

International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma

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ABSTRACT

Background:

Severe or therapy-resistant asthma is increasingly recognised as a major unmet need.

Purpose:

Supported by the American Thoracic Society (ATS) and European Respiratory Society (ERS), a Task Force reviewed the definition and provided recommendations and guidelines on the evaluation and treatment of severe asthma in children and adults.

Methods:

We performed a literature review followed by discussion by an expert committee according to the GRADE approach to develop specific clinical recommendations.

Results:

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.

Conclusion:

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

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Executive Summary

The ATS-ERS 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 were made. See the unabridged online version of the document for detailed discussion of the definition of severe asthma , phenotypes and recommendations for practice.

Definition of severe asthma

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 2 for doses in adults and children) plus a second controller (and/or systemic CS) to prevent it from becoming “uncontrolled” or which remains “uncontrolled“ despite this therapy.”

Methodology

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 preparing 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 randomized controlled trials 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 categorized 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 resulting recommendations.

The strength of recommendations is expressed as either strong (We recommend...) or conditional (We suggest...) and has explicit implications (Table 1). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

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.	Recognize 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.

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, e.g. 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	conditional	very low	The recommendation to use sputum eosinophil counts to guide therapy in adults places a higher value	Because at the present time, measurement of sputum eosinophils has not yet been sufficiently standardized and is not

		counts performed in centres experienced in using this technique rather than by clinical criteria alone.			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.	widely available we suggest such an approach be used only in specialized 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 recognize 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 standardized 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 FeNO 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 FeNO.	
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 6 and above, with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance if their total serum IgE level is 30 to 700 IU/mL (in 3 studies the range was wider – 30 to 1300 IU/mL). Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare 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.
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 randomized trials is only available for adults. Because of the probable adverse effects of methotrexate and need for monitoring therapy we suggest that any use of methotrexate is limited to specialized centres and only in patients who require daily OCS. If a decision to use methotrexate is made, a chest x-ray, complete blood count with differential and platelets, liver function tests, serum creatinine and transfer factor to carbon monoxide (DL _{CO}), 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 allergic bronchopulmonary aspergillosis (ABPA).	conditional	very low	The recommendation to use antifungal agents in patients with severe asthma and ABPA places a higher value on possible reduction of the risk of exacerbations and improved symptoms, and a lower value on avoiding possible adverse effects, drug interactions and increased use of resources.	In children, the evidence is limited to isolated case reports. Children should be treated with antifungals only after the most detailed evaluation in a specialist severe asthma referral centre. As antifungal therapies are associated with significant and sometimes severe side-effects, including hepatotoxicity, clinicians should be familiar with these drugs and follow relevant precautions in monitoring for these, observing the limits to the duration of treatment recommended for each.

	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 sensitization 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 sensitization) places a higher value on avoiding possible adverse effects, interactions of antifungal agents with other medications and increased use of resources, and a lower value on uncertain possible benefits.	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.
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 utilizing an invasive physical intervention are unknown. Specifically designed studies are needed to define its effects on relevant objective primary outcomes such as exacerbation rates, and on long-term effects on lung function. Studies are also needed to better understand the phenotypes of responding patients, its effects in patients with severe obstructive asthma (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.

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 health care 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 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 American Thoracic Society and the European Respiratory Society 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 biologic therapies are increasingly showing efficacy.

METHODS

Committee Composition and Meetings

This guideline represents a collaborative effort between the ATS and ERS. The Committee consisted of clinicians and researchers with recognized expertise in severe asthma (21 pulmonologists of whom 3 were pediatricians, 2 pathologists and 2 physiologists plus one scientist) and an ATS methodologist (JLB) with expertise in the guideline development process and the application of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [3].

Nine face-to-face meetings were held between 2009 and 2012 coinciding with the ATS and ERS annual conferences during which the Committee discussed and decided about the scope of the document, the specific questions to be addressed and the existing research evidence. Multiple conference calls were also held and frequent email correspondence was used to discuss specific issues requiring the input from all committee members.

Disclosure of Potential Conflicts of Interest

Committee members disclosed all potential conflicts of interest according to the ATS and ERS policies. The chairs (KFC and SEW) 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 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.

Document preparation

The definition of Severe Asthma was reviewed with reference to the previous definitions [1, 2, 4, 5] and to more recent definitions [6, 7], and in relation to the definition of asthma control and asthma severity of the ATS/ERS Task Force [8]. In addition, the Committee reviewed information obtained from all cohorts available in the public domain by a thorough review of the literature and by the expert knowledge of the Committee members [9-13]. An updated version of the Definition was then prepared and discussed at face-to-face meetings with several iterations following contribution of the entire Committee. For the sections on Phenotyping, Evaluation and Therapy, these were prepared by subgroups of the Committee by review of the literature and by expert knowledge of the Committee members. These sections were then circulated to the whole group and discussed further at face-to-face meetings, with subsequent revisions made.

Formulating specific clinical questions and determining outcomes of interest

The Committee identified several questions related to the definition, phenotyping, diagnosis and treatment of severe asthma. The Committee drafted a list of 24 specific questions about the diagnosis and treatment of severe asthma and ranked them by priority. Eight specific questions were chosen to be explicitly answered with recommendations for clinical practice. The remaining questions are listed in the online supplementary material 2 and will be addressed in the updates of these guidelines.

The Committee selected outcomes of interest for each question following the approach suggested by the GRADE Working Group [14]. All outcomes were identified a priori and the Committee explicitly rated their relative importance for decision making. Ranking outcomes by their relative importance can help to focus attention on those outcomes that are considered most important and help to resolve or clarify potential disagreements.

Evidence Review and Development of Clinical Recommendations

Evidence summaries (online supplementary material 1) for each question were prepared by the ATS methodologist following the GRADE approach [3] using GRADEpro software version 3.6 [15]. The summaries of evidence were reviewed by all committee members and corrections made when appropriate. We based the evidence summaries on existing up-to-date well done systematic

reviews. Systematic reviews were supplemented, if necessary, with additional recent randomized controlled trials (RCTs). When there was no recent valid systematic review available, we did not perform rigorous systematic reviews, but we systematically searched MEDLINE and/or Cochrane Central Register of Controlled Trials (CENTRAL) for relevant studies (search strategies are provided in the online supplementary material 2). We also queried the authors of identified trials and committee members for any additional studies that we had not identified. We did not search for observational studies to look for evidence about the important outcomes that were not reported in the RCTs. However, when there was no RCT available to provide evidence about any outcome of interest we did look for the best available evidence to support recommendations.

When possible and justified we combined the results of identified studies using meta-analysis using the Cochrane Collaboration Review Manager 5.1.6 [16]. All reviewed original studies were evaluated to inform judgments about the available evidence. We assessed the risk of bias at the outcome level using the Cochrane Collaboration's risk of bias tool [17]. Subsequently, we assessed the quality of the body of evidence (i.e. confidence in the estimated effects) for each of the outcomes of interest following the GRADE approach [18] based on the following criteria: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publications bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding. Quality was categorized into 4 levels ranging from very low to high quality.

During the meetings and conference calls, the Committee developed recommendations based on the evidence summaries. For each recommendation, the Committee considered and agreed on the following: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options and the assumptions about the values and preferences associated with the decision. The Committee also explicitly took into account possible extent of resource use associated with alternative management options. Recommendations and their strength were decided by consensus and no recommendation required voting. The Committee agreed on the final wording of recommendations and remarks with further qualifications for each recommendation. The final document including recommendations was reviewed and approved by all members of the committee.

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 1 provides suggested interpretation of strong and conditional recommendations by patients, clinicians and health care policy makers.

Document review

A final draft document was reviewed by each member of the Committee, finalized, approved, and submitted to the ATS and ERS for peer review. The document was revised to incorporate the pertinent comments suggested by the external reviewers and the input provided by the ATS Documents Editor and the ERS Guidelines Director.

Priorities for revision of these guidelines

Guidelines are living documents. To remain useful, they need to be updated regularly as new knowledge accumulates. This document will also need revision because it only covers a limited number of clinical questions. Many other questions relevant to the management of patients with severe asthma have been identified by the Committee as potentially important (online supplementary material 2) but have not yet been addressed. The Committee intends to regularly update the document but not later than in 2015.

HOW TO USE THESE GUIDELINES

The ATS/ERS 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.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its 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 (Box 1)

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 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 [6].

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 2 for doses in adults and children) plus a second controller (and/or systemic CS) 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, leukotriene modifier or theophylline and/or continuous or near continuous systemic CSs as background therapy [5, 19-21]. This definition is similar to the recent Innovative Medicine Initiative, but does not address the group of patients identified by the World Health Organization (WHO) with untreated severe asthma [6, 7]. 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 2011 ATS-ERS Taskforce focuses on severe asthma refractory or insensitive to currently available medications,

including CSs, and asthma complicated by comorbidities, the types of greatest concern to the countries primarily served by the two societies [6].

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: ACQ consistently >1.5 or ACT <20 (or “not well controlled” by NAEPP or GINA guidelines over the 3 months or evaluation [20, 22])
- 2) Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year
- 3) Serious exacerbations: at least one hospitalization, Intensive Care Unit stay or mechanical ventilation in the previous year
- 4) Airflow limitation: $FEV_1 < 80\%$ predicted (in the presence of reduced FEV_1/FVC defined as less than the normal lower limit) following a withhold of both short- and long-acting bronchodilators.

Evidence for any one of these four criteria while on current high-dose therapy identifies the patient as having “severe asthma” (Box 1). Patients who do not meet 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, physiologic 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, functional to patient-oriented characteristics with the goal to improve therapy (Figure 1). Detailed efforts in this regard require organization and integration of these defining characteristics into clinically recognizable 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 [23]. 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 Evaluation).

There are currently two strategies to delineate phenotypes: hypothesis-based and unbiased approaches. Unbiased analyses are being applied to a broad range of clinical, physiologic and biologic characteristics, utilizing unsupervised hierarchical clustering stepwise discriminant and other approaches [11, 13, 24, 25]. The Severe Asthma Research Program (SARP), using predominantly clinical characteristics, identified five clusters of asthma among 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 women with moderate FEV₁ reductions and frequent oral corticosteroid (CS) use, and a later onset but long duration very severe, less atopic group, with less reversible airflow limitation [11]. Another adult asthma cohort analysis from the Leicester group included sputum eosinophil counts and identified 4 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 [13]. In both cluster analyses, severe asthmatics were distributed among several clusters supporting the heterogeneity of severe asthma. Finally, a SARP study of children found 4 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 [26].

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 recognized clinically (late onset eosinophilic and early onset atopic/allergic), supporting the identification of these phenotypes in particular [27, 28].

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 [13, 26, 27, 29-31]. Early childhood-onset asthma (over a range of severity) is characterized by allergic sensitization, a strong family history and more recently, non-allergy/atopy related genetic factors [13, 27, 32]. Late-onset, often severe asthma is associated with female gender, reduced pulmonary function despite shorter disease duration, and in some subgroups, a strong association with persistent eosinophilic inflammation, nasal polyps and sinusitis and often aspirin sensitivity (aspirin-exacerbated respiratory disease) and respiratory tract infections, but less support for specific genetic factors [11, 13, 27, 33, 34]. 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 [35].

Occupational exposures have also been associated with late onset, and often severe asthma [36]. 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 [37, 38]. Tobacco smoke and environmental air pollution are routinely linked as risk factors for more severe asthma [39, 40]. Both personal smoking and obesity have been linked to CS insensitivity, also associated with severe asthma [41, 42]. Recurrent exacerbations in adult severe asthma are more frequent in patients with co-morbid conditions such as severe sinus disease, gastro-oesophageal reflux,

recurrent respiratory infections and obstructive sleep apnoea [43]. Sensitization to fungi such as aspergillus has also been associated with severe asthma development in adults [44, 45]

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 (GWAS) 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 characterization [32, 46]. Other studies have compared more severe asthma with non-asthma controls or smaller cohorts with mild disease and have identified similar genes [47]. 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 [32, 48]. Understanding the functional biology of these gene variants may help identify biomarkers in relation to phenotypes and new pharmacotherapies. For example, single nucleotide polymorphisms (SNPs) in the IL4-receptor alpha (IL4R α) specifically associate with persistent airways inflammation, severe asthma exacerbations and submucosal mast cells supporting functional alterations in the IL4 pathway influencing allergic inflammation in some severe asthmatics [29]. Another recent paper showed that variation in IL6- receptor (IL-6-R) associated with lower lung function and more severe asthma subphenotypes suggesting another therapeutic target [49]. Finally, there is evidence that genetic variation in a number of genes may interact and influence lung function, asthma susceptibility and severity [50]. 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 biologic therapies could exhibit more difficult-to-control asthma and be classified as more severe [51, 52].

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 Th2 function, subsequent allergic airways disease and T-cell production of IL-13 has been proposed from murine studies [53, 54].

Another study reported alterations in specific miRNA in asthmatic CD4 and CD8 T-cells [55], but the relevance for severe asthma remains to be ascertained.

Inflammation and Adaptive Immunity (Figure 2)

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 categorized into eosinophilic, neutrophilic, and/or paucigranulocytic [13, 28, 56-58]. The concomitant presence of both eosinophils and neutrophils (mixed cellularity) has been reported to be associated with the most severe disease [59]. 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 CS [59-61]. The neutrophilic and eosinophilic components of sputum can vary substantially on a monthly basis [62]. However, sputum eosinophilia appears more stable, especially in severe asthma, when examined over longer yearly periods in adults [63]. This stability appears to be less in children [64]. The mechanisms behind these diverse inflammatory profiles are likely complex, varied, and related to CS sensitivity [65, 66]. 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 [13, 67-69]. Whether the Th2 profile is similar to that observed in CS-naïve patients awaits further study, but would be supported by studies demonstrating efficacy of anti-IL-13 antibody in improving FEV₁ in adult patients with moderate-to-severe asthma [70, 71]. Evidence for a Th2 pattern in severe asthmatic children remains controversial [72, 73]. Inflammation associated with high expression of Th2 cytokines has also been associated with mast cells (MC) [74]. MCs are increased in airway smooth muscle and epithelial compartments in asthma where they have been linked to poor asthma control and airway hyperresponsiveness [75, 76].

The mechanisms for airway neutrophilia are less clear. CSs themselves can contribute to the neutrophilia to some degree and even Th1 factors may play a role [77, 78]. Th17 immunity has been implicated as a cause for neutrophilia, primarily in murine models of asthma, with some supporting data from severe asthma [77, 79-81].

The underlying mechanisms for severe asthma in those patients with no/little 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 [60, 66].

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 [53, 73, 82]. Patterns of exhaled volatile organic compounds also differ between asthmatics with fixed airflow limitation and patients with COPD supporting their potential in the phenotyping of severe asthma [83, 84]. Finally, exhaled nitric oxide (FeNO) has been extensively evaluated in mild to moderate asthma and the ATS has recently published specific guidelines for FeNO use in these patients [85]. Cross-sectional studies of severe asthma have indicated some potential usefulness of FeNO as a measure of symptom frequency [86] and as an index of the most obstructed and frequent user of emergency care [87].

Respiratory infections

The role of infections particularly viral infections in asthma exacerbations is well-established and their contribution to asthma development and progression increasingly recognized; however, the relation to asthma severity has rarely been addressed [88-90]. 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* [34, 91, 92]. Emerging data indicate an altered microbiome in asthma as measured by 16sRNA, but the role of bacteria in severe asthma requires further study [93]. Positive *Haemophilus influenzae* and *Pseudomonas aeruginosa* 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 [94]. 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 [34].

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 [95, 96]. Toll-like receptor signalling may also be impaired, leading to inadequate Type I and III interferon (IFN) responses which decrease viral clearance [97]. In addition, the antimicrobial activity of airway epithelial cells and their production of β -defensins is reduced when these cells are exposed to T-helper type 2 (Th2) cytokines, while allergic inflammation leads to a reduction in cathelicidin antimicrobial peptide [98, 99]. In contrast, other elements of innate immunity may be enhanced, including increased expression of TSLP, IL-25, and IL-33 in airway cells from patients with severe asthma [81, 100, 101]. 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 FeNO 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 FEV₁ [87, 102-104]. In addition, higher levels of oxidative stress has been associated with a reduction in superoxide dismutase and s-nitrosothiol depletion [105, 106].

The expression of TNF- α has been reported to be increased in severe asthmatic airways, and recent genomic and proteomic approaches have suggested increases in IL-1 β in certain asthmatics, in conjunction with neutrophilia [107-109]. 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 [110].

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 patients with milder asthma [111-113].

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 [114]. First, the epithelium in severe asthma is reported to be thicker than in mild-moderate asthma [115], with altered proliferation, apoptosis and release of pro-inflammatory factors [116]. Second, autopsy and biopsy studies have linked an increased amount of airway smooth muscle to asthma severity, airflow obstruction and bronchial hyperresponsiveness [82, 117-120]. 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 [121, 122].

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 [28, 123, 124]. Patients with severe asthmatics also have increased expression of TGF- β isoforms and collagen deposition as compared to mild asthmatics, again in association with eosinophilic asthma, with evidence for remodelling in the peripheral airways as well [28, 125]. Indeed, increased production and altered composition of extracellular matrix in the small airways is characteristic of fatal asthma [125].

High resolution computed tomographic studies of airway structure are providing quantitative morphometry of the airways and distal lung in adults with severe asthma, but with less is known in children [126-129]. In adults, there are relationships to lung function and more severe exacerbation-prone disease. These structural changes lead to ventilatory defects that can be visualized by magnetic resonance imaging with hyperpolarized helium [130]. Initial studies suggest that neutrophilic inflammation may be linked to air trapping, while biopsy-measured epithelial thickness predicts airway wall thickness obtained from HRCT scans [127, 128].

Physiology

Chronic airflow limitation which is less responsive to bronchodilators and inhaled or oral CS therapy is observed in some severe asthma phenotypes [9, 11, 26]. Chronic airway obstruction may result in airway closure or uneven ventilation of small airways, which associates with severe exacerbations [131]. Severe asthmatics were found to exhibit air trapping (reduced FVC in relation to FEV₁/FVC) when compared with non-severe asthmatics at matched levels of airflow limitation measured by FEV₁/FVC ratio [132]. Bronchodilator use in patients with low baseline FEV₁ 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 [127, 133, 134]. One of the SARP clusters was characterized by severe airway obstruction, with continued β -agonist reversibility, but without reversibility into the normal range, and in association with sputum neutrophilia [11]. Day-to-day variations in lung function are also less variable in severe asthmatics [135]. 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 gender, smoking, increased FeNO and African ancestry are contributors, while interestingly, allergic status may be protective [104, 136].

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 [137]. Whether this is related to the reported loss of alveolar attachments in asthma deaths remains to be confirmed [138].

Studies of bronchial hyperresponsiveness in terms of its sensitivity and maximal responses have not yet proven 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 [135, 139]. 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 to mild-moderate asthma suggest these fluctuation patterns may also be a phenotypical characteristic [140].

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 Box 2.

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 co-morbidities and 3) the initial determination of phenotypes which may be useful in optimizing 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 uncontrolled asthma has been reported to be as high as 12-30% [141, 142]. The evaluation should start with a careful history with emphasis on asthma symptoms including dyspnea (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 [143].

Children and adults should be evaluated for other conditions that may mimic or be associated with asthma (Table 5). As confirmation of reversible airflow limitation is part of the diagnosis of asthma, spirometry with both inspiratory and expiratory loops, assessed pre- and post-bronchodilator administration should be obtained [144]. 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 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 has variable airflow obstruction, but this is difficult in practice. Children with severe asthma often have normal lung function and no acute response to bronchodilators [145]. Children with a normal FEV₁ both before and after a short acting β -agonist may show a bronchodilator response in terms of FEF₂₅₋₇₅ [146]. However, the utility of FEF₂₅₋₇₅ 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 specialized centre where patients can undergo a systematic evaluation, resulted in 30-50% of patients previously called severe, being classed as difficult-to-control [141, 147, 148]. Many children with asthma will also be found not to have severe, treatment-refractory asthma after a thorough evaluation [149] and approximately 50% of children referred for severe asthma have persistent symptoms and poor control because of inadequate disease management [148].

Question 1: Should chest high-resolution computed tomography (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)?

We assumed that if some comorbid or masquerading condition were suspected (see Table 3), patients would be investigated with the appropriate diagnostic strategy for that condition. We also assumed that investigation for some conditions would involve a testing strategy in which chest HRCT would only be done depending on the results of tests performed earlier in the diagnostic pathway (e.g. in a patient suspected of allergic bronchopulmonary aspergillosis, a skin prick test (SPT) to aspergillus antigen would be done first and chest HRCT would only be done when SPT turned out positive). Therefore, the question that clinicians face would be whether chest CT should be done in patients with severe asthma who do not have any other apparent indications for that test.

Summary of the evidence

We did not find any systematic review or primary study that investigates the results of using chest high resolution computed tomography (HRCT) in screening patients with severe asthma for potential comorbid or masquerading conditions.

In the absence of such studies, we took a two-step approach to answer this question. First, we intended to estimate the prevalence (probability) of comorbid or masquerading conditions in patients in severe asthma, reasoning that if these conditions were sufficiently infrequent, one would not recommend chest HRCT however accurate this test might be. Second, if the masquerading conditions were frequent enough, we would review the accuracy of chest HRCT in the diagnosis of these conditions among patients with severe asthma.

We identified several observational studies that were of potential interest. However, four studies did not report outcomes of interest (i.e. comorbid or masquerading conditions) or reported them in a way that precluded conclusions [134, 150-152]. Two were case series with no information about the number of sampled patients (i.e. no denominator) [153, 154], in one a diagnosis of comorbid/masquerading condition was done prior to HRCT [155], and in the last one, an HRCT was done only in selected patients with apparent indications for the test (irrespective whether selection criteria were reported in the article or not) [126, 156-159].

Eight studies reported the results of chest HRCT in patients with asthma [160-164]. Grenier and colleagues investigated 50 patients with asthma without obvious changes on chest radiograms

and reported bronchiectasis (defined by comparing the diameters of the bronchial lumen and homologous pulmonary arteries, and by absence of normal distal tapering of the bronchial lumen as assessed on HRCT scans) in 28%. However, it is most likely that fewer than 20% of these patients might have had severe asthma (Aas score 4 or 5 [165] defined as >5 episodes totalling ≥ 6 months per year with prolonged obstruction following most episodes, chronic symptomatic obstruction with restriction of function, or chronic, incapacitating asthma with severe, acute exacerbations in spite of continuous medication following adequate and safe dosage regimens). Similarly, Paganin and colleagues reported two studies that investigated 13 and 37 patients with possible severe asthma (Aas score 4 or 5) and no particular selection criteria; the sampled population was also not described [161, 162]. In both studies, the majority of patients had bronchiectasis and many had emphysema. Jensen and colleagues reviewed charts of 30 patients with severe asthma (an HRCT was done prior to the study as part of the patients' evaluation for unreported reasons) [159]. The authors found bronchiectasis in 20% of patients. HRCT results of those patients with severe asthma was compared to 14 patients with bronchiolitis obliterans. The mosaic pattern of attenuation was more frequent in bronchiolitis obliterans than severe asthma (50% vs. 3%) but no other differences were identified. Hudon and colleagues reported 16 patients with asthma and incomplete reversibility despite administration of ICS and ≥ 30 mg of prednisone daily for 2 weeks. Bronchial dilatation was noted in 6 of those patients [166]. Boulet and colleagues reported bronchial dilatation in 6 of 12 similar asthmatic patients with irreversible component of airway obstruction [167]. In another study Boulet and colleagues reported the results of HRCT done in 39 of 49 corticosteroid-naïve patients with mild stable asthma; they found no bronchiectasis but did find emphysema-like changes in 4 patients of whom 3 were smokers [167]. Takemura and colleagues described finding bronchial dilatation in 23 of 37 patients with stable asthma, four of whom had severe asthma according to GINA but the results for those patients were not reported separately [163]. Finally, Yilmaz and colleagues reported a case series of 68 elderly patients with asthma that was unlikely to be severe (FEV_1 among "early onset" asthma patients was 77% and among "late onset" – 100%) [164]. Eight of 37 "early onset" asthma patients had emphysema and 5 had bronchial dilatation. None of the "late onset" asthma patients had any changes in HRCT.

We found no studies reporting the prevalence of other comorbid or masquerading conditions in patients with severe asthma. We were also not able to identify any studies that report the accuracy of chest HRCT in diagnosing any of the comorbid conditions among those patients.

In the apparent absence of published evidence about the utility of chest HRCT in patients with severe asthma and no specific indications for the test, we relied on unsystematic observations of such patients in the clinical practice of Committee members.

Desirable consequences

Potential benefits of chest HRCT in patients with severe asthma include identification of a comorbidity or a masquerading condition that would influence treatment decisions and possibly improve patient outcomes. However, we were unable to identify any study that would allow an estimate of the prevalence of the coexisting or masquerading conditions where chest HRCT would be useful.

Undesirable consequences

The downside of chest HRCT include the risks associated with an exposure to radiation burden and psychological stress, and increased resource expenditure. Patients with falsely positive results of chest HRCT may suffer additional harm from subsequent unnecessary diagnostic and therapeutic procedures.

Conclusions and research needs

There is substantial uncertainty about the benefits of chest HRCT in patients with severe asthma who have no other specific indications for performing this test. It is not known how prevalent are comorbid and/or masquerading conditions that could be detected with chest HRCT and, when appropriately treated potentially leading to better patient outcomes. It is also not known what is the accuracy of a chest HRCT in detecting those conditions in patients with severe asthma. Properly-designed epidemiological studies of prevalence of comorbid and masquerading conditions, if done, may have an important influence on this recommendation.

The Committee agreed that performing chest HRCT in patients with severe asthma to differentiate among patients with different phenotypes is premature, given the uncertainty about the choice and efficacy of available treatment options in subgroups selected based on a given phenotype.

What others are saying

Neither Global Strategy for Asthma Management and Prevention (GINA) [168] nor the NHLBI National Asthma Education and Prevention Program [4] and British Thoracic Society guidelines [169] make any recommendations about the use of chest HRCT in patients with asthma.

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, e.g. 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 Co-morbidities and Contributory Factors (Box 3, online supplementary material 3, table S2)

Difficult-to-control and severe asthma are often associated with co-existing conditions. 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% [141, 147, 170]. Poor inhaler technique is also common and should be addressed [148]. 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 [170]. If non-adherence is present, clinicians should empower patients to make informed choices about their medicines and develop individualized interventions to manage non-adherence [170]. Cost alone can have substantial impact on adherence.

Problematic childhood asthma with poor or non-adherence to treatment present 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 [148]. 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 epidemiologic 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 [9, 10]. The association between allergy and asthma severity is stronger in children [145, 171]. 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 [172].

Evidence for rhinosinusitis has been reported to be as high at 75-80% [10, 173]. 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.

Gastroesophageal reflux (GERD) is present in 60-80% [9-11, 33, 173], but clinical trials with anti-reflux therapy generally show little to no effect on asthma control [174-176]. The role of “silent” gastroesophageal reflux disease (GERD) as a cause of poor asthma control in general may be over-emphasized, but the child with gastrointestinal symptoms and problematic asthma should be evaluated and treated for GERD [176]. Although the impact of treatment of sinusitis and GERD on severe asthma is not yet clear, when these co-morbidities are present, they should be treated as appropriate to improve these conditions. Both GERD and rhinosinusitis can worsen vocal cord dysfunction. In addition, symptoms arising from GERD and rhinosinusitis may masquerade as asthma.

Obesity is also a common co-morbidity associated with difficult asthma, although the relationship to asthma may vary by age at onset, with implications for treatment [37, 38].

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 CS therapy [39, 42]. Environmental tobacco smoke exposure is also associated with adverse asthma outcomes in children and adults [40]. Measurement of urine or salivary cotinine should be considered, often revealing evidence of passive smoke exposure [148].

Early-life exposures and sensitization to various allergens, especially to moulds, occur in children with severe asthma [145]. Evidence supporting a therapeutic environmental response to 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 [177]. 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% [178]. 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 [179]. Often

these conditions are under-diagnosed, so appropriate psychiatric evaluation and referral to a specialist is recommended [180]. Some assessment of family psychosocial stress using standardized questionnaires or direct interviews can be helpful. Unfortunately, the benefit of psychiatric treatment on asthma outcomes has not been well-established [180] 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 those interventions on asthma outcomes [181].

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

Step 3. Approaches to Asthma Phenotyping

Asthma, and severe asthma in particular, are increasingly recognized as heterogeneous processes, not all of which may respond similarly to current therapies or have the same clinical course (see Phenotyping section). Currently, there are no widely-accepted asthma definitions of specific phenotypes. However, identifying certain characteristics of certain phenotypes may eventually promote targeted and/or more effective therapies as well as help to predict different natural histories which may be of benefit to some patients [11, 13]. In that regard, eosinophilic inflammation, allergic/Th2 processes and obesity have been identified as characteristics or phenotypes which may be helpful when considering nonspecific (CS) and specific (targeted) therapy (eg, anti-IgE, anti-IL5 and anti-IL13 antibody treatments) [13, 38, 55, 69, 70, 182-186]

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 [11, 13, 27, 32, 37]. 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 CS therapy, and perhaps to targeted therapies such as anti-IL-5 or anti-IL-13, as well

[28, 43, 69, 70, 182-184]. The role of sputum neutrophilic inflammation in guiding therapy is generally less studied, with considerable day-to-day variability in patients with severe asthma [62]. It has been associated with reduced response to corticosteroid therapy [182]. While these measurements are available at many specialized centres, further research into their utility as well as standardization 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 asthmatic patient[38]. These characteristics may be addressed by asking questions about age at onset (albeit acknowledging the problems of retrospective recall), evaluating body mass index (BMI), measuring lung eosinophils (usually in induced sputum) and assessing levels of atopy, with or without purported biomarkers for Th2 inflammation. These Th2 markers include exhaled nitric oxide (FeNO), which is widely available and serum periostin (currently available only for research and not applicable to children) and even blood eosinophils (online supplementary material 3, table S4 and Therapy Section for further details) [70, 187]. 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. FeNO 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 FeNO and serum IgE differentiate severe asthma in children but not adults with severe asthma, and support a prevalent Th-2 driven pattern of airway inflammation [145]. However, a bronchoscopic study did not support a defining role for Th-2 cytokines in children with severe asthma [72]. Furthermore, the clinical expression of severe asthma in children is highly variable and distinct severe asthma phenotypes are less well defined in children as they are in adults [26]. 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 [188].

Other than blood eosinophils, biomarker measurements require either specialized 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 Therapy section on clinical recommendations).

4. Therapy

This section discusses the management of severe asthma as defined in this document with (i) established therapies (ii) recently-developed therapies and (iii) future approaches that will require phenotypic characterisation. Despite their widespread use and endorsement, the efficacy of some traditional controller medications, including long acting β -agonists, leukotriene modifiers and theophylline has not been well documented in severe asthma. In fact, the nature of the definition 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 less efficacy in this population. 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 4).

Using established asthma medications

Corticosteroid insensitivity

As defined in this document, severe asthma involves CS insensitivity, with persistent lack of control despite CS therapy or worsening of asthma control on reduction or discontinuation of CS therapy. Thus, although CSs 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 CS insensitivity. Severe asthmatics are often referred to as CS-dependent, refractory or CS-insensitive asthmatics. In 30% of severe adult asthma patients, OCS are required in addition to ICS to maintain some degree of asthma control [9, 10, 33, 134]. Intramuscular injections of triamcinolone as a maximal dose of CS therapy can improve asthma control, reduce sputum eosinophils and increase FEV₁ [189, 190], 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’ CS unresponsive to a

single intramuscular injection of triamcinolone, indicating that 89% of the patients had some degree of corticosteroid responsiveness [171]. Thus, the term CS insensitivity is more appropriate than CS resistance.

CS 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 [191-194], but the relation of these in vitro studies to in vivo responses is not well understood. CS insensitivity has been associated with different co-morbid conditions such as obesity [195], smoking [196], low vitamin D levels [197, 198], and non-eosinophilic (low-Th2 inflammation) mainly in adults [199]. In children, less is known about the role of these mechanisms.

While the eosinophilic or ‘Th-2 high’ asthma phenotype, characterized by high expression of Th2 cytokines, IL-5 and IL-13, identifies inhaled CS responsiveness in patients with milder asthma, eosinophilic inflammation may persist in some severe asthma patients despite high dose ICS, and even systemic CSs [10, 28, 72, 200] [184, 201]. 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 [72]. In adults, a non-eosinophilic phenotype appears to form a large subgroup of asthma [28, 200, 201], with data from a mild-to-moderate cohort [201], showing relatively poor CS sensitivity. Understanding the mechanisms underlying these different types of CS insensitivity could lead to novel treatments such as p38 mitogen-activated protein kinase (MAPK) inhibitors and histone deacetylase-2 (HDAC-2) recruiters [202, 203].

In the 1990s, several agents with immunosuppressive properties such as methotrexate, cyclosporin A, gold salts and intravenous immunoglobulin G were studied as CS-sparing agents with the aim of reducing the dose of maintenance OCS. Although these agents may be considered to improve CS insensitivity, their efficacy is uncertain, and they are associated with significant side-effects [204-208].

Inhaled and oral CS therapy

The high-dose range for the individual ICSs are shown in Table 2. 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 [209]. 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 CS-sparing effect) [209] [210]. Although even higher doses of ICS (above 2000 mcg/day) 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 (2,400-4,000 mcg of beclomethasone equivalent). However, this is often not practical in severe asthma since these patients are already maintained on high doses of ICS [211, 212]. Therefore, when standard medications are inadequate, OCS 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 3 bursts of OCS in the previous year [9, 10, 31, 134]. 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 CS use have been proposed, the use of sputum eosinophils and/or exhaled nitric oxide levels for guiding therapy in severe asthma remains controversial [85] (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 [189, 190]. The reasons for its efficacy may include enforced adherence or the greater potency of triamcinolone compared to other CS in clinical use.

Systemic CS use has been associated with an increased risk of fracture and cataracts [213, 214], while high doses of ICS are associated with an increased risk of adrenal suppression and growth retardation in children [213, 215-217]. Systemic CS-related weight gain may further impact negatively on asthma control [218]. In prepubertal children, the initial use of 400 µg of budesonide daily led to a small decrease in initial height (mean of -1.3 cm), that was accompanied by a persistent reduction in adult height, although the decrease was neither progressive nor cumulative [219]. Therefore, use of continuous systemic CSs, 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 [220].

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[221]. 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 CS 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 [33, 134]. Step-wise increases in the dose of ICS, in combination with a LABA, improves 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 Asthma Control Questionnaire or Asthma Control Test ACQ-7/ACT) remain at an uncontrolled level [210, 221, 222]. In poorly-controlled pediatric asthma on low-dose ICS, addition of LABA's were the most effective add-on therapy to ICS compared to 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 [223]. 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 (nebulized or aerosol-administered) β -agonist has not been confirmed [224].

Increased use of β -agonists may paradoxically lead to worsening asthma control as has been described in mild-to-moderate asthma patients treated with SABAs or LABAs without ICS [225-228]. 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 [229].

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 inhaled corticosteroid therapy compared to Mexican Americans and Puerto Ricans [230]. African-Americans suffering from asthma were reported to have more treatment failures compared with whites, particularly when taking long-acting β -agonists [231]. 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 [232]. 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 [233, 234]. Although considered to be less effective, they are well tolerated and may be used alternately with β -agonists for as-needed use throughout

the day. The routine use of nebulizers 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 [235]. The use of a pressurised metered dose inhaler (pMDI) with a spacer has been shown to be as effective as a nebulizer in both adults and children with worsening asthma or with an exacerbation [236].

Slow-release theophylline

In patients with moderate asthma, theophylline improved asthma control when added to ICS [237]. In an exploratory study of smoking asthmatics with CS insensitivity, theophylline with low dose ICS improved peak expiratory flow rates and asthma control [238], raising the possibility that theophylline could improve CS insensitivity in some people. However, no such studies have been performed in children or adults with severe asthma [239]. 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 CSs or improving symptoms in moderate asthma [19, 223]. Addition of a leukotriene receptor antagonist or synthesis inhibitor has shown some efficacy on lung function when added to ICS in 3 studies of adults with moderate to severe asthma who were not taking LABAs. Two of these studies were performed in aspirin-sensitive asthma in whom systemic CSs were used in 35% [240-242]. 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 [243]. Whether the phenotype of aspirin-sensitive asthma responds 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 [244, 245]. In patients taking high doses of ICSs and LABAs, the addition of tiotropium bromide provided improvements in FEV₁, reduced as-needed use of short-acting β 2-adrenergic agonists and modestly reduced the risk of a severe exacerbation [244, 246]. 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 FeNO. 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 anti-fungal treatments, and the newer treatment of bronchial thermoplasty.

A: 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?

Summary of the evidence

We found one systematic review reported in two publications [247, 248]. This review included three randomized controlled trials in adults [182, 249, 250]. We identified one more trial in children that was published after the search for the systematic review was done [251]. We used the results of the systematic review to inform the recommendation in adults (we extracted

additional data from the original studies when necessary) and the study by Fleming and colleagues [251] to inform the recommendation in children.

The proportion of patients that fulfilled criteria for refractory/severe asthma was explicit in some, but not all of the studies. One study [182] included 74% of patients with severe asthma, the other approximately 20% [249] and the third one – approximately 60% [250]. All studies included only adult patients. No study measured and/or reported absence from school/work, death, admission to the intensive care unit, and the need for intubation and ventilation.

Studies had a degree of clinical heterogeneity including definition of asthma exacerbations and cut-off levels for percentage of sputum eosinophils required to alter the management. Follow-up in the studies ranged from 1 to 2 years. The total number of patients and observed events is low for most outcomes. The confidence in the estimated effects (quality of the evidence) is very low in adults and in children (see evidence tables for question 2). The only randomized trial in children did not assess most of the critical outcomes – we did not search for observational studies, but we assumed that the evidence for many critical outcomes would come from observational studies with additional limitations.

Desirable consequences

The rate of asthma exacerbations requiring oral corticosteroids was lower in adults who had treatment adjusted according to sputum eosinophils (rate ratio: 0.33, 95% CI: 0.19 to 0.57). Over a follow-up period of 1–2 years this may mean 72 (95% CI: 46 to 87) fewer exacerbations per 100 patients. The effect on other outcomes was estimated imprecisely and does not exclude appreciable benefit or appreciable harm with treatment guided by measurement of sputum eosinophils (see evidence tables for question 2).

Undesirable consequences

No study reported important harms from measuring sputum eosinophils. One study reported that sputum induction with hypertonic saline was well tolerated and the mean fall in FEV₁ was 9.3% (range: 0 to 15.2)[250].

Other considerations

One study reported that sputum induction was successful in 552 of 632 (87%) attempts [182]. The same study reported a possible decrease of cost of treatment of severe asthma in one hospital setting when guiding treatment with sputum eosinophils was used (mean difference: US\$ 314 per year lower, 95% CI: 941 lower to 313 higher).

Conclusions and research needs

Net clinical benefit from treatment guided by sputum eosinophil count, compared to treatment guided by clinical criteria alone is uncertain. The limited data suggest that the rate of exacerbations requiring the use of oral corticosteroids may be reduced and there may be little or no difference in other outcomes deemed critical for decision-making. Further well designed and rigorously executed randomized trials that measure and properly report [252, 253] patient-important outcomes are needed, as are studies of patients identified to have an eosinophilic phenotype. If done, they are likely to have an important impact on this recommendation.

What others are saying

Global Strategy for Asthma Management and Prevention (GINA) does not make a recommendation about measurement of sputum eosinophilia [168]. NHLBI National Asthma Education Prevention Program states that “other markers, such as sputum eosinophils and FeNO, are increasingly used in clinical research and will require further evaluation in adults and children before they can be recommended as a clinical tool for routine asthma management” [4]. The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend clinicians “consider monitoring induced sputum eosinophil counts to guide steroid treatment” in patients with “difficult asthma” [254].

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 standardized 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 standardized and is not widely available we suggest such an approach be used only in specialized 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 recognize that different choices will be appropriate for different patients.

Question 3. Should treatment guided by exhaled nitric oxide (FeNO) in addition to clinical criteria, rather than treatment guided by clinical criteria alone, be used in patients with severe asthma?

Summary of the evidence

We found one systematic review addressing that question, the results of which have been published in two documents [247, 255]. We found 2 additional randomized trials that were published after the search for that review was completed [47, 256]. Four studies explicitly included children [47, 257-259], one included adolescents [260], and three studies enrolled

adults [256, 261, 262]. One study explicitly enrolled pregnant women of whom only 40% received inhaled corticosteroid; we did not include this study since we considered its results too indirect to inform our recommendation [256].

No study explicitly enrolled patients with severe asthma – most patients had mild to moderate disease, at best including a minority of severe asthmatics. No study measured quality of life and resource use (cost) and no study reported mortality, need for intubation or ventilation, and dose of oral corticosteroids. We amended data from the review by Petsky and colleagues [255] with the data from a more recently published study [47] and we extracted data about outcomes not reported in the systematic review from the original studies. We combined results across studies without dividing them into those including children or adults since we observed consistent estimates of all effects across all studies (see evidence table for question 3).

Desirable consequences

A small reduction in the risk and the rate of asthma exacerbations was observed in the studies including patients with mild and/or moderate asthma (see evidence table for question 3). However, it is uncertain, whether one can expect similar effects in patients with severe asthma. Effects of measuring exhaled NO were small for most outcomes of interest and estimated very imprecisely, precluding judgments about possible benefits.

Undesirable consequences

We found no important harms from measuring exhaled NO except for the increased use of resources (cost of testing).

Other considerations

The outcomes of the reviewed studies depended on the selection, number and range of FeNO cut-off values in the therapeutic strategy algorithms [263]. It cannot be excluded that using different cut-off points would lead to different outcomes.

Conclusions and research needs

There is insufficient evidence for using therapy guided by exhaled NO compared to therapy guided by symptoms alone in children and adults with severe asthma. More research of the utility of FeNO measurement to guide treatment in patients with different phenotypes of asthma is needed.

What others are saying

Global Strategy for Asthma Management and Prevention (GINA) does not make a recommendation about measurement of exhaled nitric oxide [168]. NHLBI National Asthma Education Prevention Program states that “other markers, such as sputum eosinophils and FeNO, are increasingly used in clinical research and will require further evaluation in adults and children before they can be recommended as a clinical tool for routine asthma management” [4]. The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines state only that “controlled studies using FeNO to target treatment have not specifically targeted adults or children with difficult asthma” [254]. The recent ATS guidelines state that “using regular FeNO measurements as the basis for adjusting the dose of ICS therapy have failed to show important benefits” and that “FeNO measurements cannot be recommended for this purpose” [264].

Recommendation 3

We suggest that clinicians do not use FeNO 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 FeNO.

B: Therapeutic Approaches

Question 4. Should a monoclonal anti-IgE antibody be used in patients with severe allergic asthma?*Summary of the evidence*

We found 3 systematic reviews [265-267] published in 2006 and 2011 that addressed that question. All 3 systematic reviews included studies that enrolled patients with moderate to severe asthma. One systematic review focused solely on quality of life [265]. We reviewed all original publications from those reviews and additional RCTs we identified [268-283]. We excluded 8 studies that were deemed by the Committee members not to be performed in patients with severe asthma [268, 272-274, 279, 280]. To inform this recommendation, we selected only those studies that explicitly recruited adult/adolescent patients [269, 275-277, 281, 283] and children [271, 278] with severe asthma. When possible, we combined their results in a meta-analysis (see evidence profile for question 13).

Studies included adolescent and adult patients (>12 years of age) with allergic asthma. All patients received inhaled corticosteroids (on average mean doses in the studies were 1000 µg/day [range: 570 to 2000]). Long-acting β-agonists (LABA) were used by 39 to 100% of patients. Use of oral corticosteroids was variable – from 100% in one study [276, 284] to 0% in two studies [276, 283]. Omalizumab was administered subcutaneously in a minimum dose of 0.016 mg/kg/IgE (IU/mL) every 4 weeks or 0.008 mg/kg/IgE (IU/mL) every 2 weeks. Median follow-up in the studies was 30 weeks (range: 16 to 48 weeks).

No trial in adults reported proportion of symptom-free days and/or nights, absence from school/work, need for ICU admission, need for intubation and ventilation, and resource use.

Two additional studies included children aged 6 to 20 years with moderate to severe asthma [271, 278]. Studies included children with asthma and IgE-mediated allergy to at least one perennial allergen. In one study 64% children had severe asthma [278] and in the other 73% had moderate to severe asthma [271]. Omalizumab was administered according to the dosing tables similarly to the studies in adults (i.e. 0.016 mg/kg/1 IU/ml of IgE). The overall quality of evidence was low to very low mainly due to the risk of bias and indirectness of the evidence.

No trial in children measured and/or reported daily dose of systemic corticosteroids, need for ICU admission, need for intubation and ventilation, emergency department visits, morning PEF and resource use.

Desirable consequences

Use of omalizumab in adult and adolescent patients, compared to placebo, improved quality of life (by at least 0.5 point in AQLQ, which is considered to be a minimal important difference) in 8 more patients out of 100 receiving omalizumab rather than placebo (65% vs. 57%; RR: 1.19, 95% CI: 1.08 to 1.30; 4 studies), improved asthma control (mean difference: 0.87 point in ACQ, 95% CI: 0.6 to 1.14; 1 study), and reduced the risk of exacerbation requiring the use of oral corticosteroids (RR: 0.73, 95% CI: 0.56 to 0.94). Omalizumab also reduced the risk of hospitalization for asthma, but the results are imprecise and do not exclude no benefit (RR: 0.52, 95% CI: 0.27 to 0.99; 1 study) (see evidence table A for question 13).

In children use of omalizumab reduced the need for corticosteroid courses (mean difference 14 fewer courses per 100 patients per 60 weeks; 95% CI: 5 to 21), increased the number of symptom-free days by 6–23 days per 60 weeks, reduced the risk of hospitalization (5 fewer children hospitalized per 100 treated for 60 weeks (95% CI: 1 to 6). The effect of omalizumab on quality of life, asthma control, and absence from school was negligible in those studies. However, the confidence in those estimates is low or very low (see evidence table B for question 13).

Undesirable consequences

Based on the case series of over 39,000 patients, postmarketing reports and data supplied by the manufacturer it has been estimated that use of omalizumab is associated with 0.09% risk of anaphylaxis [285, 286]. Omalizumab must be administered every 2 or 4 weeks in slow subcutaneous injection that requires an increased number of clinic visits. A cost effectiveness analysis based on INNOVATE trial estimated an incremental cost-effectiveness ratio (ICER) to be US\$ 49,839 (95% CI: 36,405 to 75,764) assuming 3.1% mortality rate [287]. ICER increased to US\$ 57,173 in sensitivity analysis with an assumption of 2% mortality, and US\$ 114,975

assuming no effect on mortality. The authors of a health technology assessment of omalizumab in children aged 6 to 11 estimated the most plausible ICER for the subgroup of children with severe asthma and at least 3 exacerbations in the previous year to be US\$ 129,739 per QALY gained [288].

Other considerations

Adults and children with severe asthma considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacologic treatment and appropriate allergen avoidance and a total serum IgE level of 30 to 1300 IU/mL.

Currently it is not possible to identify potential responders to omalizumab therapy. In a retrospective analysis, Hanania and colleagues showed that those with the highest levels of blood eosinophils, FeNO and serum periostin had the greatest reduction in exacerbation rates [275]. Additional research of phenotypes of patients with severe asthma may help to identify those patients most likely to benefit from anti-IgE therapy.

Conclusions and research needs

The net benefit from using omalizumab in patients with severe asthma is uncertain, because of inability to identify those who might respond to therapy and a high additional cost of treatment.

What others are saying

Global Strategy for Asthma Management and Prevention (GINA) states that “addition of anti-IgE treatment to other controller medications has been shown to improve control of allergic asthma when control has not been achieved on combinations of other controllers including high-doses of inhaled or oral corticosteroids” [168]. NHLBI National Asthma Education Prevention Program recommends that “omalizumab may be considered as adjunctive therapy in step 5 or 6 care for patients who have allergies and severe persistent asthma that is inadequately controlled with the combination of high-dose ICS and LABA” [4]. The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines do not make a specific

recommendation but only state that “omalizumab treatment should only be initiated in specialist centres with experience of evaluation and management of patients with severe and difficult asthma” [254]. The UK National Institute for Health and Clinical Excellence (NICE) recommends omalizumab as an option for the treatment of severe persistent IgE-mediated asthma as add-on therapy to optimised standard therapy (i.e. full trial of, and documented compliance with, high-dose inhaled corticosteroids and long-acting β -2 agonists in addition to leukotriene receptor antagonists, theophylline, oral corticosteroids and β -2 agonist tablets and smoking cessation) [289]. NICE does not recommend using omalizumab for the treatment of severe allergic asthma in children aged 6 to 11 years [290] based on a systematic review that found lower risk of asthma exacerbations in a subgroup of children with severe asthma only if they have experienced at least 3 clinically significant exacerbations in the previous year and estimated the cost of therapy to be substantially higher than that normally considered to be cost-effective use of UK NHS resources [288].

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 6 and above) with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance, if their total serum IgE level is 30 to 700 IU/mL (in 3 studies the range was wider – 30 to 1300 IU/mL). Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare 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?

Summary of the evidence

We found two systematic reviews [204, 291] published in 1998 and one non-systematic review with meta-analysis published in 1997 [292] that addressed this question. We assessed the methodological quality of the systematic reviews using the AMSTAR tool [293] and we chose the review by Davies and colleagues [204] as more rigorous and comprehensive. This review has been last updated in January 2004.

We identified one additional randomized trial of methotrexate in patients with asthma who required oral corticosteroids [294] that has been published since the search for the review by Davies and colleagues was done. We chose the review by Davies and colleagues [204] to prepare the evidence table and, when possible, we combined its results with the results of the additional RCT [294].

All studies included adult patients with corticosteroid dependent asthma defined by patients who have been taking daily corticosteroid dosage usually in excess of prednisolone 7.5 mg/day for at least 6-12 months. Dose of methotrexate is usually once weekly (usually 10 to 15 mg orally). Mean follow-up in the studies was 6 months (range: 13 to 48 weeks).

No trial measured or reported asthma symptoms, quality of life, absence from school/work, death, ICU admission, intubation and ventilation, hospitalization and resource use. In addition, corticosteroid adverse effects were not measured or reported.

No trial included children. We identified only three case series including altogether 20 children (3–16 years) with steroid dependent asthma treated with methotrexate [295-297]. We did not use that information for this recommendation since we assumed that even the indirect evidence from trials in adults would be of similar or higher quality.

Desirable consequences

There is possibly a small benefit from using methotrexate in reducing daily dose of oral corticosteroids (mean difference: 3.7 mg/day [95% CI: 0.2 to 5.4]).

Undesirable consequences

There is probably an increased risk of adverse effects, however, the evidence from the included trials is very imprecise and prone to bias. An increased risk of hepatic adverse effects (relative risk: 6.3 [95% CI: 3.0 to 12.7]) and gastrointestinal adverse effects (relative risk: 1.8 [95% CI: 1.1 to 2.8]) was observed, however, we were not able to determine their severity. The estimates of the risk of other adverse effects were very imprecise and do not exclude either harm or no effect (see evidence table for question 5).

Conclusions and research needs

The net benefit from using methotrexate in patients with severe asthma who require daily oral corticosteroids is uncertain. The benefits accrued from a reduction of daily maintenance dose of corticosteroid has to be balanced against adverse effects from long-term treatment with methotrexate. There is a need for rigorously designed and executed randomized trials of methotrexate in patients with severe asthma at step 5 that measure and properly report important patient outcomes including asthma control and adverse effects of both methotrexate and corticosteroids.

What others are saying

Global Strategy for Asthma Management and Prevention (GINA) concludes that the “small potential to reduce the impact of corticosteroid side-effects is probably insufficient to offset the adverse effects of methotrexate” [168]. NHLBI National Asthma Education and Prevention Program concludes that “current evidence does not support the use of methotrexate for the treatment of asthma” [4]. The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines state that a three month trial of methotrexate may be given (once other drug treatments have proved unsuccessful) in a centre with experience of using

that drug – its risks and benefits should be discussed with a patient and treatment effects should be carefully monitored) [254].

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 randomized trials is only available for adults. Because of the probable adverse effects of methotrexate and need for monitoring therapy we suggest that any use of methotrexate is limited to specialized centres and only in patients who require daily OCS. If a decision to use methotrexate is made, a chest x-ray, complete blood count with differential and platelets, liver function tests, serum creatinine and transfer factor to carbon monoxide (DLCO), are recommended prior to and after commencing therapy.

Question 6. Should macrolide antibiotics be used in patients with severe asthma?

Summary of the evidence

We found two systematic reviews [298, 299] that addressed this question. The review by Richeldi and colleagues was the more recent and comprehensive [299]. However, only two of the included studies enrolled patients with severe asthma [300, 301].

We identified six additional randomized trials of macrolide antibiotics in patients with asthma [302-307] that have been published since the search for the review by Richeldi and colleagues was done, of which two recruited patients with severe symptoms [305, 306].

We chose the four studies that enrolled patients with severe asthma to inform this recommendation [300, 301, 305, 306]. We extracted the data from the original publications and when possible combined them in meta-analysis.

Two studies included children [300, 306] and two included adults [301, 305]. These studies included patients with asthma that could be considered of moderate or high severity. Two studies included children and adults receiving systemic corticosteroids. Three of the studies included patients likely to have met Global Initiative for Asthma (GINA) [168] and the ATS [254] criteria for severe asthma. However, two of those studies were done before high potency inhaled corticosteroids and long-acting beta agonists were commonly available. The more recent study was done generally in children on high dose inhaled corticosteroids [306], but who had normal lung function and minimal symptoms. There were 3 macrolides studied. Troleandomycin, which was studied in the older studies [300, 301], was used at $\frac{1}{4}$ of the dose recommended for antibiotic therapy, while clarithromycin and azithromycin were used at standard antibiotic doses [305, 306], making a comparison difficult. Follow-up in the studies ranged from 8 weeks to 12 months.

No trial measured or reported admission to the intensive care unit, need for intubation and ventilation, absence from school/work, and resource use.

Desirable consequences

There is possibility of a benefit from using macrolide antibiotics in patients with severe asthma in terms of reducing daily dose of oral corticosteroids and reducing the need for hospitalization. However, the results were very imprecise and any estimates of the effects are very uncertain (see evidence table for question 12).

Undesirable consequences

Any estimate of potential adverse effects is very uncertain due to small number of patients and inadequate reporting (see evidence table for question 12). There is a risk of development of bacterial resistance to macrolides. Some of the macrolides (troleandomycin and clarithromycin) also increase systemic levels of CSs, explaining some of their effects.

Conclusions and research needs

The net benefit from using macrolide antibiotics in patients with severe asthma is uncertain.

There is a need for rigorously designed and executed randomized trials of macrolide antibiotics in patients with severe asthma that measure and properly report patient-important outcomes, including adverse effects. Available studies were done in patients with moderate to severe asthma, not further characterized. There is a need for studies of macrolide antibiotics in patients with severe asthma who have been carefully phenotyped, including age at onset, type of inflammation and clinical/historical presentation. Future research, if done, may have an important impact on this recommendation.

What others are saying

Recommendations on macrolide antibiotics are not currently included in either NAEPP [4] or GINA [168] guidelines.

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?

Summary of the evidence

We found one systematic review of azoles in patients with allergic bronchopulmonary aspergillosis (ABPA) associated with asthma [308]. We identified one additional trial of itraconazole in patients with asthma and fungal sensitization [309]. We identified two additional studies that enrolled patients with severe asthma and fungal sensitization or ABPA [310, 311]. One study included patients sensitized to *Trichophyton* sp. and other dermatophytes [311] and the Committee considered its results too indirect to inform this recommendation. The other study (n = 20) compared nebulized natamycin with saline inhalations in patients with ABPA [310]. We considered this latter study as not contributing information for this recommendation because we believed it used an obsolete treatment strategy. None of the trials enrolled children and none measured and/or reported absence from school or work and cost.

The overall quality of the available evidence (confidence in the estimated effects) across all outcomes of interest that were deemed to be critical for the recommendation is very low, mainly due to a very serious imprecision of many estimates and serious indirectness of some outcomes.

Desirable consequences

In patients with asthma and ABPA itraconazole reduced the rate of exacerbations requiring oral corticosteroids (mean difference: 0.9 exacerbations fewer per 15 patients in 4 months of observation (95% CI: 0.22 to 1.58). Antifungal treatment also reduced symptoms of asthma although the magnitude of an effect is difficult to establish since baseline symptom scores were not reported. In patients with asthma sensitized to fungi but without ABPA antifungal treatment improved quality of life (mean difference: 0.86 point on AQLQ higher; 95% CI: 0.15 to 1.57) with at least a minimal important change being likely achieved in larger proportion of patients (RR: 1.68; 95% CI: 0.88 to 3.19). Other potentially beneficial effects were not estimated precisely enough to exclude either an appreciable benefit, no effect, or even an appreciable harm.

Undesirable consequences

Based on available information, there was no difference between the groups receiving antifungal treatment, compared to placebo, in the risk of adverse effects but the limitations in their reporting preclude their meaningful interpretation. There is also a concern about hepatotoxicity and drug interactions with antifungal agents in patients receiving other medications but none of the studies commented about this outcome.

Other considerations

There are little data about geographical differences in prevalence of ABPA in patients with asthma but it appears low in North America and much of Europe. Based on the knowledge of the Committee members, clinical practice of using antifungal agents in patients with severe asthma and ABPA varies from not using them at all to using them in very selected patients – those with structural lung changes who failed conventional treatment with inhaled and oral corticosteroids. Those patients would usually receive an antifungal agent for 16 weeks. However, there is a substantial uncertainty whether this treatment is beneficial. Little is also known about relative efficacy of continuous administration compared to repeated courses of antifungal treatment.

Conclusions and research needs

The net benefit from using antifungal agents in patients with severe asthma and ABPA is uncertain. Outcomes were reported inconsistently and all estimates are very imprecise due to very small number of patients. Additional well designed and executed randomized trials that would measure and report all patient-important outcomes, including all adverse effects, in patients with severe asthma and ABPA, if done, will almost certainly influence this recommendation.

What others are saying

Neither Global Strategy for Asthma Management and Prevention (GINA) [168] nor the NHLBI National Asthma Education Prevention Program [4] and British Thoracic Society guidelines [169] make any recommendations about the use of antifungal agents in patients with 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 sensitization 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 sensitization) places a higher value on avoiding possible adverse effects, interactions of antifungal agents with other medications and increased use of resources, and a lower value on uncertain possible benefits.

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?

Summary of the evidence

We found one systematic review [312] and 2 narrative reviews [313, 314] of bronchial thermoplasty in patients with asthma. All included the same 3 randomized trials: a study in patients with asthma of variable severity [20], and 2 studies specifically including patients with severe asthma – one comparing thermoplasty with usual care [315] and one with a sham procedure [313].

We did not find any other RCTs of bronchial thermoplasty in patients with asthma. We identified additional 2 reports of the follow-up of patients from 2 included RCTs [316, 317], and 2 case series [318, 319] but we used only the evidence from RCTs to inform this recommendation. However, one of the follow-up studies of patients enrolled in an RCT provided results for treated group only [316] and the other reported results after 3 years of follow-up of 73% patients randomized to thermoplasty and 38% patients randomized to usual care alone [317]. We considered only the data after 3 years of observation of both intervention and control groups.

We could not rely on the available systematic review to summarize the evidence, since it did not summarize most of the outcomes of interest specified by our Committee. Instead, we extracted all relevant data from the primary studies and combined the results in meta-analysis, when appropriate. Studies included adult patients (mean age 40 years, 59% females) with moderate to severe asthma (range of mean values in the studies: pre-bronchodilator FEV₁ 63–80% predicted, daily dose of ICS equivalent to 1351–2333 mcg budesonide, oral corticosteroids 0–47% of patients [mean dose in those who received them 6–16 mg/d], proportion of symptom-free days 5–34%).

Bronchial thermoplasty was performed during three bronchoscopy procedures separated by at least 3 weeks. In two studies control subjects had three treatment visits at similar intervals to subjects in the bronchial-thermoplasty group. In one study the sham bronchoscopy procedures were performed that were identical to bronchial thermoplasty procedures except no radio-frequency energy was delivered. Most effects of bronchial thermoplasty are estimated

imprecisely due to small number of events for each of the outcomes and relatively small total number of patients in the trials.

Desirable consequences

Bronchial thermoplasty likely increases the proportion of patients who achieve at least minimal clinically important improvement in quality of life, but current estimates are imprecise and do not exclude no difference (RR: 1.23, 95% CI: 1.04–1.45; the proportion of people whose quality of life improved was very high in the sham therapy group [64%]). Thermoplasty also reduced number of days missed from school or work (mean difference 2.6 days fewer, 95% CI: 2.3–2.9).

Undesirable consequences

Bronchial thermoplasty increased the risk of hospitalization (RR: 2.3, 95% CI: 1.3–3.9). All 3 studies reported only “respiratory adverse effects”; no study reported overall adverse effects or overall serious adverse effects. Bronchial thermoplasty increased the risk of respiratory adverse effects in the initial treatment phase (RR: 1.13, 95% CI: 0.99–1.28 [number of patients with at least 1 adverse event]; rate ratio: 3.3, 95% CI: 2.4–4.5 [number of adverse events]), irrespective of their severity (see evidence table for question 8 in online supplement 2). Thermoplasty seemed to have little or no impact on the risk of adverse effects during subsequent period of time. One study reported all adverse effects together (RR: 0.88, 95% CI: 0.77–1.01) and two studies reported number of patients with at least one individual adverse event: dyspnea (RR: 0.90, 95% CI: 0.69–1.17), wheezing (RR: 1.13, 95% CI: 0.76–1.68), cough (RR: 0.98, 95% CI: 0.65–1.48], upper respiratory tract infection (RR: 2.24, 95% CI: 1.00–5.01] and lower respiratory tract infection (RR: 1.17, 95% CI: 0.25–5.52).

No study measured or reported comparative cost of treatments (use of resources). However, cost of a typical bronchoscopic investigation ranges from \$1,500 to \$4,000 and this procedure will require 3 outpatient bronchoscopic procedures using a disposable catheter costing \$2,500 for each procedure. The radiofrequency controller device, costs approximately \$59,000, similar to other generators, will also need to be purchased by the centre.

Conclusions and research needs

The net benefit from using thermoplasty in patients with severe asthma is uncertain. Reduction of days missed from work/school and likely improvement of quality of life needs to be balanced against higher risk of hospitalization and adverse effects as well as the cost associated with the procedure and treatment of adverse effects. Most available estimates of effects of bronchial thermoplasty are imprecise, hence, there is a need for additional well designed and executed randomized trials that would measure and report all patient-important outcomes, including all adverse effects. Assessment of long-term safety of bronchial thermoplasty is also needed. There is also need for a systematic analysis of comparative cost of thermoplasty versus other treatments, since the balance of benefits and downsides of bronchial thermoplasty in patients with severe asthma highly depends on the associated consumption of healthcare resources.

What others are saying

Global Strategy for Asthma Management and Prevention (GINA) states that “bronchial thermoplasty is a possible option” in adult patients whose asthma remains uncontrolled despite medical treatment and warns that “caution should be used in selecting patients for this procedure” [320]. British Thoracic Society guidelines for advanced diagnostic and therapeutic flexible bronchoscopy in adults state that the place of bronchial thermoplasty “in the treatment of asthma remains to be established and we recommend that treatment should be limited to a few specialist centres in carefully selected patients” [169]. The NHLBI National Asthma Education Prevention Program [4] do not make a recommendation about the use of bronchial thermoplasty in patients with 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 utilizing an invasive physical intervention are unknown. Specifically-designed studies are needed to define its effects on relevant objective primary outcomes such as exacerbation rates, and on long-term effects on lung function. Studies are also needed to better understand the phenotypes of responding patients, its effects in patients with severe obstructive asthma ($FEV_1 < 60\%$ 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 personalized 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 responder to therapy remains problematic. More recent experimental biologic approaches targeting specific asthmatic inflammatory pathways have reported positive results and are beginning to help define immuno-inflammatory phenotypes/endotypes (Tables 4 & 5).

While the anti-IL5 antibody, mepolizumab, was not beneficial in unselected adult patients with moderate asthma [321], when studied in severe asthma patients with persistent sputum eosinophilia, two anti-IL-5 antibodies, mepolizumab and reslizumab, have been shown to decrease exacerbations, OCS use as well as improve symptoms and lung function to varying degrees [68, 69, 187]. 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 [67].

An antibody to IL-13, lebrikizumab, improved FEV₁ in moderately-severe asthmatic adults, without affecting exacerbations and asthma symptoms [70]. In a post-hoc analysis, this antibody improved prebronchodilator FEV₁ in the group with evidence for Th2 inflammation as measured by elevated serum periostin levels, a proposed surrogate marker of Th2 activity or FeNO [70, 322]. 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 [71]. A study in moderate-to-severe asthma of a monoclonal antibody to the IL-4R α , that blocks both IL-4 and IL-13, was negative [323]. Whether prior biologic 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 asthmatic adults [110], 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 biologic 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 (c-kit) and platelet-derived growth factor improved asthma control in adults when compared to placebo in the face of a reducing dose of oral CS; however, there was no effect on lung function [324]. Daclizumab, a humanised IgG1 monoclonal antibody against the IL-2R α chain of activated lymphocytes improved FEV₁ and asthma control in moderate-to-severe asthmatic adults inadequately controlled on ICS [325]. 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 [326]. 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 CS and bronchodilators, and other controllers recommended for moderate-to-

severe asthma. The addition of the first targeted biologic 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 biologic 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 biologic agents and of emerging inflammatory and molecular phenotypes will generate and lead to safe and effective biomarker-driven approaches to severe asthma therapy.

Figure Legends

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

Figure 2. Potential immune-inflammatory and cellular interactions contributing to the pathogenesis of phenotypes of asthma. Abbreviations: CXCL8: CXC chemokine ligand 8; CXCL9-11: CXC chemokine ligand 9-11; CCL24/26: CC chemokine ligand 24/26; DUOX 2: Dual oxidase 2; EPO: Eosinophil peroxidase; IFN γ : Interferon γ ; IgE: Immunoglobulin E; IL-4: interleukin 4; IL-5: interleukin 5; IL-13: Interleukin 13; iNOS: inducible nitric oxide synthase; MUC5AC: Mucin 5AC; NO: Nitric oxide; PGD₂: Prostaglandin D₂; TGF β : Transforming growth factor- β ; Th1: T-helper type 1 cell; Th2: T-helper type 2 cell; TSLP: Thymic stromal lymphopoietin.

Box 1. Definition of severe asthma for patients 6 years old and above

Asthma which requires treatment with guidelines suggested medications for GINA Stages 4-6 asthma (high dose inhaled CS* and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for $\geq 50\%$ of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy.

- I. *Uncontrolled* asthma defined as at least one of the following:
 1. *Poor symptom control*: ACQ consistently >1.5 , ACT ≤ 19 (or “not well controlled” by NAEPP/GINA guidelines)
 2. *Frequent severe exacerbations*: 2 or more bursts of systemic CSs (>3 days each) in the previous year
 3. *Serious exacerbations*: at least one hospitalization, 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)
- II. *Controlled* asthma that worsens on tapering of these high doses of inhaled CS or systemic CS (or additional biologics)

* The definition of High dose ICS is age-specific (See Table 2)

Abbreviations:

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; CS: Corticosteroids; GINA: Global Initiative for Asthma; LABA: long-acting β_2 -agonists; NAEPP National Asthma Education and Prevention Program.

Box 2.

Priority questions on phenotypes

1. The validation of the eosinophilic vs non-eosinophilic, and of the Th2 predominant vs 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 – can imaging be used to non-invasively address these issues?
6. Is there an altered microbiome and virobiome in the airways of severe asthma?

Box 3. Co-Morbidities 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 apnea
7. Hyperventilation syndrome
8. Hormonal influences: Premenstrual, menarche, menopause, thyroid disorders
9. Gastroesophageal reflux disease (symptomatic)
10. Drugs: Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β -adrenergic blockers, angiotensin converting enzyme inhibitors (ACE-inhibitors)

Table 1. 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.	Recognize 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.

Table 2. Definition of high daily dose of various inhaled corticosteroids in relation to patient's 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)	>1000 (DPI or CFC MDI) >500 (HFA MDI)
Budesonide	800 (MDI or DPI)	>800 (MDI or DPI)
Ciclesonide	>160 (HFA MDI)	>320 (HFA MDI)
Fluticasone propionate	500 (HFA MDI or DPI)	>500 (HFA MDI or DPI)
Mometasone furoate	500 (DPI)	>800 (DPI)
Triamcinolone acetonide	1200	>2000

CFC: Chlorofluorocarbon; DPI: Dry powder inhaler; HFA: Hydrofluoroalkanes; MDI: Metered-dose inhaler.

Notes: 1) Designation of low, medium and high doses is provided from manufacturers' recommendations where possible.

2) As CFC preparations are taken from the market, medication inserts for HFA preparations should be carefully reviewed by the clinician for the equivalent correct dosage.

Table 3. Diseases which can masquerade as severe asthma

<i>Children</i>
Dysfunctional breathing / Vocal cord dysfunction (VCD)
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 tumor
Mediastinal mass / Enlarged lymph node
Congenital heart disease
Interstitial lung disease
Connective tissue disease
<i>Adults</i>
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, ACE-I)
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

TABLE 4: Placebo-controlled studies of new treatments in severe asthma

Author	Severity/n	Design	Treatment	Outcomes	Summary Results
Wenzel et al, 2009 [110]	Severe/309	R, db, pc, p	Golimumab, anti TNF α , 24 w	FEV ₁ , exacerbations AQLQ, PEFR	FEV ₁ unchanged, no reduction in exacerbations, AQLQ, PEFR. Adverse profile side-effects
Pavord et al, 2012 [67]	Severe, with 2 or > exacerbations in past year/621	R,db,pc,p	Mepolizumab (75, 250 or 750 mg infusions at 4 weeks), anti-IL-5, 52w	Rate of exacerbations	All doses reduced exacerbations by 39 to 52%. No effect on ACQ, AQLQ or FEV ₁ .
Haldar et al, 2009 [187]	Severe/61	R, db, pc, p	Mepolizumab, anti-IL5, 50w	Exacerbations Symptoms, FEV ₁ , AQLQ, AHR, sputum and blood eos	Reduced exacerbations Improved AQLQ, reduced eos
Nair et al, 2009 [69]	Severe/20	R,db,pc,p	Mepolizumab, anti-IL5, 50w	Exacerbations, oral steroid reduction	Reduced exacerbations, eosinophils and OCS dose
Kips et al, 2003 [327]	Severe/26	R, db, pc, p	SCH55700, anti-IL-5, 12 w	Sputum and blood eos, symptoms, FEV ₁	Reduced blood sputum eos No other significant outcomes
Castro et al 2011, [68]	Poorly-controlled on high-dose inhaled CS/53	R, db, pc, p	Reslizumab, anti-IL-5, 12 w	ACQ FEV ₁ Sputum eos	Improved ACQ score Reduction in sputum eosinophils Improved FEV ₁
Corren et al, 2010 [323]	Moderate-severe/294	R, db, pc, p	AMG317, anti-IL-4R α antibody, blocks IL-4 and IL-13, 12 weeks	ACQ scores, exacerbations	No effect on ACQ or exacerbations
Corren et al, 2011 [70]	Moderate-severe/219	R, db, pc, p	Lebrikizumab, anti-IL13 antibody, 24 weeks	Change in prebronchodilator FEV ₁	Improved FEV ₁ , compared to placebo, with greatest changes in high levels of periostin or FeNO group (post hoc analyses). No effect on ACQ5 or diary measures. Exacerbations were 60% lower in treated group with high Th2.
Piper et al,	Moderate-to-	R, db, pc,	Tralokinumab	Change from	No change in ACQ-

2012 [71]	severe/194	p	(150, 300, or 600 mg), IL-13 neutralising monoclonal antibody, 3 months	baseline in ACQ-6 at week 13	6 at 13 weeks. FEV ₁ increase of 0.21L versus 0.06L 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 et al, 2009 [324]	Severe, CS-dependent/44	R, db, pc, p	Masitinib (3, 4.5 and 6 mg/kg/day), c-kit & PDGFR tyrosine kinase inhibitor, 16 w	oral CS dose ACQ, FEV ₁	No difference in OCS dose. ACQ improved, no difference in FEV ₁
Busse et al, 2008[325]	Moderate to severe/115	R, db, pc, p	Daclizumab, IL-2R antagonist, 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 et al, 2012 [326]	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; AQLQ: Asthma quality of life questionnaire; AHR: Airway hyperresponsiveness; ACQ: Asthma Control Questionnaire; ED: Emergency Department; eos: eosinophil; FeNO: level of nitric oxide in exhaled breath; neu: neutrophil; OCS: Oral corticosteroids; SABA: Short-acting β-agonist; yr: year; w: week.

Table 5. Potential phenotype-targeted therapies in severe asthma¹.

Characteristic	Associations	Specifically-targeted treatments
Severe allergic asthma	Blood and sputum eosinophils High serum IgE High FeNO	Anti-IgE (adults & children) Anti-IL4/IL-13 Anti-IL4 Receptor
Eosinophilic asthma	Blood and sputum eosinophils Recurrent exacerbations High FeNO	Anti-IL5, Anti-IL-4/-13 Anti-IL-4Receptor
Neutrophilic asthma ²	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-IL13 Bronchial thermoplasty
Recurrent exacerbations	Sputum eosinophils in sputum Reduced response to ICS ± OCS	Anti-IL5 Anti-IgE (adults and children)
Corticosteroid insensitivity	Increased neutrophils in sputum ²	p38 MAPK inhibitors Theophylline (adults and children) Macrolides (adults and children)

¹ Unless otherwise stated, these potential treatments apply to adults

² Note: neutrophilic asthma is rare in children

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