Key points

- Not all patients with "difficult-to-control" asthma have "severe asthma". Many of them have either an incorrect diagnosis, or mild–moderate asthma with unrecognised aggravating factors, or are non-compliant with prescribed therapy.
- For a diagnosis of severe asthma, it is necessary to confirm the diagnosis of asthma, to evaluate and treat endogenous and exogenous aggravating factors, and to closely follow the patient for ≥6 months.
- Severe asthma is a heterogeneous condition with different phenotypes. Defining clinical phenotypes is necessary to improve understanding of underlying mechanisms, to help guide current treatment and to provide clues for novel therapeutic interventions.
- Despite intensive multi-drug treatment with high-dose inhaled and oral corticosteroids, many patients with severe asthma remain uncontrolled. There is an urgent need for new, more-effective treatments.

Severe asthma

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Educational aims

- To help the reader distinguish between "difficult-to-control", "refractory" and "severe" asthma.
- To discuss the initial approach to and assessment of a patient with difficult-to-control asthma.
- To inform the reader how to recognise different clinical phenotypes of severe asthma.
- To outline management strategies and discuss treatment modalities.

Summary

"Severe asthma" refers to asthma that remains difficult to control despite intensive multi-drug therapy, extensive assessment and management of comorbidity, and long-term observation by an asthma specialist.
The three main clinical phenotypes of severe asthma include asthma with frequent severe exacerbations, asthma with chronic airflow limitation, and steroid-resistant asthma.
Many patients with severe asthma are oral-steroid dependent. Classical steroid-sparing drugs (gold, methotrexate, cyclosporin) are only weakly effective and have unacceptable side-effects. Monoclonal antibodies against immunoglobulin (Ig)E and tumour necrosis factor (TNF)-α have shown clinical benefit in subgroups of patients with severe asthma, and large studies are under way to confirm these promising findings.

Asthma is a chronic inflammatory disorder of the airways, characterised by episodic dyspnoea, cough and wheezing, associated with hyperresponsiveness of the airways to a variety of environmental stimuli. The majority of patients with asthma have mild or moderate disease, and can achieve reasonable asthma control by the regular use of anti-inflammatory and bronchodilating medications. There remains, however, a small subset of asthmatic patients who remain symptomatic and suffer from frequent exacerbations or persistent airflow limitation despite the use of maximal doses of inhaled medication.

These patients, often labelled with "severe", "difficult-to-treat", "therapy-resistant" or "steroid-dependent" asthma, are responsible for a disproportionate share of the morbidity and healthcare costs associated with the disease. The exact prevalence of these patients who apparently are unresponsive to maximum recommended therapy is not known, but may fluctuate around 5–8% of the total asthma population, depending on the definition.

A European Respiratory Society Task Force adopted the term "difficult" asthma in 1999, which was defined as [1]:

"asthma, poorly controlled in terms of chronic symptoms, with episodic exacerbations, persistent and variable airway obstruction and continued requirement for short-acting β-agonists and high doses of inhaled corticosteroids".

In 2000, the American Thoracic Society (ATS) defined "refractory asthma" by one or two major and two or more minor criteria, based on medication requirement, asthma

Table 1 Diagnostic criteria for refractory asthma

Major criteria
Use of oral corticosteroids ≥50% of the time
Continuous use of high-dose inhaled corticosteroids (≥1,200 g·day^{-1} beclomethasone or equivalent)
Minor criteria
Requirement for daily treatment with long-acting β-agonists, theophylline or leukotriene antagonists
Daily asthma symptoms requiring rescue medication
Persistent airway obstruction (FEV_1 <80% predicted); diurnal PEF variability 20%
≥1 urgent care visits for asthma in the last year
≥3 courses of oral steroid bursts in the last year
Prompt deterioration with ≤25% reduction in oral or inhaled corticosteroid dose
Near fatal asthma event in the past

FEV_1: forced expiratory volume in one second. At least one major and two or more minor criteria are required for the diagnosis of refractory asthma. Table modified from [2].

symptoms, frequency of asthma exacerbations and degree of airflow limitation (table 1) [2].

The National Heart Lung and Blood Institute/World Health Organization definition (updated 2005 version; [3]) included patients requiring oral corticosteroids to remain under control, as well as patients treated with moderate doses of inhaled corticosteroids combined with long-acting bronchodilators who remained uncontrolled and had reduced lung function. A workshop on severe asthma in Paris 2005 [3] proposed to reserve the term severe asthma for those patients who have refractory asthma [2] and remain difficult to control despite extensive re-evaluation of diagnosis, management and observation by an asthma specialist for at least 6 months.

The latter definition of severe asthma is probably the most appropriate to indicate patients who are eligible for novel anti-asthma therapies.

Table 2 Alternative diagnoses in difficult-to-control asthma in adults

COPD
Bronchiectasis
Congestive heart failure
Central airway obstruction by:
Foreign body
Tumour (benign/malign)
Sarcoidosis
Tracheobronchomalacia
Cystic fibrosis
Recurrent pulmonary embolism
Obstructive bronchiolitis
Recurrent aspiration
Vocal cord dysfunction
Allergic bronchopulmonary aspergillosis
Churg–Strauss syndrome

COPD: chronic obstructive pulmonary disease.

How to approach the patient with difficult-to-control asthma

When confronted with a patient with difficult-to-control asthma for the first time, it is important to investigate the factors that could be preventing a normal response to asthma medication. These factors include: incorrect diagnosis; continuing exposure to sensitising agents; unrecognised aggravating comorbidities; and non-compliance with therapy.

Incorrect diagnosis

The diagnosis of severe asthma is based on a firm diagnosis of asthma in the first place. Symptoms of dyspnoea are subjective, and wheeze on auscultation may be associated with many other conditions. Therefore, the diagnosis must be confirmed by objective evidence of variable airflow obstruction or airway hyperresponsiveness.

Patients' specific history and past medical evaluation, especially in relation to age of onset of the disease, atopy, family history, concurrent rhinosinusitis, smoking habits and occupational exposure, may be helpful in verifying or questioning the diagnosis of asthma. In case of doubt, alternative diagnoses should be excluded by performing additional investigations (table 2).

Inspiratory and expiratory flow–volume loops and laryngoscopy may be helpful in assessing potential upper airway abnormalities that masquerade as asthma, in particular vocal cord dysfunction. An abnormal chest radiograph may point towards hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis or Churg–Strauss syndrome. An elevated D-dimer is suggestive of recurrent pulmonary embolism, and fibreoptic bronchoscopy may reveal obstruction of the central airways by endobronchial lesions or external compression. A summary of investigations to be performed in patients with difficult-to-control asthma is given in tables 3 and 4.

Continuing exposure to sensitising agents

After the diagnosis of asthma is confirmed, numerous factors can contribute to lack of control of the disease. Ongoing (low-dose) allergen exposure at home or at work can aggravate the

Table 3 History and physical examination of patients with difficult-to-control asthma

Medical history
History of asthma development
Age of asthma onset
Atopic syndrome and family history of asthma
Management of disease and response to treatment
Smoking history
Severity of disease
Severe asthma exacerbations and hospitalisation in past year
Admissions to asthma centres ever
Number of ICU admissions ever
Exogenous aggravating factors
Exposure to allergens, occupational agents, chemicals
Use of aspirin, NSAIDs, β-blockers, ACE inhibitors, oestrogens
Influence of foods or food additives (nitrite, sulphite)
Endogenous aggravating factors
Rhinosinusitis or previous surgery for nasal polyps
Gastro-oesophageal reflux
History of psychiatric disease
Obstructive sleep apnoea
Influence of menstruation
Miscellaneous
Adherence with medications
Adverse effects of treatment
Psychosocial circumstances
Physical examination (specific points of attention)
Body mass index
Evidence of comorbidities (e.g. nasal polyps)
Evidence of alternative diagnoses (e.g. cardiac failure)
Evidence of adverse effects of treatment

ICU: intensive care unit; NSAID: non-steroidal anti-inflammatory drugs; ACE: angiotensin-converting enzyme.

inflammatory process in the airways, thereby increasing the severity of asthma. Hidden sensitising agents should actively be looked for and adequately addressed. A home visit by a community asthma nurse or a site visit at the workplace may be very informative in this respect. Once the relationship with the sensitising agent has been established, the patient must be encouraged to take avoidance measures to prevent worsening of the asthma condition.

Smoking is another important factor that may contribute to the lack of adequate response to inhaled corticosteroid treatment. Asthmatic smokers have a blunted response to corticosteroids, have more severe and more frequent exacerbations, and a more rapid decline in lung function. Smoking cessation programmes are, therefore, a critical aspect of severe asthma management.

Table 4 Laboratory investigations and diagnostic tests for patients with difficult-to-control asthma

Diagnostic tests
Peripheral blood
Erythrocyte sedimentation rate
Full blood count (eosinophils)
Total serum IgE
Specific IgE to common and less common allergens
Free-T4, thyroid-stimulating hormone
Lung function
Spirometry (pre- and post-bronchodilator)
Lung volumes
Arterial blood gases
Histamine challenge test
Radiology
Chest radiography
Sinus CT scan
Additional tests for comorbidities and alternative diagnoses
Nasal endoscopy
24-hour oesophageal pH monitoring or trial with proton pump inhibitors
Polysomnography
Bronchoscopy
High-resolution CT scan of the thorax
D-dimer
ANCA
IgG against Aspergillus fumigatus

CT: computed tomography; ANCA: antineutrophilic cytoplasmic antibody.

Unrecognised aggravating comorbidities

Several comorbidities and aggravating factors may contribute to the severity of asthma. Comorbidities include: chronic rhinosinusitis; recurrent respiratory tract infections; gastro-oesophageal reflux; obstructive sleep apnoea; psychological dysfunctioning; and obesity.

Chronic sinusitis has been suggested to play a causal role in difficult-to-control asthma. Sinonasal inflammation can result in worsening of lower airway disease, potentially induced by post-nasal drip, a nasobronchial reflex, or inflammatory mediators. Proper medical and surgical management of sinusitis in the asthmatic patient has been shown to result in both improved sinonasal and asthmatic symptoms, with fewer physician visits and a decreased need for medication in several patients.

Respiratory infections, in particular those that are viral in origin, may be responsible for frequent asthma exacerbations. However, in

addition, bacteria, including atypical, have been linked to more severe asthma and asthma exacerbations, in particular when sinusitis is present.

Pathological gastro-oesophageal reflux is considered a potential trigger of asthma, even in the absence of oesophageal symptoms. The mechanisms of acid-induced bronchoconstriction include a vagally mediated reflex, increased airway responsiveness and microaspiration of gastric content. Although there is some debate as to whether treatment for gastro-oesophageal reflux results in an overall improvement in asthma, most authors agree that subgroups of patients may gain benefit.

Snoring and obstructive sleep apnoea syndrome have been suggested to trigger nocturnal asthma attacks and, indeed, improvement of asthma control after nasal continuous positive airway pressure therapy has been demonstrated in some unstable asthmatic patients.

Psychosocial factors have been shown to be linked with poor asthma control and severe asthma attacks. Psychiatric problems in asthmatic patients are associated with significantly more hospitalisations, emergency visits and unscheduled visits to healthcare providers. Psychological dysfunctioning is also known to be associated with poor compliance with therapy, which is probably an important factor contributing to loss of asthma control.

Obesity has also been implicated as an aggravating factor in severe asthma. Obese patients have more severe asthma symptoms, a greater number of emergency visits and more days when wheezing is present. Several studies show that these patients do not exhibit more impaired lung function or more intense airway inflammation, but have a high prevalence of the above-mentioned comorbid factors, in particular gastro-oesophageal reflux, sleep apnoea syndrome and psychopathology.

Recognition of comorbidities is an essential component of the assessment of the severe asthmatic, although the impact of treating these comorbid conditions on asthma outcomes is sometimes disappointing.

Non-compliance with therapy

Compliance with therapy is often sub-optimal in asthma. One of the reasons is probably that if satisfactory control is achieved, symptoms stop acting as a reminder to take treatment. Indeed, several studies suggest that adherence is somewhat better in more severe disease. Compliance is an important issue, but how to assess and manage poor compliance remains a major challenge.

Predictors of poor compliance include psychological problems, missed appointments, complexity of treatment and lack of insight into illness. Structured asthma management plans have been shown to greatly enhance compliance: <20% of patients who get a prescription adhere to treatment, while ~70% of patients are compliant with therapy when given a structured asthma education and management plan [4].

By using a structured diagnostic protocol, one or more potential causes of lack of control will be detected in the vast majority of patients with difficult-to-control asthma. In patients in whom none of the above-mentioned aggravating factors can be detected or who do not improve after management of the identified factors, the possibility of a incorrect diagnosis should be reconsidered, which might require additional specific investigations (table 4). If the diagnosis remains consistent with severe asthma, an evaluation with a trial of systemic corticosteroid therapy (preferably intravenous or intramuscular to circumvent the possibility of non-compliance) may be useful to assess the best attainable lung function, and to create the optimal condition for inhaled anti-inflammatory treatment to penetrate deep into the airways and the paranasal sinuses. Needless to say that maximum attention should be paid to the inhalation technique.

Outcomes to assess and monitor severe asthma

Although spirometric measures are fundamental outcomes in the diagnosis and follow-up of patients with mild and moderate asthma, they are of less value in severe asthma. This is because a large proportion of patients with severe asthma will have developed fixed airflow limitation with loss of reversibility. Measures of airway inflammation and patient-oriented outcomes might be more important in assessing and monitoring disease severity in these patients.

The type and degree of airway inflammation can be estimated by indirect measures, such as exhaled nitric oxide and inflammatory cells in induced sputum, and quantitatively assessed in mucosal biopsies obtained by fibreoptic bronchoscopy.

Patient-oriented outcomes, including health status, disease control and quality of life, can be assessed by objective and validated questionnaires. Questionnaires for the assessment of composite health status and asthma control have recently become available.

Phenotyping patients with severe asthma

Severe asthma is not a homogenous entity, but a multifaceted condition that can be subdivided into different subtypes [5]. Specific phenotyping of severe asthma has become an important area of research over the last decade. The value of phenotyping is to guide current therapy, increase understanding of the pathophysiology and natural history of the disease, and link specific phenotypes to genotypes in order to develop targeted treatments.

Phenotyping can be done on the basis of:

- asthma severity (mild, moderate, severe or near-fatal asthma);
- asthma history (childhood- or adult-onset asthma);
- the pattern of bronchoconstriction (brittle or stable asthma);
- the presence or absence of atopy (atopic or intrinsic asthma);
- the major trigger factor (gastric asthma, aspirin-sensitive asthma, hormonal asthma);
- the type of airway inflammation (predominantly eosinophilic or neutrophilic); or the response to treatment (steroid-sensitive, steroid-dependent or steroid-resistant asthma).

From a clinical point of view, three categories of severely asthmatic patients seem to be of particular importance: 1) those with frequent severe asthma exacerbations; 2) those with fixed airway obstruction; and 3) those with oral-steroid dependency. Together, these three categories encompass the vast majority of patients referred to the pulmonologist with difficult-to-control asthma.

Refractory asthma with frequent severe exacerbations

Many patients with severe asthma suffer from recurrent severe exacerbations despite apparently appropriate therapy. Severe exacerbations of asthma impose significant healthcare problems, both for the individual and for society.

Factors known to precipitate asthma exacerbations are respiratory viral infections, atypical bacterial infections (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*), exposure to allergens, occupational agents or environmental pollutants, and discontinuation of regular corticosteroid therapy. In addition, comorbid factors, including chronic rhinosinusitis, gastric reflux, obstructive sleep apnoea syndrome and psychological dysfunctioning, may be associated with recurrent exacerbations (figure 1) [6].

Psychological dysfunctioning is known to be associated with poor compliance with therapy, which is an important factor contributing to loss of asthma control. Not surprisingly, psychiatric problems in asthmatic patients are associated with significantly more hospitalisations, emergency visits and unscheduled visits to healthcare providers.

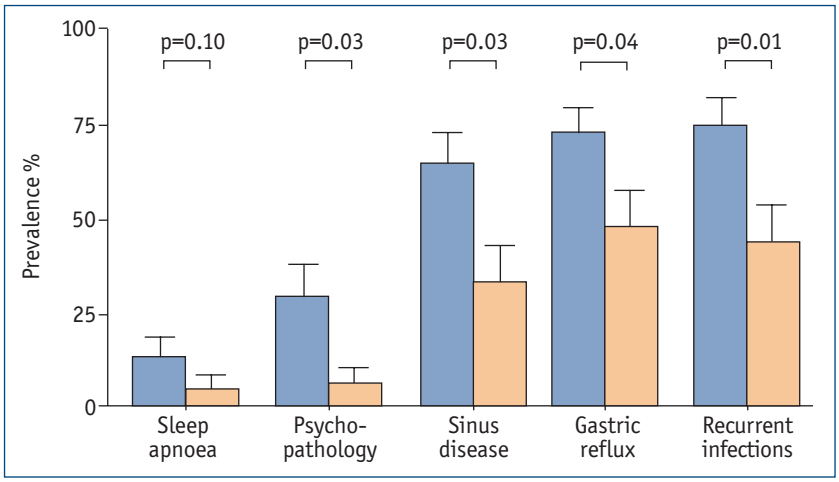


Figure 1
Comorbid factors in patients with (blue) and without (orange) frequent severe asthma exacerbations. Figure reproduced with permission from [6].

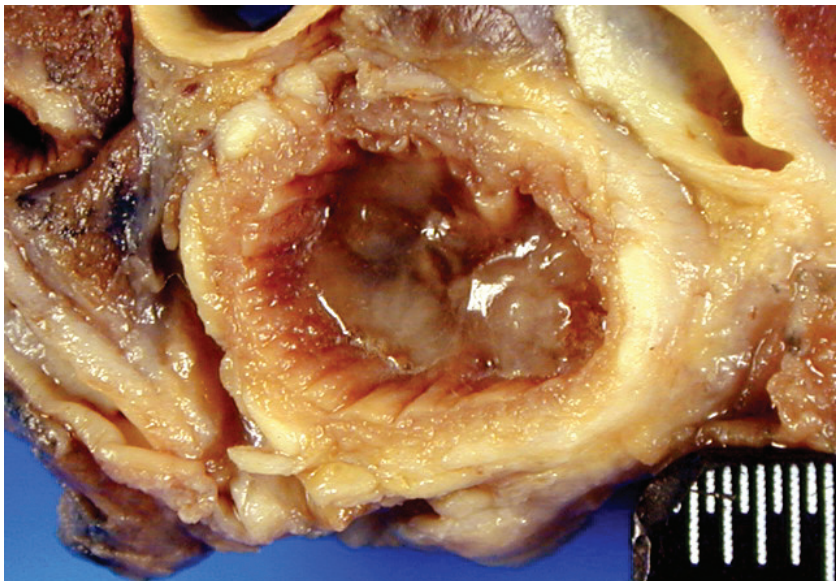


Figure 2
Macroscopic appearance of an airway filled with tenacious mucus from a patient who died during an asthma exacerbation. Figure reproduced with permission from T. Mauad (Dept of Pathology, Sao Paulo University Medical School, Sao Paulo, Brazil).

Fatal and near-fatal asthma represent the most extreme manifestations of severe asthma exacerbations. Hospitalisation and emergency visits during the previous year and psychosocial factors seem to be most important risk factors. Lower socio-economic status, less access to medical care, ethnic origin, depression, denial, psychiatric problems and illicit drug abuse are all recognised determinants for a lethal exacerbation.

The pathophysiological features associated with frequent or (near-) fatal exacerbations in asthma are largely unknown, but studies suggest that these patients have a decreased perception of dyspnoea, increased airway responsiveness, and evidence of air trapping and early airway closure.

Pathological changes associated with fatal asthma are occlusion of the airways with tenacious sputum plugs (figure 2), infiltration of the airway mucosa with predominantly eosinophils and neutrophils, hyperplasia of goblet cells, thickening of the reticular layer, and hypertrophy of bronchial smooth muscle and mucosal glands.

The pathological changes in the lungs of patients who have died from asthma differ depending on whether their asthma attacks were sudden or of a more prolonged duration. Short-course cases have more smooth muscle shortening, higher blood levels of salbutamol and higher ratios of neutrophils to eosinophils when compared with long-course cases, who have more mucus in the lumen.

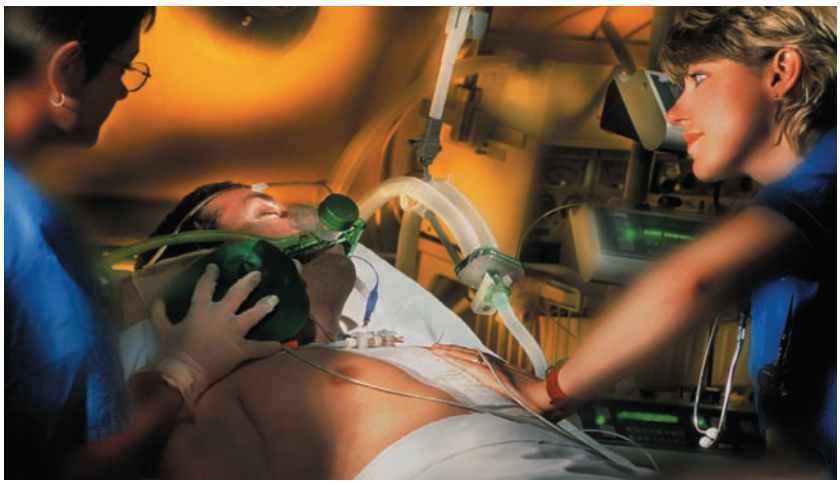
The lungs of patients who have died from asthma do not deflate, suggesting extensive air trapping. Air trapping, which is the result of early airway closure during expiration is likely to facilitate excessive airway narrowing and is, therefore, considered to be one of the key factors in the pathogenesis of fatal asthma attacks.

Within the spectrum of recurrent severe asthma exacerbations, the term "brittle asthma" has been proposed to describe two clinical phenotypes: type I and II brittle asthma. Type I brittle asthma refers to asthma that remains unstable, with "chaotic" variation in peak expiratory flow despite considerable medical therapy. The patient with type 1 brittle asthma most uniformly has gastro-oesophageal reflux, possibly as a consequence of high-dose anti-asthma medication. Brittle asthma type II is a rare condition, characterised by sudden life-threatening attacks, against a background of normal lung function and well-controlled disease. Proposed trigger factors for sudden attacks include IgE- and non-IgE-mediated drug reactions, anaphylactic food reactions, and exposure to high doses of an allergen or occupational sensitiser.

In some patients, severe exacerbations seem to be exclusively related to specific triggers or circumstances, as in premenstrual asthma and aspirin-induced asthma attacks. Although premenstrual worsening of asthma symptoms is common (in up to 40% of all asthmatic females), severe premenstrual exacerbations are rare. Such exacerbations are characterised by an impaired response to systemic corticosteroids and inhaled β_2-agonists, probably due to decreased receptor density during the luteal phase. Management of severe premenstrual exacerbations is inconclusive. Case reports in the literature have described beneficial effects of oestradiol, oral contraceptive pills and gonadotropin-releasing analogues.

Aspirin or non-steroidal anti-inflammatory drugs have been implicated as trigger factors of sudden asthma attacks, occasionally resulting in respiratory insufficiency requiring mechanical

Figure 3
Mechanical ventilation in a patient with a near-fatal attack of asthma.



ventilation (figure 3). The airways of these patients are typically empty of sputum plugs, suggesting a predominance of extreme smooth muscle spasm rather than mucosal inflammation. The pathophysiological mechanisms of aspirin-induced asthma are not fully understood, but presumably related to disproportionally increased sensitivity to cysteinyl leukotrienes or excessive release of these mediators. Clinical studies indicate that inhibition of cyclooxygenase-1 and not cyclooxygenase-2 by aspirin precipitates asthmatic attacks. This is confirmed by the finding that aspirin-sensitive patients can tolerate the cyclooxygenase-2-selective analgesic drug celecoxib.

Refractory asthma with chronic persistent airflow limitation

A different pattern of severe refractory asthma is represented by patients with irreversible airflow limitation. Some 23–49% of adult patients with severe asthma have been shown to develop persistent airflow limitation, despite apparently appropriate therapy and in the absence of other risk factors, such as smoking and environmental insults. Potential risk factors of an accelerated decline in forced expiratory volume in one second (FEV_1) in asthma include increased airway hyperresponsiveness, bronchodilator reversibility and refractory eosinophilic airway inflammation. In addition, environmental tobacco-smoke exposure, severity of childhood asthma and a subnormal lung function in childhood have all been shown to be related to a low level of FEV_1 in adult life. Reviewing the evidence from several studies, it appears that patients with adult-onset, non-atopic ("intrinsic") asthma are at particular risk for an increased decline in lung function, possibly related to chronic or recurrent infections with specific respiratory pathogens.

The nature of persistent airflow limitation in asthma is still unknown, but is presumed to be due, at least in part, to structural changes in the airways, so-called "airway remodelling". Remodelling processes in asthmatic airways include thickening of the airway wall due to subepithelial fibrosis, hypertrophy or stiffening of airway smooth muscle, and hyperplasia of mucous glands and goblet cells. In addition, oedema, vascular dilatation and increased numbers of blood vessels may contribute to the thickening of the airway wall. The mechanisms of these changes and the contribution of each of these features to symptoms, abnormal physiology and natural history of the asthmatic patient are still unclear.

The pathology of remodelling and persistent airflow obstruction in asthma differs from that seen in chronic obstructive pulmonary disease (COPD), and is characterised by higher numbers of eosinophils in peripheral blood and airway walls, lower numbers of neutrophils, higher CD4+/CD8+ ratio of T-cells and a thicker reticular layer of the epithelial basement membrane [7]. Fibroblast accumulation and airway smooth muscle hypertrophy in proximal airways is another characteristic of chronic airflow obstruction in asthma. Airway fibroblasts from severe asthmatics seem to be of the synthetic phenotype, with altered production capabilities, whereas airway smooth muscle hypertrophy may be related to the action of Cys-leukotrienes acting in synergy with interleukin-13 and interferon-γ. The importance of the epithelial mesenchymal trophic unit has been shown in previous studies, as well as the potential role of the ADAM33 gene, which is abundantly expressed in airway fibroblasts and smooth muscle cells in patients with asthma.

WENZEL *et al*. [8] have described a subpopulation of severely asthmatic patients exhibiting elevated numbers of eosinophils as well as neutrophils in bronchial biopsies. As compared to patients without eosinophils, these patients appeared to have an increased thickness of the sub-basement membrane associated with increased concentrations of transforming growth factor-β in bronchial biopsies, a cytokine assumed to play a role in fibrotic changes in asthmatic airways. The concept that persistent eosinophilic inflammation may be a marker of the activity of the remodelling process in the airways is further supported by the finding that sputum eosinophilia appeared to be the only independent factor associated with persistent airflow limitation in a study investigating severely asthmatic patients. Refractory eosinophilic airway inflammation might be the reflection of a clinical asthma phenotype exhibiting more severe and active disease. Alternative explanations for persistence of eosinophils in induced sputum despite high doses of inhaled corticosteroids include ongoing inflammation in regions of the airways that are not or hardly accessible to inhaled drugs, such as the small airways. This fits in with the observation that patients with severe asthma, in particular those with persistent airflow obstruction, have more peripheral airway dysfunction and inflammation than patients with mild asthma [9].

Refractory asthma with corticosteroid dependence or resistance

The third group of patients with severe asthma constitutes those who are steroid dependent or resistant. Steroid-dependent patients do not necessarily suffer from frequent severe exacerbations or irreversible airflow limitation, but simply need moderate-to-high daily doses of oral corticosteroids to control their symptoms and live a quasi-normal life. Although these patients may be satisfied with their treatment in the short term, they are at risk of serious side-effects in the long run. The reasons why these patients are resistant to normal doses of (inhaled) medication and need high doses of systemic corticosteroids to control their asthma are unknown.

Corticosteroid resistance is an extremely complicated and poorly understood condition, and many factors may contribute to it [10]. Possible mechanisms include the down-regulation of glucocorticosteroid receptors (GR) secondary to prolonged steroid treatment itself, reduced GR binding affinity of inflammatory cells, reduced availability of GR due to complex formation of GR with cytokine-activated transcription factors activator protein-1 and nuclear factor-κB, reduced histone deacetylation, or the action of the β-isoform of the glucocorticoid receptor. In addition, the chronic use of β_2-agonists, viral infections and endogenous female sex hormones have been proposed to be causal factors in secondary steroid resistance.

Complete steroid resistance in asthma is an extremely rare condition, and is defined as an absence of any response to systemic steroids given for a prolonged period of time (*e.g.* 40 mg prednisolone per day for 14 days) in the presence of asthma symptoms, bronchodilator response to inhaled β_2-agonists and diurnal variation in peak expiratory flow >15%. Proposed mechanisms of complete, primary steroid resistance include familial abnormalities of steroid receptors, pharmacokinetic abnormalities and cellular abnormalities.

Educational questions

1. Which of the following is the ATS definition of refractory asthma based on:
   a) The presence of airway remodelling.
   b) The occurrence of at least three respiratory infections per year.
   c) The amount of anti-asthma medication required.
   d) The degree of airway hyperresponsiveness.
   e) All of the above.
2. Which of the following clinical phenotypes of severe asthma is rare:
   a) Aspirin-sensitive asthma.
   b) Brittle asthma type II.
   c) Asthma with frequent exacerbations.
   d) Steroid-dependent asthma.
   e) Asthma with chronic persistent airflow limitation.
3. Airway eosinophilia in asthmatics on oral corticosteroids is:
   a) Extremely rare.
   b) Associated with more severe asthma.
   c) A proof of non-compliance with therapy.
   d) Associated with gastric reflux.
   e) Pathognomic of Churg–Strauss syndrome.
4. Which of the following factors is not a known risk factor for a (near-) fatal asthma attack:
   a) Lower socio-economic status.
   b) Depression.
   c) Illicit drug abuse.
   d) Genetic predisposition.
   e) Emergency visits for asthma in the past year.
5. Patients who are symptomatic despite high doses of inhaled corticosteroids may improve by which of the following means:
   a) Nasal corticosteroids.
   b) Leukotriene modifiers.
   c) Inhaled extra-fine aerosol corticosteroids.
   d) Anti-IgE antibody.
   e) All of the above.

How to manage patients with difficult-to-treat and severe asthma

The management of patients with difficult-to-control asthma should ideally be undertaken in a multidisciplinary asthma centre with extensive expertise in evaluating and treating these patients. Specialised centres have access to tests that are not routinely available, such as measurement of nitric oxide in exhaled air, analysis of induced sputum cells and supernatant, and examination of bronchial biopsies, that will add to the medical evaluation. It may take several months to complete a full diagnostic and management protocol, and to eliminate the exogenous and endogenous factors that aggravate asthma. An algorithm for the management of patients with difficult and severe asthma is given in figure 4.

In some patients, admission to hospital may even be required to exclude environmental exposure to hidden allergens, sensitisers or trigger factors, to explore the influence of psychosocial factors, or to check compliance with therapy. By paying attention to these factors, the control of refractory asthma can be improved substantially.

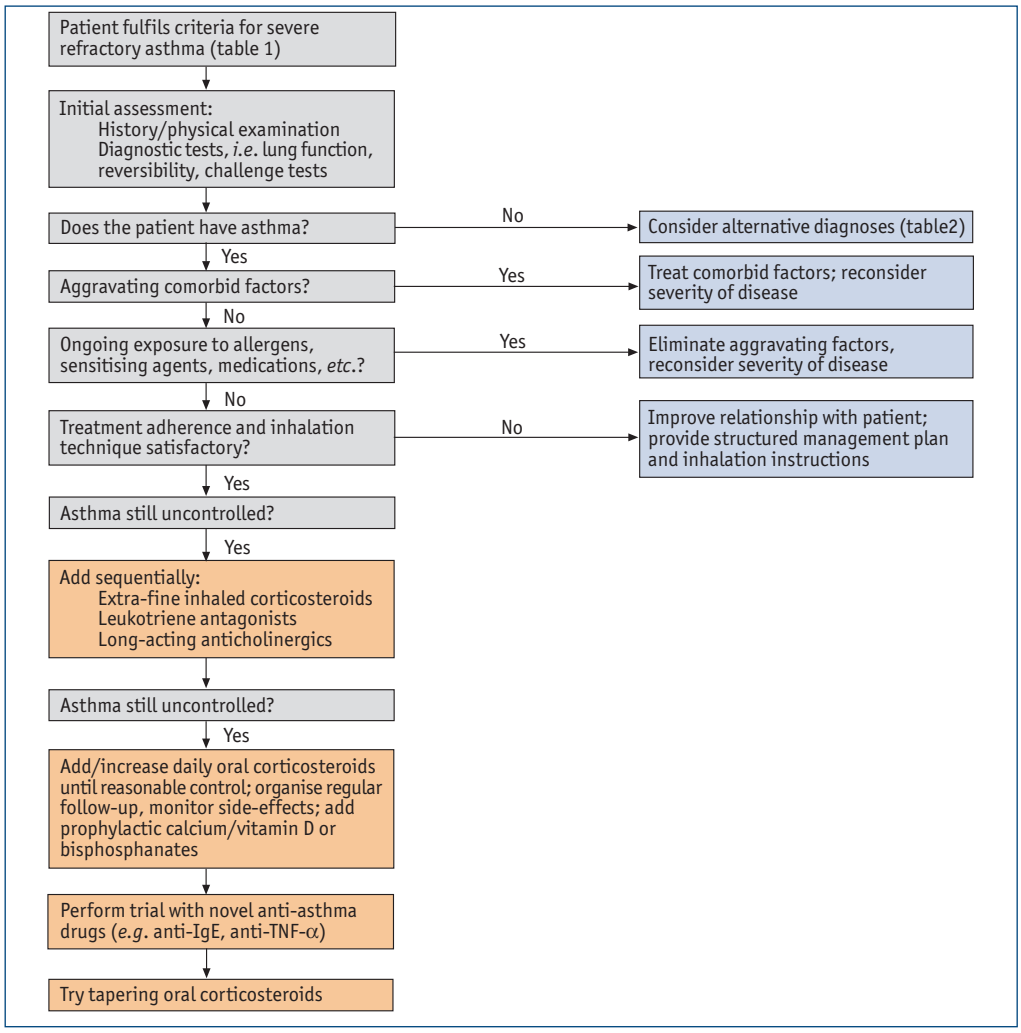


Figure 4
Algorithm for the management of patients with difficult and severe asthma.

Education

Education of patients to improve self-care is another element of the integrated management process of patients with difficult-to-control asthma. Studies have suggested that a lack of self-management coupled with medical non-adherence is an important factor in hospitalisation and asthma death. A good dialogue between patients and care providers is strongly encouraged. Intensive education might help these patients to better self-manage their asthma.

Rehabilitation programmes

Rehabilitation programmes are highly recommended for patients with difficult-to-treat asthma. Many patients are debilitated by their condition, by inactivity and sedentary lifestyle, or by the side-effects of systemic corticosteroid therapy. Exercise programmes have proved to have health-related benefits, to improve the quality of life and to increase exercise performance and fitness.

Pharmacotherapy

Pharmacotherapy of severe asthma is based primarily on high-dose inhaled corticosteroids (>1,000 µg per day of beclomethasone

dipropionate), combined with long-acting inhaled β_2-agonists, as outlined in the guidelines. In case of insufficient response to the above medications, and after evaluation and treatment of endogenous and exogenous aggravating factors, additional treatments can be tried: inhaled extra-fine aerosol corticosteroids might benefit the patient with peripheral airway inflammation; patients with chronic rhinosinusitis may improve with nasal corticosteroids; those with aspirin sensitivity may respond to leukotriene modifiers; and, in cases of evident allergic symptoms, anti-IgE therapy may be effective.

To date, there is no approved treatment for intervention in non-atopic patients who remain uncontrolled with recurrent exacerbations and chronically impaired lung function despite intensive multi-drug treatments. Many of these patients require continuous systemic corticosteroid treatment to keep their asthma under control and to prevent irreversible loss of lung function. Systemic steroid therapy is, however, associated with serious side-effects including osteoporosis, skin thinning, diabetes, hypertension, cataract formation and myopathy, and every effort should be undertaken to minimise the dose of these drugs. In this context, it is important for physicians to be aware that patients may have different ideas from doctors regarding optimal asthma control or optimal dosing of systemic steroids. With continuous high-dose systemic steroid therapy, the goal must be to find the optimal balance between therapeutic efficacy and short- and long-term side-effects of the drug.

Although initial reports with treatments such as oral gold, methotrexate and cyclosporin were encouraging, experience over the past decades has been disappointing. Meta-analyses have shown that there is insufficient evidence to support the use of these drugs in the routine treatment of severe asthma as steriod-sparing agents. In most cases, the limited steroid-sparing efficacy of these drugs appeared to be insufficient to offset the serious side-effects.

Promising new asthma therapies include humanised monoclonal antibodies against TNF-α. These drugs have been shown to produce remarkable clinical responses in chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease. Recent evidence suggests that patients with refractory asthma also show clinical benefit. Three clinical trials, an open-label study with etanercept in 17 patients [11], a double-blind placebo-controlled trial with etanercept in 10 patients [12] and a double-blind parallel trial with infliximab in 38 patients with severe asthma [13] have shown improvements in symptoms, lung function, airway hyperresponsiveness and the number of asthma exacerbations. Large-scale studies are now under way to confirm these promising findings.

Conclusion

Not all patients with "difficult-to-control" asthma have "severe" asthma. A diagnosis of severe asthma requires confirmation of asthma by objective means, removal of causal and aggravating factors, and adequate education of the patients. In most patients with severe asthma, oral steriods remain the mainstay of treatment, while steriod-sparing immune-suppressant drugs have shown disappointing efficacy. Severe asthma is a heterogenous condition, and conscientious clinical phenotyping of the patients is essential for a better understanding of the underlying mechanisms and the development of novel therapies.

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Suggested answers

1. c
2. b
3. b
4. d
5. e