The mechanisms, diagnosis, and management of severe asthma in adults

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There has been a recent increase in the prevalence of asthma worldwide; however, the 5–10% of patients with severe disease account for a substantial proportion of the health costs. Although most asthma cases can be satisfactorily managed with a combination of anti-inflammatory drugs and bronchodilators, patients who remain symptomatic despite maximum combination treatment represent a heterogeneous group consisting of those who are under-treated or non-adherent with their prescribed medication. After excluding under-treatment and poor compliance, corticosteroid refractory asthma can be identified as a subphenotype characterised by a heightened neutrophilic airway inflammatory response in the presence or absence of eosinophils, with evidence of increased tissue injury and remodelling. Although a wide range of environmental factors such as allergens, smoking, air pollution, infection, hormones, and specific drugs can contribute to this phenotype, other features associated with changes in the airway inflammatory response should be taken into account. Aberrant communication between an injured airway epithelium and underlying mesenchyme contributes to disease chronicity and refractoriness to corticosteroids. The importance of identifying underlying causative factors and the recent introduction of novel therapeutic approaches, including the targeting of immunoglobulin E and tumour necrosis factor \( \alpha \) with biological agents, emphasise the need for careful phenotyping of patients with severe disease to target improved management of the individual patient’s needs.

Since there have been several recent overviews of severe asthma\(^1\) this review will focus on the underlying mechanisms, risk factors, diagnosis, and natural history, with comments on management where there are mechanistic implications. Most patients with asthma have mild to moderate disease, which is well controlled by a combination of anti-inflammatory drugs, especially corticosteroids and \( \beta_2 \)-adrenoceptor agonists. However, in about 10% of patients, asthma remains symptomatic despite treatment with high-dose inhaled corticosteroids and long-acting \( \beta_2 \) agonists. Patients with refractory asthma have the greatest impairment of their lifestyles and account for a disproportionate use of health-care resources through hospital admissions, unscheduled doctors visits, and use of emergency services.\(^6\) In 2000, the American Thoracic Society reported on an expert workshop on severe asthma including the development of a consensus definition based on various major and minor criteria.\(^5\) However, as noted by Moore and Peters in their review,\(^6\) this definition has not yet been subject to prospective assessment (panel). The incorporation of health-care use would strengthen the definition by identifying patients with the greatest morbidity.\(^7\) Indeed, a previous hospital admission for asthma is reported to increase the risk of asthma mortality by tenfold.\(^7\) A proportion of patients with severe asthma have a disease that is eminently treatable but that remains misdiagnosed, under-diagnosed, or under-treated. Asthma severity can also result from poor adherence to treatment, most frequently because of fears over side-effects of inhaled corticosteroids or difficulties with using inhaler devices.\(^8\) These factors should be checked before diagnosis of refractory disease. A trial of oral corticosteroids and careful supervision by a specialist clinic are usually sufficient to establish suboptimum treatment and correct this problem.

Search strategy and selection criteria

Our search included a detailed appraisal of the published peer-reviewed research using the NCBI PubMed website as well as source literature that the authors have accumulated because of a major ongoing interest in severe asthma. Keywords used in the search were “severe asthma”, “classification”, “pathophysiology”, “remodelling”, “treatment”, “diagnosis”, and “natural history”. We only reviewed articles published within the past 10 years in English.

Panel: American Thoracic Society workshop consensus for definition of severe/refractory asthma

Major characteristics
- Treatment with continuous or near continuous (≥50% of year) oral corticosteroids
- Need for treatment with high-dose inhaled corticosteroids

Minor characteristics
- Need for additional daily treatment with a controller medication (eg, long-acting \( \beta \) agonist, theophylline, or leukotriene antagonist)
- Asthma symptoms needing short-acting \( \beta \) agonist use on a daily or near-daily basis
- Persistent airway obstruction (FEV1 <80% predicted, diurnal peak expiratory flow variability >20%)
- One or more urgent care visits for asthma per year
- Three or more oral steroid bursts per year
- Prompt deterioration with ≥25% reduction in oral or intravenous corticosteroid dose
- Near-fatal asthma event in the past

*Definition requires that at least one major criterion and two minor criteria are met, other disorders have been excluded, exacerbating factors have been treated, and patient is generally compliant.
Subphenotypes

Most mild-moderate asthma is associated with atopy, but in the most severe and chronic phenotype other characteristics emerge. Refractory asthma is a heterogeneous disorder that can be subdivided on the basis of different clinical aetiological, physiological, or pathophysiological characteristics. Although most cases of severe asthma begin in early childhood as persistent wheezing associated with atopy, adult-onset asthma is commonly non-allergic and often misdiagnosed because it possesses some characteristics of chronic obstructive pulmonary disease. The pathology of late-onset asthma is similar to that of the classic allergic form with evidence of T-helper-2 (Th2) inflammation and tissue remodelling in both forms of the disease (figure 1). These features are also present in childhood asthma from its onset, which suggests that from its inception the disease is more than simple airway inflammation. Tobacco smoking is also an important factor that contributes to asthma severity by enhancing resistance to corticosteroids and by eliciting an intense neutrophilic response. The main purpose of attempting to classify subphenotypes of severe asthma is to guide treatment and indicate prognosis.

Contributing factors to asthma severity

In most cases, multiple factors are responsible for difficult-to-treat asthma. Many of the risk factors that contribute to disease chronicity are also triggers of worsening asthma and exacerbations, indicating complex interactions with the environment.

Environmental exposures

Although atopy is less common in severe asthma, according to the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) survey in Europe, it was present in about 60% of patients in whom perennial allergens, including those derived from house dust mite, cockroaches, and fungi (especially Aspergillus and Alternaria species), contribute to ongoing disease. Bronchopulmonary allergic aspergillosis is a rare but important asthma subtype because if left untreated it can lead to bronchiectasis. However, even in the presence of atopy, severe asthma becomes less dependent on aeroallergen exposure, with other environmental factors, such as infection and exposure to air pollutants, assuming greater importance. The exception is occupational sensitisers, which may be classified as immunoglobulin E dependent—eg, acid anhydrides, bakers asthma—or non-immunoglobulin E dependent—eg, di-isocyanates. Late-onset asthma should raise awareness of occupational exposures and, if suspected, appropriate steps should be taken to confirm this diagnosis, such as peak expiratory flow monitoring in and out of the workplace. Cigarette smoking also leads to deteriorating asthma, causing more symptoms, more severe and frequent exacerbations, and an accelerated decline in baseline lung function over time.

Adverse drug effects

Asthmatic airways are highly dependent on continued β2-adrenoceptor stimulation and as a result administration of β blockers can lead to severe asthma that is refractory to β2-adrenoceptor agonists. Asthma is, therefore, a contraindication for this drug class. Inhibitors of angiotensin converting enzyme and adenosine for cardiovascular diseases are also associated with deterioration of asthma. However, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) present the most common and difficult problems. Aspirin intolerance has emerged as a prominent risk factor of severe asthma in both the ENFUMOSA and TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) studies. In a further detailed study of 500 patients with
aspirin-intolerant asthma,7 51% needed oral corticosteroids and 24% had received inhaled corticosteroids in the previous 2 months. In the TENOR study, aspirin intolerance predicted an increased level of persistent airflow obstruction.26 Aspirin-intolerance can occur as a triad of rhinitis, flushing, and asthma and is associated with excess cysteinyi leukotriene formation. Aspirin-intolerant asthma is four-times less common in children than in adults, although in part it could have a genetic basis with polymorphic variation in the cysteinyi leukotriene synthetic enzymes and their receptors.26 Although a wide range of NSAIDs can trigger worsening asthma in patients with aspirin-intolerant asthma, these drugs are restricted to the non-selective cyclo-oxygenase inhibitors (eg, indomethacin, ibuprofen) because cyclooxygenase-2 inhibitors (eg, celecoxib, refecoxib) do not elicit this adverse effect.29 There is increasing evidence that by inhibiting cyclooxygenase-1, the protective effect exerted by endogenous prostaglandin E₂ on leukotriene generation by mast cells, eosinophils, and macrophages in the airways is removed. As might be predicted, patients with aspirin-intolerant asthma usually respond well to treatment with cysteinyi leukotriene receptor antagonists such as montelukast.10 Other factors that have been associated with severe asthma are obstructive sleep apnoea and vocal-cord dysfunction, both of which need a high level of suspicion and special physiological tests to confirm their presence.31,32

**Psychopathology**

Severe asthma has long been associated with psychological and psychiatric disorders, which are particularly strong risk factors for frequent emergency room visits and asthma mortality with depression, anxiety, panic or fear, and behavioural problems that adversely affect disease control.8,33–35 Asthma and this psychopathology can mutually potentiate each other through direct psychophysiological pathways, non-adherence with treatment, exposure to asthma triggers, and reduced perception of asthma symptoms.36

**Endocrine factors**

Severe asthma is two to three times more common in women than in men, as shown in the ENFUMOSA²⁶ and TENOR²⁶ studies. At its inception in childhood, asthma is more common in boys, but during the early teenage years severe asthma becomes more common in girls than in boys and this pattern persists into adulthood.²⁶ The higher prevalence of adult-onset asthma and severe asthma in women than in men is probably the result of endocrine factors since strong associations have been reported with the menstrual cycle,²⁷ whereas in pregnancy asthma commonly improves, especially in the mid and late trimesters.²⁸ However, the discovery of a genetic polymorphism of the oestrogen receptor affecting disease severity also provides a genetic basis for some of these endocrine effects.²⁹ Thyrotoxicosis is a recognised endocrine factor leading to loss of asthma control.⁴⁰ Obesity is a newly recognised risk factor for both asthma and its severity, especially in women,³⁶,⁴¹ with weight loss being accompanied by improved asthma control.⁴² In addition to the link with obesity, endocrine factors, such as leptin and other adipokines such as adiponectin and resistin, also have actions on immune and inflammatory cells.³¹

**Comorbidity**

The coexistence of chronic rhinitis, nasal polypsis, and sinusitis contribute to asthma severity.³⁷,⁴³ There is ample evidence to show that adequate treatment of these upper airway diseases is beneficial to asthma by mechanisms not clearly understood. The “one airway” concept developed by the WHO ARIA Group⁴³ has drawn attention to the importance of treating the whole of the respiratory tract when managing asthma. Gastro-oesophageal reflux is also commonly associated with chronic asthma both in adults and children,⁶ possibly related to the proximity of the organs and neural connections. However, whereas evidence that treatment of reflux is reported to have little overall effect on asthma control,²⁷ two studies⁴⁸,⁴⁹ indicate that proton-pump inhibitors in patients with symptomatic reflux improve asthma control in severe disease.

**Mechanisms of severe asthma**

Until relatively recently, all asthma cases were regarded as being similar, differing only in severity and therefore requiring treatment that differed only in the dose, route, or frequency of corticosteroid and β₂-adrenoceptor agonist required to control the disease. However, with the identification of asthma subphenotypes this view is being challenged.²⁹ Research over the past two decades has identified allergic pathways as being fundamental to asthma with a prominent part played by a subset of T cells (designated Th2-like) that produce cytokines and chemokines implicated in the regulation of immunoglobulin E and the maturation, recruitment, priming, and activation of mast cells, basophils, and eosinophils. Allergic pathways that contribute to airway dysfunction in mild-moderate asthma are largely sensitive to corticosteroids. However, in more severe asthma the inflammatory profile commonly changes with greater involvement of neutrophils and evidence of tissue destruction and airway remodelling (figure 2).³¹,³² The airways in severe asthma exhibit characteristics of a chronic wound with evidence of ongoing epithelial injury and repair.³³ As in any wound, responses to injury create the necessary stimuli to recruit the underlying mesenchyme to participate in the repair process through the release of a range of growth factors such as epidermal growth factor (EGF), transforming growth factor α (TGFα), amphiregulin, heparin-binding like growth factor (HB-EGF), keratinocyte growth factor (KGF),
fibroblast growth factors (FGFs), insulin-like growth factors (IGFs), vascular endothelial growth factors (VEGFs), and transforming growth factor-β (TGFβ), which together promote remodelling and vasculo-genesis. The airway epithelium displays characteristics of injury and stress with over expression of EGF receptors and reduced anti-oxidant defences. Disordered epithelial function and augmentation of mesenchymal responses emphasise the potential role of the epithelial-mesenchymal trophic unit (EMTU), which is associated with lung development and disease chronicity and remodelling (figure 2). This process includes increased matrix deposition in the subepithelial lamina reticularis of the basement membrane, disruption of elastin filaments, and the deposition of types 1, 3, 5, and 6 repair collagens and proteoglycans throughout the airway wall (including the smooth muscle) leading to thickened and stiffer airways. The relation between thickened and stiffer airways to hyper-responsiveness is not clear, although changes to airway smooth muscle are likely to be important. In severe asthma the spiral bundles of smooth muscle increase both in number and size and spread upwards to affect the large airways (including the tracheae) and peripherally to affect the respiratory bronchioles and alveolar ducts. Within this new microenvironment the ability to recruit, retain, and activate selective inflammatory cells such as monocytes, mast cells, and neutrophils changes. Thus, despite high-dose inhaled and oral corticosteroids, mast cells persist or even increase, especially those within and close to the airway smooth-muscle bundles with many of these cells containing high concentrations of TNFα. In patients on high doses of inhaled corticosteroids TNFα is also raised in bronchoalveolar lavage fluid and in airway biopsies at mRNA level. Mast cells are also an important source of interleukin 13, a cytokine with potential for driving both inflammatory and remodelling processes. Factors that maintain activation of the EMTU might include allergens—especially those with biological activities (eg, those derived from house dust mites, fungi, and cockroaches)—repeated virus infections linked to exacerbations, and air pollutants (eg, outdoor, indoor including environmental tobacco smoke).

Corticosteroid responsiveness

If dependency on glucocorticoids is essential for maintaining asthma control, then any defects in this pathway will be problematic. Corticosteroid treatment is
effective in only about 70% of the general population with asthma. In severe asthma the proportion of patients with reduced responsiveness to inhaled and oral corticosteroids is higher than in mild-moderate disease. A wide range of mechanisms have been proposed for corticosteroid refractoriness, including proinflammatory cytokine activation of p38 mitogen-activated protein kinase (which interferes with the nuclear translocation of corticosteroid receptors), reduced acetylation of a lysine residue in histone-4 of the nuclear chromatin leading to reduced activation of anti-inflammatory genes, and increased expression of the corticosteroid receptors alternatively spliced β variant that serves as a dominant negative inhibitor by competing with the fully functional variant GRα. Th-2 cytokines have also been proposed to play a part in severe corticosteroid refractory asthma with CD4+ T-cells from refractory asthmatics being less able to produce the anti-inflammatory cytokine interleukin 10 in response to dexamethasone than cells from patients sensitive to corticosteroids. Genetics could also have a role in reducing corticosteroid sensitivity. Weiss and colleagues examined 31 single nucleotide polymorphisms in 14 candidate genes in the corticosteroid pathway in patients with asthma undergoing a steroid intervention trial and have identified one gene, corticotrophin-releasing hormone receptor-1 (CRHR-1), which contained a polymorphism associated with corticosteroid responsiveness in three different asthmatic populations.

Airway remodelling
All studies of chronic severe asthma have identified a degree of fixed airflow obstruction as a distinctive characteristic. However, there is a subgroup of severe asthma with highly unstable airways and marked bronchial hyper-responsiveness detected even after inhalation of isotonic saline, which has been described as brittle asthma. These patients are at great risk of unexpected severe bronchoconstriction, which may be catastrophic. Patients are often young, female, and highly atopic. By contrast, most difficult-to-treat chronic asthma is accompanied by reduced baseline lung function, which is only partly reversible with a β2 agonist and is accompanied by increased lung volumes, reduced vital capacity, and a degree of hypoxaemia. High resolution CT reveals thickened airways that increase in proportion to disease severity and are inversely proportional to the level of bronchial hyper-responsiveness, possibly suggesting that remodelling of the airways is a mechanism for protecting them against repeated bronchoconstriction. Although the significance of airway remodelling in asthma is controversial, factors that predispose to an accelerated decline in lung function over time include tobacco smoking, male sex, concurrent rhinosinusitis, and persistent sputum eosinophilia. In a systematic analysis of bronchial biopsies in patients with differing severity of asthma, Pepe and co-workers reported that the airway smooth muscle both increases in amount and also becomes more superficial. Such changes in smooth muscle could be relevant to the function of an asthma susceptibility gene encoding a disintegrin and metalloproteinase 33 (ADAM33). This is a novel asthma susceptibility gene identified by positional cloning, whose polymorphism is associated not only with asthma and bronchial hyper-responsiveness but also with an accelerated decline in lung function over time at a population level, in asthma, and in chronic obstructive pulmonary disease, suggesting a role for ADAM33 in chronic airway injury and repair. Other abnormalities associated with disease severity include loss of elastic recoil and increased lung compliance, both of which are risk factors for near fatal asthma. Airway remodelling of the most peripheral airways and loss of alveolar-airway attachments can contribute to these abnormalities. As asthma becomes more severe, another important characteristic is a diminished perception of dyspnoea, of which the underlying mechanism is unknown. Such patients are clearly at heightened risk of a life-threatening attack.

Increased mucus production is another characteristic of asthma, which is especially problematic in severe disease. Goblet-cell metaplasia is partly driven by neutrophil-dependent EGF receptor signalling, and interactions with specific cytokines, especially TNFα and interleukin 13 indicate that this neglected component of asthma is tractable with new therapeutic approaches. Not only does the amount and viscoelastic properties of mucus increase in severe asthma, but also the production of mucus spreads to the small airways where its effect on lung function is likely to be substantial.

Asthma exacerbations
Asthma exacerbations are acute worsening of the disease with durations of 3 days or more and a need for unscheduled health-care intervention with an increase in treatment and a suspension of normal activities. Severe asthma is characterised by two or more exacerbations per year. Until recently, there has been little attempt to understand the underlying causes of these events, other than attributing them to allergen exposure or under-treatment. With the availability of gene-based detection methods most exacerbations of asthma seem to be virus-related, with common cold viruses being especially important. Virus-induced exacerbations occur at particular times of the year and are accompanied by lower-airway neutrophilia, are relatively refractory to corticosteroids, and have been linked to increased asthma mortality. Patients with severe asthma do not have more virus episodes than non-asthmatics or mild asthmatics, but when infected the effect on lower airway function in asthma is substantial. In non-asthmatics, infection of epithelial cells with rhinovirus initiates a cascade of events that leads to inhibition of viral replication, programmed cell death, and, as a consequence, effective viral elimination. However, in asthma,
irrespective of severity, these processes are defective because of a deficiency of interferon-β production. This finding raises the possibility of restoring this innate immune response through use of exogenous interferon β by inhalation or by induction of its increased production by asthmatic airway epithelial cells as a novel therapeutic intervention to prevent severe exacerbations in those at greatest risk. Detection of rhinovirus up to 6 months after an exacerbation and evidence for rhinovirus infection in infancy as a strong predictor of subsequent persistent wheezing suggest that respiratory viruses might also be important in the origins and persistence of asthma. Certain bacteria are also associated with exacerbations of asthma, especially *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. In the study by Wark and colleagues, more than a third of patients with acute severe asthma showed a rise in *C pneumoniae*-specific antibodies and these patients had a more intense inflammatory response with marked sputum neutrophilia and raised serum concentrations of eosinophil cationic protein compared with people with acute asthma in whom *C pneumoniae* antibodies were not detected. The presence of these micro-organisms in sputum and lung biopsies is also associated with disease severity and a poor clinical outcome. In this respect, the strong association found between the number of airway CD8+ T cells, which are an important line of defence against infection and long-term decline in lung function, is of particular interest.

Outdoor air pollutants also aggravate asthmatic airways; ozone, particulates, sulphur dioxide, and oxides of nitrogen are all associated with increased hospital admissions and unscheduled use of health-care resources during air-pollution episodes. As referred to earlier, an important cause of exacerbations is suboptimum controller therapy and breakthrough airway inflammation. Under these circumstances the level of sputum eosinophilia is particularly useful as shown by Green and co-workers in a 12-month study of moderate-severe asthma showing that a treatment strategy directed at normalising sputum eosinophilia reduced exacerbations and hospital admissions without the need for additional anti-inflammatory therapy. Measurement of exhaled nitric oxide is also reported to be a good marker in severe refractory asthma with persistent eosinophilia.

**Chronic airway inflammation**

Although chronic asthma is associated with airway eosinophilia, when the disease adopts a severe phenotype the inflammatory profile commonly changes to the presence of neutrophils alone or in combination with eosinophils. Initially this process was thought to be a

Figure 3: Possible cellular targets for TNFα in severe corticosteroid refractory asthma

ICAM-1=interstitial cell adhesion molecule. VCAM-1=vascular cell adhesion molecule. MAPK=mitogen-activated protein kinase. TNFα is stored in granules and is released in large amounts from mast cells and macrophages as a result of immunological stimulation. In the airways, TNFα elicits a general inflammatory response mainly through enhanced release of pro-inflammatory and chemotactic mediators and upregulation of adhesion molecules. These series of events will ultimately lead to chronic eosinophilic and neutrophilic infiltration and irreversible airway remodelling. TNFα also has a potent direct effect on the airway smooth muscles leading to an increase in airway hyper-responsiveness. Adapted from Clin Sci 2005; 109: 135–42 with permission of Portland Press.
response to increasing inhaled corticosteroids because, by contrast with their proapoptotic effect on eosinophils, these drugs enhance neutrophil survival.19 However, in severe asthma the neutrophils also seem to be in an activated state16 with their numbers correlating with indices of airway damage20,21 and reduced corticosteroid responsiveness.22 These changes can be explained by a change in the inflammatory pattern away from Th2 towards a Th1-like pattern with increased expression of TNFα and interferon-γ.101 The importance of TNFα as a multifunctional cytokine in severe refractory asthma has been strengthened by showing up to 30-fold increases in gene expression in the Airways and enhanced circulating mononuclear cell expression of membrane precursor TNF, TNFα-cleaving enzyme (TACE, ADAM17) and its receptors, p75 and p55,104 as well as increased secretion of soluble TNFα even in the presence of high-dose inhaled or oral corticosteroids.105 The mechanisms responsible for this change in inflammatory phenotype are not known, although TNFα has been shown to increase the level of the β-isoform of the corticosteroid receptor106 and it has multiple effects on inflammatory and structural cells in the Airways (figure 3).

There exists a group of patients with severe asthma in whom there is scant evidence of inflammation but where there occurs an increase in Airways smooth muscle (pauci-inflamatory asthma).115,116 Although this finding could represent the irreversible consequence of chronic inflammation that resolves with corticosteroids, it might represent yet another phenotype of severe asthma in which inflammation is not a major feature. An increase in Airways smooth muscle is a characteristic feature of chronic asthma and yet its relation with concurrent inflammation is unknown.73,117,118 There is evidence that smooth muscle in asthma is highly abnormal in exhibiting a secretory and remodelling phenotype, but at the same time behaving differently from normal in its response to both contractile and relaxant agonists.119 A defect in the ability of corticosteroids to inhibit Airways smooth muscle cells obtained from patients with severe asthma from proliferation has been shown to involve increased expression of ineffective splice variants of the CCAAT/enhancer binding protein-α (C/EBPα) pathway.120 The importance of Airways smooth muscle in severe asthma warrants further attention to its role in the pathobiology and its association with the inflammatory components of the disease.

Role of small Airways
Pathology studies in patients who have died from asthma reveal extensive involvement of the peripheral Airways with inflammatory, smooth muscle, and remodelling responses (figure 1).111 Transbronchial biopsies have confirmed peripheral Airways involvement in severe asthma including the alveoli.121 Additionally, the distribution of inflammatory cells also changes with greater infiltration of the adventitial region with a range of inflammatory cells including chymase-positive (connective tissue-type) mast cells.212 Since a similar mast-cell phenotype is also present in increased numbers within the smooth-muscle bundles of large Airways,122 the mast cell is emerging as an important inflammatory cell in chronic asthma. Extensive small-Airways involvement in severe disease has important implications for inhaled drug delivery and might explain the increased efficacy of the hydrofluoroalkane formulations of inhaled corticosteroids and systemically available drugs.

Diagnosis and assessment of severe asthma
Although new algorithm-based approaches are being tested for diagnosis and subphenotyping of severe asthma,113 none has yet been validated in a clinic setting. However, a series of key steps might include establishing asthma as the diagnosis, assessing underlying factors (including under-treatment and poor adherence), and providing an asthma phenotype. Although the diagnosis of asthma according to established guidelines should be relatively straightforward, the presence of phenotypes where there is a substantial degree of fixed airflow obstruction, reduced diurnal variability, and extensive small-Airways disease could be problematic.116,117 In such cases, detailed lung function, including measurement of lung volumes and assessment of small Airways function, chest radiograph, CT, and, if the baseline FEV1 is more than 60% of predicted, methacholine bronchial provocation, is helpful. Of particular value is sputum cytology with a focus on eosinophils and neutrophils.123 Exhaled nitric oxide (eNO) is a useful non-invasive guide to eosinophilic inflammation,124 but since many patients are already taking corticosteroids at initial presentation values may be normal.125 Care must be taken to exclude bronchiolitis obliterans, bronchopulmonary allergic aspergillosis, Churg-Strauss syndrome, and paradoxical vocal-cord closure. Assessment of atopic status, appraisal of the upper Airways for evidence of rhinosinusitis, and consideration of gastro-oesophageal reflux are part of the clinical workup.

According to management guidelines, asthma severity may be classified into steps on the basis of clinical treatment. When the patient is already receiving treatment, severity should be based on the clinical characteristics present and the step of the daily medication regimen being taken (table). The severity of acute asthma exacerbations is often underestimated by patients, their relatives, and health-care professionals and is an important factor contributing to mortality.126 Specific factors linked to mortality include a history of life-threatening attacks, a hospital admission within the past year, previous intubations for asthma, psychopathology, comorbidities, recent reductions or cessation of corticosteroids, and poor adherence with prescribed treatment.

Management of severe asthma
Figure 4 shows an algorithm for the treatment of severe asthma. In accordance with global guidelines, tertiary
prevention aims to reduce exposure to known inducers and triggers to improve asthma control. However, there is little evidence that treating such factors has much effect on asthma control; for example, although inhaled allergens are known to be important in driving asthmatic inflammation, allergen-avoidance strategies have generally been disappointing.121 Standard treatment for severe asthma includes high-dose inhaled corticosteroids combined with a long-acting β2 agonist as the preferred add-on therapy, often administered by a single inhaler device.122 Alternatives are a cysteinyl leukotriene receptor antagonist123 and sustained release theophylline.124 These treatments can also be added to the combination therapy. Because corticosteroids by inhalation begin to lose their efficacy as the dose increases above 800–1000 μg beclometasone dipropionate-equivalents per day and because both local and systemic side-effects (osteo- porosis, skin thinning, and cataracts) increase, care should be taken with doses in excess of 2000 μg/day, especially in patients beyond middle age.125 A new corticosteroid, ciclesonide, seems to have a greater therapeutic index but has not yet been approved for high-dose use in severe asthma.126 If required, long-term oral corticosteroids should be used at the lowest possible dose. A recent Cochrane review concluded that use of long-acting β2 agonists allows up to 57% reduction of inhaled corticosteroids.127 There is also strong evidence that adequate inhaled corticosteroid treatment substantially reduces asthma mortality128 and hospital admissions129 for severe asthma. The wider use of inhaled corticosteroids in asthma is the most likely explanation for the decline in mortality seen over the past 3–5 years in various countries that have implemented asthma guidelines. However, in a large European survey that involved 14 countries, only 17% of patients with persistent symptomatic asthma were using inhaled corticosteroids on a daily basis130 with very wide inter-country differences in their uptake. The effects of corticosteroids on airway remodelling and on other aspects of the natural history of asthma is controversial, with some aspects responding (eg, accelerated decline in lung function131 and thickening of the lamina reticularis132) and others (eg, smooth-muscle hypertrophy and hyperplasia) not responding. Corticosteroid-sparing treatments include methotrexate, cyclosporine A, and oral gold, but in general these treatments have limited effects and have appreciable side-effects. A Cochrane review of the benefit of adding fixed doses of methotrexate to oral corticosteroids in patients with corticosteroid-dependent asthma has concluded that the evidence is conflicting.133 However, as in rheumatoid arthritis, for the best results the dose of methotrexate should be tailored to the severity of the patient’s symptoms.

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<thead>
<tr>
<th>Patient symptoms and lung function on current therapy</th>
<th>Current treatment step*</th>
<th>Level of severity</th>
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<tr>
<td>Step 1: Intermittent</td>
<td>Intermittent</td>
<td>Intermittent</td>
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<td>Symptoms less than once a week</td>
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<td>Brief exacerbations</td>
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<td>Nocturnal symptoms not more than twice a month</td>
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<td>Normal lung function between episodes</td>
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<td>Step 2: Mild persistent</td>
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<td>Symptoms more than once a week but less than once a day</td>
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<tr>
<td>Nocturnal symptoms more than twice a month but less than once a week</td>
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<td>Normal lung function between episodes</td>
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<td>Step 3: Moderate persistent</td>
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<td>Moderate persistent</td>
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<td>Symptoms daily</td>
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<td>Exacerbations may affect activity and sleep</td>
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<td>Nocturnal symptoms at least once a week</td>
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<td>60% &lt;FEV1 &lt;80% predicted OR</td>
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<tr>
<td>60% &lt;PEF &lt; 80% of personal best</td>
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<td>Step 4: Severe persistent</td>
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<td>Severe persistent</td>
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<td>Symptoms daily</td>
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<td>Frequent exacerbations</td>
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<td>Frequent nocturnal asthma symptoms</td>
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<td>PEF ≤60% of personal best</td>
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Table: Classification of asthma severity by daily medication regimen and response to treatment
When *C pneumoniae* is suspected as a contributory factor in persistent airflow obstruction or exacerbations, the addition of macrolides can be effective. The complexity of multiple daily drugs is an important factor in non-adherence. In extreme circumstances bilateral lung transplantation has also had some success. As in the case of overuse of short-acting β2-adrenoceptor agonists, there has been some concern over the use of long-acting β2 agonists. A large 28-week study of salmeterol in moderate-severe asthma (SMART) was stopped prematurely because of a significant 4.4-fold increase in asthma mortality in the active treatment group. Of importance in this study was the high proportion of patients who were taking long-acting β2 agonists alone and the greater proportion of deaths that occurred in the African American subpopulation in which asthma was more severe than in the trial population as a whole. One factor that could provide an explanation for the treatment-related increase in asthma mortality relates to pharmacogenetics. For the Arg/Arg polymorphic variant of the β2 adrenoceptor, treatment of asthma with regular salbutamol results in deterioration in clinical control rather than improvement as seen with the Gly/Gly variant. In two separate trials, a similar effect has been shown for salmeterol irrespective of whether patients were taking concomitant inhaled corticosteroids. These findings, along with the reported reduced efficacy of long-acting β2 agonists in childhood asthma and warrant further assessment of this drug class, especially since a third generation of even longer acting β2-adrenoceptor agonists are currently in development. With respect to the use of short-acting β2 adrenoceptor agonists, their increased use by asthmatic patients should be used as an index of worsening asthma control mandating an increase in anti-inflammatory treatment. The use of short-acting β2 adrenoceptor agonists at high doses by a portable inhaler or nebuliser should be reserved for the treatment of exacerbations. A Cochrane review concludes that there is little evidence for the use of anticholinergics as part of add-on therapy for severe exacerbations of asthma.

High-dose intravenous human immunoglobulin is efficacious in some patients with corticosteroid-dependent severe asthma with suppressive effects on persistent inflammation, but cost and inconvenience precludes its widespread use. Assessment and subsequent treatment of rhinosinusitis forms an important part of the management plan for severe asthma, with substantial clinical improvement in disease control being reported. Treatment of gastro-oesophageal reflux with proton-pump inhibitors such as lansoprazole and esomeprazole is beneficial but only in patients in whom both conditions coexist. Attention to other comorbidities is important including weight loss in severe asthmatics who are overweight, hormonal imbalance in women in whom a strong association is established between worsening of disease and the menstrual cycle, and treatment of fungal infections, especially bronchopulmonary allergic aspergillosis.

**New approaches to treatment**

The introduction of the humanised monoclonal immunoglobulin G1 blocking antibody directed to immunoglobulin E (omalizumab) represents an advance in the treatment of severe allergic asthma when symptoms remain despite use of optimum combination treatment
In the GOAL (Gaining Optimal Asthma Control) study\(^{153}\) of 3421 patients with uncontrolled asthma in whom combination treatment was increased until total control had been achieved or 1000 μg fluticasone reached, 38% remained inadequately controlled, which fell to 31% only after oral corticosteroids were added.\(^{151}\) In a series of six phase III clinical trials in severe adult allergic asthma involving 2548 patients on omalizumab as add-on therapy, given by subcutaneous injection two to four times weekly for 28–52 weeks, benefit was achieved in multiple asthma outcome measures, including exacerbations, symptoms, lung function, and asthma-specific quality of life. However, there were only small changes in baseline spirometry.\(^{154}\) Omalizumab is dosed against the patient’s total serum concentration of immunoglobulin E (30–700 IU/mL) and bodyweight. The drug achieves its effects not only by removing circulating and tissue immunoglobulin E as small complexes, but also through promoting loss of high affinity immunoglobulin E receptors on mast cells, basophils, and dendritic cells, accompanied by reduced airway inflammation.\(^{155}\) Peak therapeutic response with omalizumab is achieved 12–16 weeks after starting treatment.\(^{156}\) Since only about two-thirds of patients respond to omalizumab, an assessment needs to be made 16 weeks after starting treatment to establish whether to continue using the physicians overall clinical assessment to arrive at this decision. As in other diseases there is a need for greater understanding of the responder and non-responder status to develop a simple test that could predict those most likely to benefit from this treatment.

As the disease progresses in severity, blockade of a Th-1 cytokine in clinical asthma might be most beneficial at the severe end of the disease spectrum.\(^{160}^{161}\) The failure of inhaled corticosteroids to reduce TNFα and Th1-derived cytokines in asthmatic airways could explain why inhaled corticosteroids have limited effects in the more severe forms of asthma and it is likely that treatments blocking TNFα and interfering with Th1-derived cytokines could represent an advance in the management of those asthma patients who are particularly resistant to the widely used treatment modalities.

Based on the increased expression in TNFα in the airways of severe refractory asthma, an exciting breakthrough has been the demonstration of efficacy of the soluble TNF receptor fusion protein etanercept; in two small studies particularly impressive results were seen against bronchial hyper-reactivity and asthma-specific quality of life with surprisingly little effect on indices of inflammation.\(^{162}^{166}\) The major action of etanercept is probably directed towards airways smooth muscle.\(^{161}\) Large clinical trials with etanercept and anti-TNFα monoclonal antibodies are now in progress. Other biological treatments that also look promising in severe asthma include interferon-α, anti-interleukin-13,\(^{167}^{168}\) and anti-CD25 (daclizumab)\(^{164}\) monoclonal antibodies. The potential costs of new targeted treatments will make it even more important to subphenotype asthma so that those most likely to respond to a specific treatment can be identified.

**Conclusions**

The recognition that there is a substantial number of patients whose asthma is not adequately controlled with conventional treatments reveals an important unmet clinical need in this disease. With the recent increasing trends in childhood asthma, the burden of severe asthma in adults is likely to increase. A combination of early diagnosis and subphenotyping of asthma taking disease severity into account will provide the basis for more accurate diagnosis and targeting of preventative and therapeutic interventions. The application of genetic, pharmacogenetic, and proteomic technologies to identify improved biomarkers relevant to severe asthma will enable the close tailoring of disease prevention and management strategies to the individual patient’s needs.

**Contributors**

STH and RP reviewed the available literature and contributed to the content of this review.

**Conflict of interest statement**

S Holgate is a UK Medical Research Council supported Clinical Professor, is a consultant for Novartis, Synairegen, Merck, Wyeth, and Centocor, and has received lecture fees from their companies. R Polosa is a consultant for Cardiovascular Therapeutics, Duska Therapeutics, and NeuroSearch and has received lecture fees from Merck and Novartis.

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