**SEVERE ASTHMA — ASSESSMENT AND MANAGEMENT**

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**ABSTRACT**

Around 5% of asthmatics have severe or difficult-to-control asthma, but they utilise a disproportionate amount of healthcare resources. Asthma that is not responding to treatment may be classified as ‘problematic severe asthma’, which is subcategorised into ‘difficult-to-treat asthma’ and ‘severe therapy-resistant asthma’. The former group includes comorbid conditions, adherence and/or technique problems, environmental allergens or irritants, and psychosocial problems, which all have to be assessed and managed before invasive investigations are undertaken to exclude other diagnoses and before stepping up treatment. A staged approach to assessment and management of problematic severe asthma is suggested. Options for therapy include high-dose inhaled corticosteroids (ICS), combinations of ICS and other controller medications, and novel therapies such as anti-IgE monoclonal antibody. New advances involve phenotyping severe asthma and individualising treatment according to the phenotype.

**INTRODUCTION**

Asthma affects approximately 300 million people worldwide. The majority of asthmatics suffer from mild-to-moderate persistent asthma; their disease can be controlled relatively easily with the current anti-inflammatory therapy available. Around 5% of asthmatics have severe or difficult-to-control asthma. Although this group is small numerically their treatment translates into high healthcare costs because of hospitalisation, as well as high indirect costs due to school and work absence.

**DEFINITIONS**

Advances in asthma research and therapy have led to the recognition of different asthma phenotypes that may respond to specific treatments. If a patient has asthma that is not responding to treatment, it is useful to use the umbrella term ‘problematic severe asthma’ and then to subcategorise it into ‘difficult-to-treat asthma’ or ‘severe therapy-resistant asthma’. Most definitions of severe asthma in adults include poorly controlled asthma despite treatment with high-dose inhaled corticosteroids (ICS) and/or oral corticosteroids (CS), a combination of other controller treatment, and a period of observation, usually 6 months (European Respiratory Society, American Thoracic Society). Definitions of severe asthma in children usually differentiate between school-aged and preschool children. In April 2009 the World Health Organization (WHO) Consultation on Severe Asthma proposed the following definition for severe asthma: ‘Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children).’ The panel subclassified severe asthma into 3 groups: (i) untreated severe asthma; (ii) difficult-to-treat severe asthma; and (iii) treatment-resistant severe asthma.

**Untreated severe asthma**

Bush and Zar point out that untreated severe asthma is an important consideration in low- or middle-income countries for two reasons: (i) there may be failure to recognise the diagnosis of asthma, or (ii) appropriate asthma treatment and delivery devices may not be available. In developed countries asthma treatment may be unavailable because of the prohibitive cost of the medication in circumstances where health insurance is not available. In South Africa we have a well-developed public health system with access to asthma therapy on the Essential Drug List, but many patients do not have access to medication through the public sector, and purchasing it privately can be very costly.

**Problematic severe asthma**

Problematic severe asthma includes both ‘difficult-to-treat’ and ‘severe treatment-resistant asthma’. In order to make the diagnosis of severe treatment-resistant asthma, it is necessary first to evaluate the patient for difficult-to-treat asthma as per Table I. The asthma symptoms often become controlled once these problems have been addressed, although sometimes the solutions are not simple.

**PROBLEMATIC SEVERE ASTHMA: CHARACTERISING THE SUBGROUPS**

**Difficult-to-treat asthma**

First of all it is important to exclude other diagnoses that may mimic asthma. In young children recurrent wheezing may be due to a number of different conditions. In older adults chronic obstructive pulmonary disease (COPD) may be difficult to distinguish from asthma and may coexist with asthma. Table II lists some of the differential diagnoses of asthma in children and adults. The differential diagnosis of asthma in older children is

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Table I. Difficult-to-treat asthma (adapted from Hedlin et al.)*

<table>
<thead>
<tr>
<th>Comorbid conditions</th>
<th>Allergic rhinitis</th>
<th>Chronic rhinosinusitis</th>
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<tbody>
<tr>
<td>Gastro-oesophageal reflux</td>
<td>Obesity</td>
<td>Medication</td>
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<td>Adherence</td>
<td>Delivery system</td>
<td>Technique</td>
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<td>Allergen exposure, including food allergy</td>
<td>Environmental exposure (ETS)</td>
<td>Smoking</td>
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<tr>
<td>Psychosocial issues</td>
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also discussed by Kerbelker and Levin in this issue of *Current Allergy & Clinical Immunology.*6

The subgroup of problematic severe asthma includes poorly controlled asthma due to comorbid conditions, adherence and/or technique problems, environmental allergens or irritants, or psychosocial problems (Table I).3 These issues must be addressed before considering stepped-up or novel therapies.

**Comorbid conditions (‘asthma plus’)**

Coexisting asthma and allergic rhinitis are common, and uncontrolled rhinitis may negatively impact asthma control (the ‘united airway’ concept).7 Similarly, gastro-oesophageal reflux and asthma are interrelated, but antireflux treatment does not necessarily improve asthma control.8,9 Vocal cord dysfunction may not only mimic asthma but may also coexist with it, and obesity is associated with asthma severity.1

**Medication: adherence, delivery system and technique**

Poor treatment adherence is the most frequent cause of uncontrolled asthma,3,10-12 in some healthcare systems it is possible to check whether prescriptions have been filled, but this does not necessarily imply that the medication is being taken. Inhaler devices may contain computer chips that record doses and times of actuation, but this is usually done in the context of clinical trials. At follow-up visits questions regarding adherence need to be carefully phrased to obtain accurate information.

Inhaler technique should be assessed at every healthcare visit and the suitability of the delivery device for the patient checked. ICS delivered by a metered-dose inhaler (MDI) should always be administered with a spacer, unless the technique is good and a device delivering a soft plume of inhaled drug is available.

**Other factors**

Hedlin *et al.* recommend that the home environment of patients with poorly controlled asthma should be assessed by a health visitor to determine exposure to passive smoking, environmental allergens, cooking fires, pollution, damp and mould.2 This is not possible in all healthcare settings, but it is important to inquire carefully about the environment. Hobbies, such as pigeon-racing and woodwork, may expose patients to allergens and irritants not previously suspected, and occupational exposures are also important. Food allergy is associated with severe asthma.1

**Psychosocial factors**

Psychological problems and psychosocial stress are risk factors for fatal and near-fatal asthma.14,15 Chen *et al.* demonstrated that factors such as poor family and peer support, and neighbourhoods with high levels of crime, violence and drug abuse all negatively affected asthma control via both biological pathways and health-related behaviour.16

**SEVERE TREATMENT-RESISTANT ASTHMA**

This category includes patients in whom the aforementioned aspects have been addressed and rectified where possible, and who have persistent asthma symptoms despite optimal management with high-dose ICS, multiple controller medications and, usually, oral CS. The level of treatment prescribed will vary according to the setting and depends on what is available.4 Two groups are identified: (i) those patients whose symptoms persist despite high doses of available medications, including oral CS; and (ii) patients whose symptoms are controlled, but with such high doses of medication that severe side-effects result.5 The terms ‘refractory asthma’ and ‘steroid-resistant asthma’ are used to describe those patients whose symptoms persist despite high doses of available medications, including oral CS.

**ASSESSMENT OF THE PATIENT WITH SEVERE ASTHMA**

This assessment is adapted from Lødrup Carlsen *et al.*17

**Step 1: Confirm the diagnosis of asthma**

Consider mimics of asthma, particularly in the young child (Table I). A detailed history and examination will go a long way in supporting or excluding the diagnosis of asthma. If uncertainty still exists, then basic special investigations should be performed, such as a chest X-ray, lung functions (above 6 years of age), allergen skin-prick or specific IgE testing, immunoglobulins, HIV test and sweat test. Exclude comorbidities such as recurrent microaspiration, snoring, recurrent upper respiratory tract infections, recurrent otitis media, recurrent tonsillitis, and recurrent bronchitis.

<table>
<thead>
<tr>
<th>Table II. Differential diagnosis of asthma in children and adults (adapted from Bel <em>et al.</em>)</th>
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<tr>
<td><strong>Children</strong></td>
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<td><strong>Older children</strong></td>
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<td><strong>Adults</strong></td>
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as gastro-oesophageal reflux. Other investigations will be guided by the history, examination and geographical situation (disease prevalence) of the patient.

**Step 2: Assess and address the basics**

This step is aimed at identifying the patient with ‘difficult-to-treat’ asthma. All the factors mentioned above must be assessed, particularly medication adherence and technique and environmental exposures. Home visits may identify problems such as adverse living conditions and allergen and/or smoke exposure. The role of allergen avoidance in established asthma is questionable, but house-dust mite avoidance may be advisable in severe asthma. Patients with severe asthma and mould allergy may benefit from antifungal therapy as well as mould avoidance measures.

**Step 3: Assess steroid responsiveness**

Once all the above have been excluded and the patient is not improving on high-dose ICS together with other controllers, a 2-week course of prednisolone is instituted and the response assessed, either clinically in a young child or objectively in older children. An alternative to prednisolone is intramuscular depot triamcinolone. Response to therapy can be assessed using the Asthma Control Questionnaire (ACQ). Measures indicating complete response are ACT score $\geq 20$; bronchodilator use fewer than 3 times per week for symptom relief; normal prebronchodilator forced expiratory volume in 1 second (FEV$_1$); and normal measures of inflammation.

**Step 4: Assess pattern of inflammation**

Patients that do not respond after steps 1-3 merit further investigation in a specialised unit. Measurement of the exhaled nitric oxide fraction (FeNO) is a non-invasive technique of measuring eosinophilic inflammation, and may actually have a place in step 1 if it is readily available. Whether FeNO has a clinical role in severe asthma remains uncertain. Fibreoptic bronchoscopy with endobronchial biopsy and broncho-alveolar lavage may be indicated so that the inflammatory response can be measured and structural airway changes excluded.

**Management of the patient with severe asthma**

The staged approach to assessment determines the therapy required to manage the patient with severe asthma. Kupczyk and Wenzel suggest that asthma phenotypes should be classified according to clinical features, genetics, natural history and pathobiology, and treatment individualised according to the phenotype (Table III).

### Table III. Phenotypic categories of asthma (adapted from Kupczyk and Wenzel and Bush and Saglani)

<table>
<thead>
<tr>
<th>Clinical and physiological phenotypes</th>
<th>Phenotypes according to triggers</th>
<th>Phenotypes according to underlying pathobiology</th>
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<tbody>
<tr>
<td>Level of current prescribed treatment</td>
<td>Induced by aspirin or other non-steroidal anti-inflammatory drugs</td>
<td>Eosinophilic</td>
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<td>Frequent exacerbations</td>
<td>Allergens</td>
<td>Neutrophilic</td>
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<tr>
<td>Chronic/irreversible airway obstruction</td>
<td>Occupational (allergens, irritants)</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Treatment resistant</td>
<td>Premenstrual</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Defined by age of onset</td>
<td>Exercise</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Future risk of complications</td>
<td></td>
<td>Paucicellular</td>
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</table>

**Non-pharmacological management**

All the issues discussed under ‘difficult-to-treat’ asthma need to be addressed, and comorbid conditions must be treated appropriately. Non-adherence with anti-inflammatory medication is particularly problematic, and results in poor asthma outcomes and high costs of treatment. Another potential consequence is the inability to diagnose refractory asthma or severe treatment-resistant asthma correctly, with resultant use of expensive therapies. A recent Cochrane review concluded that there is ‘surprisingly weak’ evidence that non-adherence can be modified. However, the current view is that non-adherence is a failure of the healthcare system that is best comprehended as ‘a variable behaviour with intentional and unintentional causes – unintentional non-adherence is linked to limitations in capacity or resources whereas intentional non-adherence is the product of a decision informed by beliefs, emotions and preferences. Adherence is influenced by the patients’ beliefs about medicines – in particular, how they judge their personal need for the treatment (necessity beliefs) relative to their concerns about potential adverse effects.

If one identifies the problem and addresses it in a medical concordance interview, continued behavioural change occurs. More complex approaches are required in people who continue to manifest non-adherence.

The environment is often very difficult to alter, but at least smoking and exposure to passive smoking should be addressed, and interventions put in place where possible.

Psychosocial issues are much more difficult to address; fewer studies are available that assess the effect of psychological interventions and family therapy on asthma outcomes.

**Pharmacological management**

### Step-up therapy

Options for step-up therapy are: increased doses of ICS, or add-on long-acting $\beta_2$-agonists (LABAs) or leukotriene-receptor antagonists (LTRAs) or theophylline, or multiple controllers, or oral CS. The BADGER trial evaluated the best step-up therapy options in children aged 6-17 years.

Ninety-eight per cent of the participants exhibited differential responses, with the best response to LABA step-up compared to LTRA or ICS step-up. In this study improved asthma control was obtained with the addition of a different controller medication compared to increasing the dose of ICS. Although the majority of the children responded best to add-on LABA, some participants showed better responses to other medications. Most paediatric guidelines recommend adding on LABAs in children older than 5 years and LTRAs in children younger than 5 years, before increasing the dose of ICS.
studies and guidelines also support adding on LABA to ICS or using combination inhalers, before increasing the ICS dose. One option is the SMART (Symbicort maintenance and reliever therapy) regimen, using budesonide/formoterol in a single inhaler as both controller and rescue therapy.27,28 If asthma control remains suboptimal, then sequential add-on therapy may be required (i.e. LTRAs, theophylline, or multiple controller drugs), although the evidence for this is poor.24 Long-term oral corticosteroids may be indicated in patients who do not respond to this regimen.

Other therapies

Anti-IgE monoclonal antibody

Omalizumab is a humanised monoclonal antibody which binds to circulating IgE and reduces levels of free IgE in the serum. It is given as a subcutaneous injection every 2-4 weeks depending on the dose and is indicated in adults and children over 6 years of age who have poorly controlled asthma with frequent exacerbations, and have allergy as an important cause of their asthma.24 Generally it is thought not to work if the total IgE is >1 500 IU/ml, although Bush and Saglani do try it in children with higher IgE levels than recommended.18,24

Corticosteroid-sparing drugs

In patients with a poor response to treatment despite requiring high-dose systemic CS, other steroid-sparing agents such as methotrexate, cyclosporin or azathioprine may be tried for a limited period, but they have the potential for severe side-effects and the evidence for their use is limited.18,24

Macrolides

Macrolides are used in respiratory conditions with largely neutrophilic inflammation, and have been tried in patients with uncontrolled asthma who have neutrophilic inflammation.24,30

Other therapies

Oral theophyllines may have a role in neutrophilic asthma as they promote neutrophil apoptosis.24 Itraconazole may be beneficial in children and adults with fungal sensitisation.24,31 Newer therapies include anti-interleukin-5 antibody, other monoclonal antibodies and bronchial thermoplasty.24,32 Vitamin D deficiency and insufficiency have been associated with wheezing, reduced lung function and asthma in both children and adults, and may be associated with steroid resistance.33 Vitamin D can currently not be recommended for treatment of severe asthma, but future research may well define a role for it as a steroid-sparing agent.33

CONCLUSION

Severe asthma in children and adults may be due to many associated factors or to true therapy-resistant asthma. Using a staged approach to the assessment of patients with problematic severe asthma may reduce the need for specialist referral and invasive special investigations, and lead to improved asthma control.24 Treatment strategies should be tailored to the cause of the problematic severe asthma and should be adapted according to the asthma phenotype.18,33

Future research trends in severe asthma combine multiple international collaborating investigators and new modelling techniques to define difficult-to-treat asthma phenotypes and approaches to therapy.3 This will hopefully lead to individualised successful management of this small but important group of patients.

Declaration of conflict of interest

SK has given talks for MSD and was sponsored to the 2010 ALLSA congress by Cipla Medpro.

REFERENCES


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• Less sedating side-effects
• Inhibits events leading to allergic inflammation
• Relieves symptoms associated with seasonal allergic rhinitis
• Relieves nasal congestion
• Rapid onset of action (1-2 hours after administration)
• Offers 24 hour relief


MIMS 2011: 516]; 96-99.