Over five million people in the UK are currently receiving treatment for asthma and the NHS spends around £1 billion a year caring for them. In the majority of cases, patients can live normal lives with minimal impact on their daily activities. Yet, an estimate of 140 patients per million population suffer from severe asthma and remain symptomatic despite correct treatment. In the UK, three people die every day from asthma. 3

There is a substantial unmet clinical need to improve treatment outcomes and to reduce the large socioeconomic burden associated with severe asthma. 5 Over the last decade significant effort has been put into place to address the management of severe asthma and a number of severe asthma networks have been established in the UK to help implement this.

The first step to better understand severe asthma is a systematic evaluation and definition of the disease. Asthma UK estimates that 75 per cent of hospital admissions for asthma are avoidable and that two in three deaths from asthma are preventable. A recent comprehensive review into asthma deaths revealed that 45 per cent of patients had not called for help during a fatal asthma attack. 3 This suggests that patients might not have been aware of the severity of their disease and/or did not recognise warning symptoms. Primary care plays an essential role in identifying and supporting a patient with undertreated or difficult to treat asthma.

Assessment
Assessment of a patient presenting with recurrent episodes of wheeze, chest tightness and/or cough requires a careful history focusing on symptoms, exacerbating triggers, occupational and environmental factors and mental health. Patients with difficult-to-control asthma characteristically suffer from untreated or undertreated co-morbidities. There is a high prevalence of co-existing psychosocial factors that may contribute to dysfunctional breathing or vocal cord dysfunction and continuous allergen exposure may also contribute to the persistence of symptoms in patients with difficult asthma.

Non-adherence to asthma medication has frequently been identified as the most common factor leading to poorly controlled asthma with studies demonstrating that patients take only up to 50 per cent of their prescribed medication correctly. 8 Poor technique can reduce
GORD
Obstructive sleep apnoea
Obesity
Mental health problems
Smoking
Allergies and/or chronic rhinosinusitis
Fungal sensitivity

Table 1. Co-morbidities that may mimic asthma symptoms and/or contribute to asthma severity

- Fungal sensitivity: Fungi can cause damage to the host by acting as an aeroallergen or by causing infection. Patients with persistently uncontrolled asthma are often chronically colonised with Aspergilus, Candida, Penicillium, and Curvularia species. Positive skin tests, an elevated total IgE and specific IgE and IgG are all diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA). ABPA can be found in 10 to 25 per cent of patients with severe asthma and has therapeutic implications in that some patients might benefit from antifungal treatment. Patients with evidence of fungal sensitisation who do not meet the criteria for ABPA are characterised as suffering from severe asthma with fungal sensitisation (SAFS).15

GORD
Patients with GORD typically suffer from cough and chest tightness, symptoms that can aggrivate or mimic asthma. GORD has been reported to be prevalent in between 12 to 85 per cent of patients with asthma. Adequate treatment of reflux symptoms results in improved asthma-related quality of life by reducing nocturnal symptoms and exacerbation frequency and some studies report reduction in the use of short-acting beta2 agonists.16

Obesity
We are observing an epidemic increase in obesity, which is an independent risk factor for asthma. Treatment of obesity-related asthma with inhaled or oral corticosteroids often proves disappointing. Yet, there is clear evidence that weight loss improves asthma control with studies demonstrating a reversal of the pro-inflammatory cytokine milieu seen in severe asthma after bariatric surgery.17,18

Obstructive sleep apnoea
Snoring, observed apnoea and poorly-controlled asthma are closely linked and patients with OSA and nocturnal asthma may have similar clinical presentations.19 Treatment with continuous positive airway pressure (CPAP) has the potential to improve asthma-related quality of life, lung function and to reduce short-acting beta2 agonist requirements.20

Psychiatric disorders
Many patients with chronic diseases suffer from anxiety and depression. They have more frequent disease exacerbations and increased healthcare utilisation, and severe asthmatics are no exception to this, especially prednisolone-dependent patients.21

Smoking
Smoking with asthma results in a more rapid decline in lung function, and more

Table 2. A patient suffering from any of the criteria listed needs to be considered for referral to a specialised asthma centre

- Consistently poor symptom control: Asthma Control Questionnaire score (ACQ) consistently >1.5 or Asthma Control Test (ACT) <20
- Frequent severe exacerbations requiring at least two courses of oral corticosteroids for a minimum of three days in the previous year
- One or more hospitalisation, intensive care unit admission or invasive ventilation in the previous year
- FEV1 <80% predicted (with FEV1/FVC reduced to less than the lower limit of normal)

Asthma exacerbations
Asthma exacerbations are defined as an increase in a patient’s symptoms requiring intensified treatments and/or unscheduled healthcare utilisation. Recurrent exacerbations are associated with a progressive decline in lung function and a high risk of severe morbidity and death; it is, therefore, critically important to identify patients at risk of exacerbating. Previous exacerbations, a predicted FEV1 <76 per cent, high levels for exhaled nitric oxide (>28ppb) and high sputum eosinophil counts have all been associated with a higher risk of asthma exacerbations and are helpful clinical biomarkers.24

The recognition of co-morbidities and exacerbation risks in every patient with severe asthma is fundamental to good-quality asthma management in primary care. Time and resource limitations in primary care necessitate referral of those with the most challenging and obstinate symptoms and is of key importance for a patient with severe asthma. The National Review on Asthma Deaths (NRAD) found...
that 43 per cent of patients who died had not had a review in primary care during the past year, and often warning signs had not been acted on.3

Referral
Patients should be considered to suffer from severe asthma after an alternative diagnosis has been excluded, co-morbidities have been treated, allergy avoidance strategies are in place and adherence with treatment and inhaler technique has been checked. Also, the severity of asthma can change over time, stressing the need for vigilant monitoring in primary care.

The 2013 international ERS/ATS guidelines classify severe asthma as a disease that requires treatment with high doses of inhaled corticosteroids (ICS) and/or systemic corticosteroids in order to obtain symptom control or which remains problematic despite this therapy.28 Any of the criteria outlined in Table 2 qualifies a patient as having ongoing symptoms and therefore severe asthma that needs referring to a specialist centre that offers a multidisciplinary service utilising a team experienced in the assessment and management of difficult asthma.26

Severe asthma requires systematic evaluation for confounding factors and exacerbating triggers and, equally importantly, confirmation that asthma is the correct diagnosis by a multidisciplinary team. Systematic assessment has the potential to identify up to half of previously deemed severe asthmatics as difficult-to-treat asthmatics.27

Treatment
Most patients with severe asthma require treatment according to Step 4 or 5 of the BTS/SIGN asthma guideline,29 ie a long-acting beta agonist (LABA) and high-dose ICS. Another option at Step 4 is to combine two long-acting bronchodilators with different modes of action. In two replicate randomised controlled trials in 912 patients the addition of tiotropium to ICS and LABA has been shown to sustain bronchodilation over 24 hours and to significantly reduce exacerbation rates when compared to placebo over a period of 48 weeks.28 Further treatment options on Step 4 of the treatment ladder include leukotriene antagonists and/or slow-release theophylline and, according to Step 5, continuous or frequent courses of oral corticosteroids.

Methotrexate is a valid agent in patients who, despite long-term treatment with oral corticosteroids, fail to gain satisfactory control of their asthma.29 Due to its substantial side-effect profile it is advised that only physicians with expertise in severe asthma prescribe methotrexate.

Continuous prophylactic treatment with a macrolide antibiotic has been proven effective in respiratory diseases due to their anti-inflammatory and immune-modulatory activity. Studies have shown a reduction in severe exacerbations in patients with non-eosinophilic asthma and a significant improvement in the Asthma Quality of Life Questionnaire score.30 However, a growing risk of population resistance to antibiotics means treatment should be carefully considered and restricted to severe asthma patients with frequent infective exacerbations.

Despite these treatment options, a number of patients remain symptomatic on a daily basis with their lives not only affected by a chronic disease, but are further impacted by the numerous and serious side-effects of oral corticosteroids. For most patients with severe asthma, standard treatment is not sufficiently effective. Severe asthma is particularly heterogeneous in its nature and certain types of patients will respond better to specific therapies than others. For the future, phenotype-specific therapies promise enhanced treatment success.31 Much effort has been directed at characterising severe asthma subgroups or phenotypes. The Severe Asthma Research Program (SARP) identified distinct sub-phenotypes by unbiased cluster analysis (see Table 3).32

Recent advances
A number of exciting therapies have been developed to improve severe asthma management. Biologicals directed against specific cytokines that are key players in driving the inflammatory process in asthma promise new therapeutic possibilities and more individualised asthma management.

Omalizumab
Omalizumab (Xolair) remains so far the most successfully applied monoclonal antibody to treat allergic asthma by reducing the exacerbation rate. Current NICE guidelines recommend omalizumab as an option for treating severe, persistent and confirmed allergic IgE-mediated asthma as an add on to optimised standard therapy in patients who need continuous or frequent (defined as four or more courses in the previous year) treatment with oral corticosteroids. A number of studies have demonstrated significant improvements in asthma-related symptoms allowing the patient to reduce the dose of corticosteroids and frequency of rescue inhaler.33–35

It appears that patients with blood eosinophilia and high levels of exhaled

---

**Table 3. Severe asthma sub-phenotypes**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early-onset allergic asthma</strong></td>
<td>Characterised by atopy and a generally good clinical response to corticosteroids and, if indicated, anti-IgE treatment. Immunologically driven by Th-2 cells.</td>
</tr>
<tr>
<td><strong>Late-onset eosinophilic asthma</strong></td>
<td>Distinguished by high sputum eosinophilia, has a poor response to corticosteroids. More frequently seen in males. Novel promising treatments include anti-IL-5.</td>
</tr>
<tr>
<td><strong>Obesity-related asthma</strong></td>
<td>Associated with adult onset and corticosteroid insensitivity and more frequently seen in women. Non-eosinophilic.</td>
</tr>
<tr>
<td><strong>Neutrophilic asthma</strong></td>
<td>Sputum neutrophils and poor response to corticosteroids.</td>
</tr>
</tbody>
</table>
nitric oxide most benefit from anti-IgE treatment.36 There is further evidence emerging that omalizumab may have a role in non-atopic asthma. A recent trial demonstrated significantly increased asthma control and a trend to reduced exacerbation rates and improved lung function in non-atopic asthma.37,38 Patients need to be made aware that treatment has to be given regularly, on a long-term basis and in specialist centres only.

Novel therapies
Promising novel treatments with steroid sparing potential targeting the cytokine pathway include the anti-interleukin-5 (anti-IL-5) antibody mepolizumab. Mepolizumab treatment has been shown to significantly reduce exacerbations and oral corticosteroid doses in patients with eosinophilia in blood and sputum.39 In the DREAM (Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma) study mepolizumab was well tolerated and displayed a good safety profile and efficacy in 621 patients over a one-year period.39

Clinical trials have also investigated targeted therapies against the Th2 cytokines IL-4 and IL-13. Periostin is a serum protein induced by IL-13, a key cytokine orchestrating bronchial hyper-responsiveness, inflammation and airway fibroblast proliferation. It has proven to be an important prognostic biomarker for treatment with the anti-IL-13 antibody lebrikizumab. A recent study demonstrated that treatment with lebrikizumab increased FEV1 in patients with a high serum periostin level.40 Other therapies under development, and yet to show any clear clinical benefit, are listed in Table 4.

Vitamin D
There has been a considerable amount of literature published linking deficiency in serum vitamin D status to chronic inflammatory lung disease such as asthma.41 Reports have shown a positive correlation between vitamin D deficiency and asthma prevalence, asthma exacerbation rate and hospital admissions.52-44 Studies suggest a role for vitamin D in severe asthma that is less responsive to corticosteroid treatment.55,46

<table>
<thead>
<tr>
<th>Table 4. Other asthma therapies currently under development but have yet to show any clear clinical benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-pharmacological therapy</strong></td>
</tr>
<tr>
<td>Chronic airway inflammation and structural changes in the airways, termed airway remodelling, are a distinct feature in severe asthma. Smooth muscle hyperplasia is a significant component of airway remodelling. Applying radiofrequency energy to sub segmental airways has been shown to reduce muscle mass at the site of thermoplasty. Trials investigating the effect of bronchial thermoplasty demonstrated a reduction in the number of severe asthma exacerbations and improvement in asthma-specific quality of life47 and a recent study found no adverse events after a five-year follow up period.48</td>
</tr>
<tr>
<td>Although guidelines recommend bronchial thermoplasty for adults with severe asthma that is not controlled on inhaled corticosteroids and LABAs, it is currently unclear which phenotypes respond best to this treatment. Studies are needed to identify the phenotype of patients that will derive significant clinical benefit most from this invasive procedure.</td>
</tr>
</tbody>
</table>

Conclusion
Asthma is a common disease and in most cases responds well to standard treatment. Severe asthma affects a minority of patients, yet they remain an ongoing challenge for healthcare professionals. A multidisciplinary systematic approach to diagnosis and treatment is essential and allows for the assessment of novel treatments for carefully-selected patients. GPs should consider referring patients who fulfil any of the severe asthma criteria to specialised centres for further investigations and management. Within the next 5–10 years multiple targeted therapies should become available that have the potential to revolutionise severe asthma care and end our dependence on oral corticosteroids for this patient population.

Recommended reading

References

Declaration of interests
Dr Nanzer has none to declare. Dr Menzies-Gow has attended advisory boards for Roche, Mundi Pharma, Boeringher Ingelheim, Amgen and Johnson and Johnson. He has also received lecture fees from Novartis, NAPP and GlaxoSmithKline, and attended international conferences with Novartis and Boeringher Ingelheim.

Dr Nanzer is a specialist registrar in respiratory medicine and Dr Menzies-Gow is a consultant in respiratory medicine, Royal Brompton & Harfield NHS Foundation Trust, London