. Confirmation that patients have picked up prescriptions from pharmacies can also provide insight [140]. If non-adherence is present, clinicians should empower patients to make informed choices about their medicines and develop individualised interventions to manage non-adherence [140]. Cost alone can have substantial impact on adherence.

TABLE 7 Comorbidities and contributory factors

1) Rhinosinusitis/(adults) nasal polyps
2) Psychological factors: personality trait, symptom perception, anxiety, depression
3) Vocal cord dysfunction
4) Obesity
5) Smoking/smoking related disease
6) Obstructive sleep apnoea
7) Hyperventilation syndrome
8) Hormonal influences: premenstrual, menarche, menopause, thyroid disorders
9) Gastro-oesophageal reflux disease (symptomatic)
10) Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β-adrenergic blockers, angiotensin-converting enzyme inhibitors

Problematic childhood asthma with poor or non-adherence to treatment presents specific issues. Adolescents are at risk because of reduced adherence to treatment and risk taking behaviours (smoking, illicit drug use) are common, leading to a higher risk of fatal episodes of childhood asthma. Poor adherence may also occur because of complicated treatment regimens, family instability, poor supervision of the child, and potentially secondary gains associated with poorly controlled asthma. Assessment in paediatric asthma should include review of rescue inhaler and prescribed controller medications during nurse-led home visits [138]. Providers may need to consider administration of medications in the supervised setting, such as at school.

Atopy and allergy have long been associated with asthma and, to some degree, with severe asthma. However, most large epidemiological studies are reporting that severe asthma is less associated with atopy/allergy than milder asthma, with a lower proportion of patients with positive skin testing [120, 141]. The association between allergy and asthma severity is stronger in children [135, 142]. In all patients, determining whether there is an association between specific IgE (as measured by skin prick testing or serum testing), on-going exposures and symptoms may help identify factors which contribute to asthma symptoms and exacerbations [143].

Evidence for rhinosinusitis has been reported to be as high at 75–80% [141, 144]. Nasal polyps are seen in a small subset of adults. Nasal polyps are unusual in asthmatic children and more often associated with cystic fibrosis and sometimes primary ciliary dyskinesia.

Gastro-oesophageal reflux (GOR) is present in 60–80% [15, 23, 120, 141, 144], but clinical trials with anti-reflux therapy generally show little to no effect on asthma control [145–147]. The role of ''silent'' GOR disease (GORD) as a cause of poor asthma control in general may be over-emphasised, but the child with gastrointestinal symptoms and problematic asthma should be evaluated and treated for GORD [147]. Although the impact of treatment of sinusitis and GORD on severe asthma is not yet clear, when these comorbidities are present, they should be treated as appropriate to improve these conditions. Both GORD and rhinosinusitis can worsen vocal cord dysfunction. In addition, symptoms arising from GORD and rhinosinusitis may masquerade as asthma.

Obesity is also a common comorbidity associated with difficult asthma, although the relationship to asthma may vary by age at onset, with implications for treatment [27, 28].

Concurrent smoking can also contribute to making asthma more difficult-to-control. Smoking appears to alter the inflammatory process which may contribute to their reported lower responses to corticosteroid therapy [29, 32]. Environmental tobacco smoke exposure is also associated with adverse asthma outcomes in children and adults [30]. Measurement of urine or salivary cotinine can often reveal evidence of passive smoke exposure [138].

Early-life exposures and sensitisation to various allergens, especially to moulds, occur in children with severe asthma [135]. Evidence supporting a therapeutic response to environmental control in severe asthma is inconsistent and inadequately studied, but a decrease in environmental ozone levels following reduction in traffic congestion was associated with improvement in asthma outcomes in an urban environment [148]. Further work on environmental exposures as a contributory factor to severe asthma is needed.

Anxiety and depression are frequently found in adults with severe asthma ranging from 25% to 49% [149]. These are also common in both children and their parents, and maternal depression and poor coping skills may be associated with reduced asthma-related quality of life [150]. Often these conditions are under-diagnosed, so appropriate psychiatric evaluation and referral to a specialist is recommended [151]. Some assessment of family psychosocial stress using standardised questionnaires or direct interviews can be helpful. Unfortunately, the benefit of psychiatric treatment on asthma outcomes has not been well-established [151] and a recent Cochrane meta-analysis evaluating psychological interventions involving various relaxation and behavioural techniques both in adults and children was not able to find firm benefit of these interventions on asthma outcomes [152].

In addition to comorbidities associated with asthma, in patients with longstanding severe or difficult-to-control asthma, assessment should be made of therapy-induced comorbidities, especially as they relate to high dose inhaled and systemic corticosteroid use (online supplementary material 3, table S3).

Step 3: approaches to asthma phenotyping

Asthma, and severe asthma in particular, are increasingly recognised as heterogeneous processes, not all of which may respond similarly to current therapies or have the same clinical course (see the section on phenotyping). Currently, there are no widely accepted definitions of specific asthma phenotypes. However, identifying certain characteristics of certain phenotypes may eventually promote targeted and/or more

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effective therapies as well as help to predict different natural histories which may be of benefit to some patients [14, 15]. In that regard, eosinophilic inflammation, allergic/Th2 processes and obesity have been identified as characteristics or phenotypes which may be helpful when considering nonspecific (corticosteroid) and specific (targeted) therapy (*e.g.* anti-IgE, anti-IL5 and anti-IL13 antibody treatments) [14, 28, 44, 58, 59, 153–156].

While no specific phenotypes have been broadly agreed upon, clinical, genetic and statistical approaches have identified an early-onset allergic phenotype, a later onset obese (primarily female) phenotype and a later onset eosinophilic phenotype, with different natural histories [14, 15, 17, 22, 27]. The age of asthma onset, *i.e.* beginning in either childhood or adulthood has been linked to differences in allergy, lung eosinophils and sinus disease. Determining either the level of 1) eosinophilic inflammation or 2) Th2 inflammation (or their absence) has the potential benefit of evaluating level of compliance/adherence, risk for exacerbations, as well as predicting response to corticosteroid therapy, and perhaps to targeted therapies such as anti-IL-5 or anti-IL-13, as well [18, 33, 58, 59, 153–155]. The role of sputum neutrophilic inflammation in guiding therapy is generally less studied, with considerable day-to-day variability in patients with severe asthma [51]. It has been associated with reduced response to corticosteroid therapy [153]. While these measurements are available at many specialised centres, further research into their utility as well as standardisation of methodology are required before these approaches can be made widely available.

Similarly, an adult-onset obese asthma phenotype may respond better to weight loss strategies than an obese, early-onset allergic asthma patient [28]. These characteristics may be addressed by asking questions about age at onset (albeit acknowledging the problems of retrospective recall), evaluating body mass index, measuring lung eosinophils (usually in induced sputum) and assessing levels of atopy, with or without purported biomarkers for Th2 inflammation. These Th2 markers include *F*eNO, which is widely available and serum periostin (currently available only for research and not applicable to children) and even blood eosinophils (see online supplementary material 3, table S4 and the therapy section for further details) [59, 157]. In children, tests for peripheral eosinophilia with a full blood count or specific (skin or blood testing) and total IgE measurements can be helpful but of limited specificity. *F*eNO may not be elevated in all children with chronic asthma, but a low level suggests other conditions, such as cystic fibrosis and ciliary dysmotility.

Biomarkers of atopy including elevated *F*eNO and serum IgE differentiate severe asthma in children but not adults with severe asthma, and support a prevalent Th2-driven pattern of airway inflammation [135]. However, a bronchoscopic study did not support a defining role for Th2 cytokines in children with severe asthma [61]. Furthermore, the clinical expression of severe asthma in children is highly variable and distinct severe asthma phenotypes are less well-defined in children than they are in adults [16]. Although various inflammatory phenotypes are suggested by sputum analysis in adults, this approach has been less informative in children in which a stable predominant sputum inflammatory phenotype has not yet been identified [158].

Other than blood eosinophils, biomarker measurements require either specialised equipment, training or assays that are not yet readily available, and the utility of any of these biomarkers in identifying clinically meaningful and therapeutically different asthma phenotypes needs to be confirmed (see the therapy section on clinical recommendations).

4. Therapy

This section discusses the management of severe asthma, as defined in this document, with: 1) established therapies, 2) recently developed therapies and 3) future approaches that will require phenotypic characterisation. Despite their widespread use and endorsement, the efficacy of some traditional controller medications, including LABAs, leukotriene modifiers and theophylline, has not been well documented in severe asthma. In fact, the nature of the definition of severe asthma itself with the requirement for treatment with a mixed combination of these medications to maintain control or to achieve control implies that these treatments may have lower efficacy in this population, provided that adherence to therapy has been ascertained. Until recently, few clinical trials were specifically designed to investigate treatments in patients with severe asthma, although this is now rapidly changing. Trials of novel molecular targeted therapies are now being evaluated mainly in the adult severe asthma population, with some evidence of efficacy and short-term safety data (table 8).

Using established asthma medications

Corticosteroid insensitivity

As defined in this document, severe asthma involves corticosteroid insensitivity, with persistent lack of control despite corticosteroid therapy or worsening of asthma control on reduction or discontinuation

TABLE 8 Placebo-controlled studies of potential new treatments in severe asthma

First author [ref.]	Severity	Subjects n	Design	Treatment	Outcomes	Summary results
Wenzel [99]	Severe	309	R, db, pc, p	Golimumab, anti TNF-α, 24 weeks	FEV_1, exacerbations AQLQ, PEFR	FEV_1 unchanged, no reduction in exacerbations, AQLQ, PEFR Adverse profile side-effects
Pavord [56]	Severe, with ⩾2 exacerbations in past year	621	R, db, pc, p	Mepolizumab (75, 250 or 750 mg infusions at 4 weeks), anti-IL-5, 52 weeks	Rate of exacerbations	All doses reduced exacerbations by 39–52% No effect on ACQ, AQLQ or FEV_1
Haldar [157]	Severe	61	R, db, pc, p	Mepolizumab, anti-IL5, 50 weeks	Exacerbations, symptoms, FEV_1, AQLQ, AHR, sputum and blood eosinophils	Reduced exacerbations Improved AQLQ Reduced eosinophils
Nair [58]	Severe	20	R, db, pc, p	Mepolizumab, anti-IL5, 50 weeks	Exacerbations, oral steroid reduction	Reduced exacerbations, eosinophils and OCS dose
Kips [159]	Severe	26	R, db, pc, p	SCH55700, anti-IL-5, 12 weeks	Sputum and blood eosinophils, symptoms, FEV_1	Reduced blood sputum eosinophils No other significant outcomes
Castro [57]	Poorly controlled on high-dose inhaled CS	53	R, db, pc, p	Reslimuzab, anti-IL-5, 12 weeks	ACQ, FEV_1, Sputum eosinophils	Improved ACQ score Reduction in sputum eosinophils Improved FEV_1
Corren [160]	Moderate-severe	294	R, db, pc, p	AMG317, anti-IL-4Rα antibody, blocks IL-4 and IL-13, 12 weeks	ACQ scores, exacerbations	No effect on ACQ or exacerbations
Corren [59]	Moderate-severe	219	R, db, pc, p	Lebrikizumab, anti-IL13 antibody, 24 weeks	Change in pre-bronchodilator FEV_1	Improved FEV_1, compared with placebo, with greatest changes in high levels of periostin or F_{ENO} group (*post hoc* analyses) No effect on ACQ-5 or diary measures Exacerbations were 60% lower in treated group with high Th2
Piper [60]	Moderate-to-severe	194	R, db, pc, p	Tralokinumab (150, 300, or 600 mg), IL-13 neutralising monoclonal antibody, 3 months	Change from baseline in ACQ-6 at week 13	No change in ACQ-6 at 13 weeks FEV_1 increase of 0.21 L *versus* 0.06 L with placebo (p=0.072) β_2-agonist use decrease of -0.68 *versus* -0.10 with placebo (p=0.020) Better response in those with higher IL-13 levels in sputum
Humbert [161]	Severe, CS-dependent	44	R, db, pc, p	Masitinib (3, 4.5 and 6 $mg \cdot kg^{-1} \cdot day^{-1}$), c-kit and PDGFR tyrosine kinase inhibitor, 16 weeks	OCS dose ACQ, FEV_1	No difference in OCS dose ACQ improved, no difference in FEV_1
Busse [162]	Moderate-to-severe		R, db, pc, p	Daclizumab, IL-2Rα chain antibody, 20 weeks	Change in FEV_1 (%) Asthma exacerbations	Improved FEV_1 Reduction in day-time asthma scores, use of SABA Prolonged time to severe exacerbations Reduction in blood eosinophils
Nair [163]	Severe asthma	34	R, db, pc, p	SCH527123, CXCR2 receptor antagonist, 4 weeks	Changes in sputum and neutrophil activation markers	Reduction in blood and sputum neutrophil Reduction in mild exacerbations No reduction in ACQ score (p=0.053)

R: Randomised; db: double-blind; pc: placebo-controlled; p: parallel; TNF-α: tumour necrosis factor-α; FEV_1: forced expiratory volume in 1 s; AQLQ: Asthma Quality of Life Questionnaire; PEFR: peak expiratory flow rate; IL: interleukin; ACQ: Asthma Control Questionnaire; AHR: airway hyperresponsiveness; OCS: oral corticosteroids; CS: corticosteroids; F_{ENO}: exhaled nitric oxide fraction; Th2: T-helper cell type 2; c-kit: stem cell factor receptor; PDGFR: platelet-derived growth factor receptor; IL-2Rα: IL-2 receptor-α; SABA: short-acting β-agonist.

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of corticosteroid therapy. Thus, although corticosteroids are the mainstay of treatment for milder forms of asthma, alternative molecular-targeted therapies may be needed in severe asthma to modulate inflammation and improve corticosteroid insensitivity. Severe asthmatics are often referred to as corticosteroid-dependent, refractory or corticosteroid-insensitive asthmatics. In 30% of severe adult asthma patients, oral corticosteroids (OCS) are required in addition to ICS to maintain some degree of asthma control [23, 120, 124, 141]. Intramuscular injections of triamcinolone as a maximal dose of corticosteroid therapy can improve asthma control, reduce sputum eosinophils and increase FEV_1 [164, 165], supporting the presence of relative insensitivity to this treatment, rather than a complete resistance. In a study of childhood difficult asthma, only 11% of 102 patients were shown to be ''completely'' corticosteroid unresponsive to a single intramuscular injection of triamcinolone, indicating that 89% of the patients had some degree of corticosteroid responsiveness [142]. Thus, the term corticosteroid insensitivity is more appropriate than corticosteroid resistance.

Corticosteroid insensitivity is variable and likely has several underlying mechanisms. It can be demonstrated in peripheral blood mononuclear cells and alveolar macrophages, and in resident cells such as airway smooth muscle cells from patients with severe asthma [166–169], but the relationship of these *in vitro* studies to *in vivo* responses is not well understood. Corticosteroid insensitivity has been associated with different comorbid conditions such as obesity [170], smoking [171], low vitamin D levels [172, 173], and non-eosinophilic (low-Th2 inflammation) mainly in adults [174]. In children, less is known about the role of these mechanisms.

While the eosinophilic or ''Th2 high'' asthma phenotype, characterised by high expression of Th2 cytokines, IL-5 and IL-13, identifies ICS responsiveness in patients with milder asthma, eosinophilic inflammation may persist in some severe asthma patients despite high dose ICS, and even systemic corticosteroids [18, 61, 141, 155, 175, 176]. Similar to adults with severe asthma, an eosinophilic-dominated profile has been observed in children, but not in relation to measurable levels of Th2 cytokines in bronchoalveolar lavage fluid or biopsies [61]. In adults, a non-eosinophilic phenotype appears to form a large subgroup of asthma [18, 175, 176], with data from a mild-to-moderate cohort [176] showing relatively poor corticosteroid sensitivity. Understanding the mechanisms underlying these different types of corticosteroid insensitivity could lead to novel treatments such as p38 mitogen-activated protein kinase inhibitors and histone deacetylase-2 recruiters [177, 178].

In the 1990s, several agents with immunosuppressive properties, such as methotrexate, cyclosporin A, gold salts and *i.v.* IgG, were studied as corticosteroid-sparing agents with the aim of reducing the dose of maintenance OCS. Although these agents may be considered to improve corticosteroid insensitivity, their efficacy is uncertain, and they are associated with significant side-effects (see GRADE question below) [179–183].

Inhaled and oral corticosteroid therapy

The high-dose range for the individual ICSs are shown in table 4. These are higher than the usual doses required to achieve maximal therapeutic effects in milder asthma. In moderate asthma, there is little response to increasing ICS doses above moderate levels [184]. However, there is individual variation in the dose-therapeutic efficacy of ICS and some evidence that higher ICS doses may be more efficacious in severe asthma (including a systemic corticosteroid-sparing effect) [184, 185]. Although even higher doses of ICS (above 2000 $\mu g \cdot day^{-1}$ of beclomethasone equivalent dose) and ultra-fine particle ICS are often tried in severe asthma, there are very few data to support this approach.

Exacerbations of asthma in mild-to-moderate asthma are reported to be effectively treated with high doses of ICS usually by quadrupling the maintenance dose (2400–4000 μg of beclomethasone equivalent). However, this is often not practical in severe asthma since these patients are already maintained on high doses of ICS [186, 187]. Therefore, when standard medications are inadequate, OCSs are often added as maintenance therapy in severe asthma.

Approximately one-third of the current SARP cohort were on regular OCS, with over half needing more than three bursts of OCSs in the previous year [21, 120, 124, 141]. The optimal timing for initiation of OCS therapy has also not been defined. Similarly, it is not yet clear whether continuous low-dose OCS are better than multiple discontinuous bursts for controlling exacerbations. While guidelines for the use of biomarkers to guide corticosteroid use have been proposed, the use of sputum eosinophils and/or exhaled nitric oxide levels for guiding therapy in severe asthma remains controversial [74] (see GRADE question below).

Intramuscular treatment with triamcinolone has been used in severe asthma with reported improvement in eosinophilic inflammation and airflow obstruction, and prevention of exacerbations [164, 165]. The reasons for its efficacy may include enforced adherence or the greater potency of triamcinolone compared with other corticosteroids in clinical use.

Systemic corticosteroid use has been associated with an increased risk of fracture and cataracts [188, 189], while high doses of ICS are associated with an increased risk of adrenal suppression and growth retardation in children [188, 190–192]. Systemic corticosteroid-related weight gain may further impact negatively on asthma control [193]. In prepubertal children, the initial use of 400 μg of budesonide daily led to a small decrease in initial height (mean: -1.3 cm), that was accompanied by a persistent reduction in adult height, although the decrease was neither progressive nor cumulative [194]. Therefore, use of continuous systemic corticosteroids, and perhaps to a lesser degree high dose ICS, should be accompanied by prudent monitoring of weight, blood pressure, blood glucose, eyes and bone density and, in children, appropriate growth. Prophylactic measures to prevent loss of bone density should be taken as per guidelines [195].

ICS are associated with an increased risk of adrenal suppression in children. The dose threshold shows individual variation, and it is not known whether the severity of the underlying asthma impacts on systemic absorption of fluticasone, as it does in adults [196]. Every effort should be made to minimise systemic absorption, for example using large volume spacers for ICS. There are no evidence based guidelines on monitoring adrenal function in children with severe asthma, but since by definition they will be prescribed high dose ICS, an annual test of adrenal function, such as a cortisol stimulation test, and even an evaluation by a paediatric endocrinologist may be helpful. Such children might benefit from carrying a steroid-warning card, and may need systemic corticosteroids at times of stress, for example during intercurrent surgery.

Short- and long-acting β-adrenergic bronchodilators

Many adult and paediatric patients with severe asthma have persistent chronic airflow obstruction despite treatment with ICS and short- and/or long-acting bronchodilators [23, 124]. Step-wise increases in the dose of ICS, in combination with a LABA, improve the prospect of control compared with the use of ICS alone, including in some patients with severe asthma. Moreover, some patients who do not achieve optimal control of symptoms show improvement in some features of clinical control reaching a more satisfactory or tolerable state, even though their composite control scores (such as the ACQ-7 or ACT) remain at an uncontrolled level [185, 197]. In poorly controlled paediatric asthma on low-dose ICS, addition of LABAs were the most effective add-on therapy to ICS compared with doubling the dose of ICS or to the addition of montelukast, but there was marked variability in the treatment response highlighting the need to regularly monitor and appropriately adjust each child's asthma therapy [198]. No such study has yet been reported in severe paediatric asthma.

In asthmatics with severe exacerbations of rapid onset (often labelled as ''brittle'' asthma), subcutaneous administration of the β-agonist terbutaline has been used but its benefit over repeated or continuous inhaled (nebulised or aerosol-administered) β-agonist has not been confirmed [199].

Increased use of β-agonists may paradoxically lead to worsening asthma control as has been described in mild-to-moderate asthma patients treated with short-acting β-agonists (SABAs) or LABAs without ICS [200–203]. Patients with severe asthma may also be receiving LABAs together with as-needed SABAs. A strong association between the use of inhaled β-agonists and asthma mortality was reported to be confined mainly to the use of β-agonists in excess of the recommended limits [204].

Racial differences in the response to β-agonists have also been reported. Thus, individuals of African racial background appear to have less short-acting bronchodilator responsiveness to SABA, even after ICS therapy, compared with Mexican-Americans and Puerto-Ricans [205]. African-Americans suffering from asthma were reported to have more treatment failures compared with white Americans, particularly when taking LABAs [206]. There are currently on-going studies looking at the influence of race and β-adrenoceptor genotype on treatment responsiveness to β-adrenoreceptors.

Whether the excessive use of β-agonists contributes to worsening control of asthma is uncertain but these patients may be at increased risk of β-agonist toxicity. In clinical practice, doses and treatment duration in both adult and paediatric severe asthma frequently exceed those recommended by expert guidelines, making it difficult to decide on a ''safe'' upper dose limit. Case reports suggest ''improvement in asthma control'' upon medically supervised reduction of β-agonists in some severe adult asthma patients taking excessive β-agonists [207]. The generic safety concerns with LABAs apply to children as well as adults, and one should be cautious in increasing above the recommended doses. There are no concerns specific to children with regards to the use of β-agonists. In children with asthma, of any degree of severity, there is no evidence that weaning down the dose of LABAs improves asthma control.

The use of ipratropium bromide aerosols for relief of symptoms is commonly used in severe asthma patients in an attempt to reduce their daily use or overuse of β-agonists, particularly in those demonstrating intolerant side-effects of β-agonists such as tremor and palpitations, as well as in the treatment of asthma exacerbations [208, 209]. Although considered to be less effective, they are well tolerated and may be used

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alternately with β-agonists for as-needed use throughout the day. The routine use of nebulisers is discouraged owing to their relative inefficiency in drug delivery and because their use has been associated with deaths in severe asthma, thought to result from reliance on their use and delays in seeking help during evolving exacerbations [210]. The use of a pressurised metered dose inhaler with a spacer has been shown to be as effective as a nebuliser in both adults and children with worsening asthma or with an exacerbation [211].

Slow-release theophylline

In patients with moderate asthma, theophylline improved asthma control when added to ICS [212]. In an exploratory study of smoking asthmatics with corticosteroid insensitivity, theophylline with low dose ICS improved peak expiratory flow rates and asthma control [213], raising the possibility that theophylline could improve corticosteroid insensitivity in some people. However, no such studies have been performed in children or adults with severe asthma [214]. Given the safety profile of low dose theophylline, it has been used in children with severe asthma before other treatments.

Leukotriene pathway modifiers

Montelukast is not as effective as LABAs when added to ICS therapy in preventing exacerbations requiring systemic corticosteroids or improving symptoms in moderate asthma [4, 198]. Addition of a leukotriene receptor antagonist or synthesis inhibitor has shown some efficacy on lung function when added to ICS in three studies of adults with moderate-to-severe asthma who were not taking LABAs. Two of these studies were performed in aspirin-sensitive asthma in which systemic corticosteroids were used in 35% [215–217]. In contrast, in a study of 72 non-phenotyped severe adult asthmatics receiving LABA and ICS, some of whom are also on OCS, the addition of montelukast did not improve clinical outcomes over 14 days [218]. Whether individuals with the phenotype of aspirin-sensitive asthma respond better than those without aspirin-sensitive asthma has not been formally addressed. There have been no specific studies of these agents in children with severe asthma.

Long-acting muscarinic antagonists

Tiotropium bromide improved lung function and symptoms in moderate-to-severe asthma patients not controlled on moderate- to high-dose ICSs with or without LABAs [219, 220]. In patients taking high doses of ICSs and LABAs, the addition of tiotropium bromide provided improvements in FEV_1, reduced as-needed use of SABAs and modestly reduced the risk of a severe exacerbation [219, 221]. There have been no studies of tiotropium in children with asthma.

Specific approaches directed towards severe asthma

The committee identified several clinical questions that are important to practicing clinicians in the management of patients with severe asthma. These questions are listed in the online supplementary material. For this initial document the committee chose to evaluate two questions concerning the phenotypic management of severe asthma and five questions relating to therapeutic approaches in adults and children. The first two management approaches evaluated were the utility use of biomarkers to guide treatment, namely sputum eosinophilia and/or F_{ENO}. The therapeutic options evaluated were the use of anti-IgE therapy, methotrexate as a steroid-sparing agent, the use of macrolide therapy, the role of antifungal treatments, and the newer treatment of bronchial thermoplasty.

Currently available biomarkers to guide therapy

Question 2

Should treatment guided by sputum eosinophil count, rather than treatment guided by clinical criteria alone, be used in patients with severe asthma?

Recommendation 2

In adults with severe asthma, we suggest treatment guided by clinical criteria and sputum eosinophil counts performed in centres experienced in using this technique rather than by clinical criteria alone (conditional recommendation, very low quality evidence).

In children with severe asthma, we suggest treatment guided by clinical criteria alone rather than by clinical criteria and sputum eosinophil counts (conditional recommendation, very low quality evidence).

Values and preferences

The recommendation to use sputum eosinophil counts to guide therapy in adults 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 recommendation not to use sputum eosinophil counts to guide therapy in children places higher value on avoiding an intervention that is not standardised and not widely available and lower value on the uncertain and possibly limited clinical benefit.

Remarks

Because at the present time, measurement of sputum eosinophils has not yet been sufficiently standardised and is not widely available we suggest such an approach be used only in specialised centres experienced in this technique. Patients who are likely to benefit from this approach are those who can produce sputum, demonstrate persistent or at least intermittent eosinophilia and have severe asthma with frequent exacerbations. Clinicians should recognise that different choices will be appropriate for different patients.

Question 3

Should treatment guided by *F*eNO in addition to clinical criteria, rather than treatment guided by clinical criteria alone, be used in patients with severe asthma?

Recommendation 3

We suggest that clinicians do not use *F*eNO to guide therapy in adults or children with severe asthma (conditional recommendation, very low quality evidence).

Values and preferences

This recommendation places a higher value on avoiding additional resource expenditure and a lower value on uncertain benefit from monitoring *F*eNO.

Therapeutic approaches

Question 4

Should a monoclonal anti-IgE antibody be used in patients with severe allergic asthma?

Recommendation 4

In patients with severe allergic asthma we suggest a therapeutic trial of omalizumab both in adults (conditional recommendation, low quality evidence) and in children (conditional recommendation, very low quality evidence).

Values and preferences

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.

Remarks

Adults and children (aged $\geqslant$6 years) 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^{-1} (in three studies the range was wider at 30–1300 IU·mL^{-1}). Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilisation, 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.

Question 5

Should methotrexate be used in the treatment of severe asthma?

Recommendation 5

We suggest that clinicians do not use methotrexate in adults or children with severe asthma (conditional recommendation, low quality evidence).

Values and preferences

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.

Remarks

Evidence from randomised 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

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specialised 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 D_{LCO}, are recommended prior to and after commencing therapy.

Question 6

Should macrolide antibiotics be used in patients with severe asthma?

Recommendation 6

We suggest that clinicians do not use macrolide antibiotics in adults and children with severe asthma for the treatment of asthma (conditional recommendation, very low quality evidence).

Values and preferences

This recommendation places a relatively higher value on prevention of development of resistance to macrolide antibiotics, and relatively lower value on uncertain clinical benefits.

Remarks

This recommendation applies only to the treatment of asthma; it does not apply to the use of macrolide antibiotics for other indications, *e.g.* treatment of bronchitis, sinusitis or other bacterial infections as indicated.

Question 7

Should antifungal agents be used in patients with severe asthma?

Recommendation 7

We suggest antifungal agents in adults with severe asthma and recurrent exacerbations of allergic bronchopulmonary aspergillosis (ABPA) (conditional recommendation, very low quality evidence).

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 sensitisation to fungi (*i.e.* positive skin prick test or fungus-specific IgE in serum) (conditional recommendation, very low quality evidence).

Values and preferences

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.

The recommendation not to use antifungal agents in patients with severe asthma without confirmed ABPA (irrespective of sensitisation) 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.

Remarks

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, *e.g.* treatment of invasive fungal infections. 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.

Question 8

Should bronchial thermoplasty be used in patients with severe asthma?

Recommendation 8

We recommend 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 (strong recommendation, very low quality evidence).

Values and preferences

This recommendation places a higher value 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.

Remarks

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 utilising 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 (FEV_1 <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.

New experimental molecular-based treatments for severe asthma

The complexity of chronic severe asthma with different underlying mechanisms (or endotypes) suggests that phenotyping patients with severe asthma and personalised therapy could lead to improved outcomes and fewer side-effects. The introduction of anti-IgE therapy for severe asthma inaugurated the era of specific therapies for certain severe asthma patients, although predicting responders to therapy remains problematic. More recent experimental biological approaches targeting specific asthmatic inflammatory pathways have reported positive results and are beginning to help define immuno-inflammatory phenotypes/endotypes (tables 8 and 9).

While the anti-IL5 antibody, mepolizumab, was not beneficial in unselected adult patients with moderate asthma [222], when studied in severe asthma patients with persistent sputum eosinophilia, two anti-IL-5 antibodies, mepolizumab and reslizumab, have been shown to decrease exacerbations and OCS use, as well as improve symptoms and lung function to varying degrees [57, 58, 157]. A larger study with mepolizumab showed efficacy in adults and adolescents solely in terms of a reduction in exacerbation rate, without improvement in FEV_1 and quality of life [56].

An antibody to IL-13, lebrikizumab, improved FEV_1 in moderately severe asthmatic adults, without affecting exacerbations and asthma symptoms [59]. In a post-hoc analysis, this antibody improved prebronchodilator FEV_1 in the group with evidence for Th2 inflammation as measured by elevated serum

TABLE 9 Potential phenotype-targeted therapies in severe asthma[#]

Characteristic	Associations	Specifically targeted treatments
Severe allergic asthma	Blood and sputum eosinophils High serum IgE High F_{ENO}	Anti-IgE (adults and children) Anti-IL-4/IL-13 Anti-IL-4 receptor
Eosinophilic asthma	Blood and sputum eosinophils Recurrent exacerbations High F_{ENO}	Anti-IL-5 Anti-IL-4/IL-13 Anti-IL-4 receptor
Neutrophilic asthma[¶]	Corticosteroid insensitivity Bacterial infections	Anti-IL-8 CXCR2 antagonists Anti-LTB4 (adults and children) Macrolides (adults and children)
Chronic airflow obstruction	Airway wall remodelling as increased airway wall thickness	Anti-IL-13 Bronchial thermoplasty
Recurrent exacerbations	Sputum eosinophils in sputum Reduced response to ICS and/or OCS	Anti-IL5 Anti-IgE (adults and children)
Corticosteroid insensitivity	Increased neutrophils in sputum[¶]	p38 MAPK inhibitors Theophylline (adults and children) Macrolides (adults and children)

F_{ENO}: exhaled nitric oxide fraction; IL: interleukin; LTB4: leukotriene B4; ICS: inhaled corticosteroid; OCS: oral corticosteroid; MAPK: mitogen-activated protein kinase. [#]: Unless otherwise stated, these potential treatments apply to adults; [¶]: neutrophilic asthma is rare in children.

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periostin levels, a proposed surrogate marker of Th2 activity or *Fe*NO [59, 223]. Another anti-IL-13 antibody, tralokinumab, did not improve symptoms but resulted in a non-significant increase in FEV1 when compared to placebo in all comers. Like lebrikizumab, it appeared to perform better in patients with detectable sputum IL-13 levels [60]. A study in moderate-to-severe asthma of a monoclonal antibody to the IL-4 receptor-α, that blocks both IL-4 and IL-13, was negative [160]. Whether prior biological phenotyping would have yielded different results is unclear. Similarly, an anti-TNF-α antibody, golimumab, was also ineffective in a study performed in adults with uncontrolled severe persistent asthma [99], but *post hoc* analysis suggested an effect in a subgroup. However, further studies are unlikely owing to serious side-effects including an increased prevalence of infections in the treated group.

Two other biological approaches have been reported in severe asthma, but without any specific phenotyping appropriate to the targets chosen. A tyrosine kinase inhibitor, masitinib, which targets stem cell factor receptor and platelet-derived growth factor improved asthma control in adults when compared with placebo in the face of a reducing dose of OCS; however, there was no effect on lung function [161]. Daclizumab, a humanised IgG1 monoclonal antibody against the IL-2 receptor-α chain of activated lymphocytes improved FEV1 and asthma control in moderate-to-severe asthmatic adults inadequately controlled on ICS [162]. A CXCR2 antagonist, SCH527123, reduced sputum neutrophilia in severe adult asthma, and was associated with a modest reduction in mild exacerbations, but without an improvement in asthma control [163]. It is unclear whether better efficacy would have been seen with additional phenotyping as the definition of sputum neutrophilia remains unsatisfactory. There is no experience of the use of monoclonal antibody treatments in children, other than omalizumab. Data from adult studies should only be extrapolated to children with great caution.

Conclusion

The treatment of severe asthma both in adults and children still relies heavily on the maximal optimal use of corticosteroids and bronchodilators, and other controllers recommended for moderate-to-severe asthma. The addition of the first targeted biological treatment approved for asthma, a monoclonal anti-IgE antibody, has led to renewed optimism of improvements in outcomes in some patients with allergic severe asthma. There is a potential for other add-on benefits of additional biological agents to providing benefit in severe asthma, especially if appropriate responder specific phenotypes of patients can be identified and selected for these highly specific treatments. This prospect provides the impetus for the search for mechanisms, pathways and biomarkers in severe asthma which are under intense study. It is hoped that the current emerging understanding of the immunopathobiology of severe asthma, of biological agents and of emerging inflammatory and molecular phenotypes will generate and lead to safe and effective biomarker-driven approaches to the therapy of severe asthma.

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