Difficult asthma

Some patients will have persistent symptoms despite apparently adequate therapy.

J O'BRIEN, *MMed, FCP (SA), FCCP*
Pulmonologist in private practice, Christiaan Barnard Memorial Hospital, Cape Town

John O'Brien trained in medicine and pulmonology at the University of Cape Town, Groote Schuur Hospital and at the New England Medical Centre in Boston, USA. He is the current president of the South African Thoracic Society (SATS) and was involved in the development of the latest SATS asthma guidelines. He has been involved in numerous clinical studies in asthma.

The South African Thoracic Society recently updated the guidelines for the management of chronic asthma.[1] The vast majority of asthma patients will achieve excellent control by following these treatment recommendations. As with all medical conditions there are, however, a group of patients who will have persistent symptoms despite apparently adequate therapy.

The American Thoracic Society published criteria for the diagnosis of refractory asthma in 2000 (Table I).[2] At least one major and two or more minor criteria are required for the diagnosis of refractory asthma. The European Respiratory Society (1999)[3] defined 'difficult/therapy-resistant asthma' as 'that which is poorly controlled in terms of chronic symptoms, episodic exacerbations, persistent and variable airways obstruction and a continued requirement for short-acting beta$_2$ agonists despite delivery of a reasonable dose of inhaled corticosteroid'.

Table I. Diagnostic criteria for refractory asthma

Major characteristics

- Use of oral corticosteroids – 50% of the time
- Continuous use of high-dose inhaled corticosteroid (-1 200 µg beclomethasone or equivalent)

Minor characteristics

- Requires daily treatment with controller medication, e.g. long-acting beta$_2$ agonist, theophylline or leukotriene antagonists, together with inhaled corticosteroids
- Daily asthma symptoms requiring rescue medication
- Persistent airway obstruction (FEV$_1$ <80% predicted; diurnal PEF variability >20%)
- One or more urgent care visits for asthma in the last year
- Three or more 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

At least one or both major criteria and two minor criteria. Requires other conditions to have been excluded.

Does the patient really have resistant asthma?

Before labelling the patient as having refractory asthma it is important to review the common treatment errors and associated factors that lead to poor control (Table II).

Poor adherence to treatment and poor inhaler technique are probably the most common reasons for suboptimal control. Patients

Table II. 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 hospitalisations in the past year
- Admissions to asthma centres ever
- Number of ICU admissions

Exogenous aggravating factors
- Exposure to allergens, occupational agents, chemicals
- Use of aspirin, NSAIDs, beta blockers, ACE inhibitors, oestrogens
- Influence of food 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 to medications
- Adverse effects of treatment
- Psychosocial circumstances

Physical examination (specific points of attention)

Body mass index
Evidence of co-morbidities (e.g. nasal polyps)
Evidence of alternative diagnoses (e.g. cardiac failure)
Evidence of adverse effects of treatment

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fail to take their medication regularly for a number of reasons. Many are unwilling to accept that they have chronic asthma and discontinue or reduce treatment as soon as there is a perceived improvement. Others, despite reassurance, are concerned about the safety of inhaled steroids. Financial concerns and affordability are

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topics patients may be reluctant to discuss. Uncommonly, psychological factors may cause the patient to choose the 'sick role' and default on treatment.

Continued exposure to airway irritants such as cigarette smoke, or external allergens such as pets sleeping on the bed, will make it very difficult to achieve control and repeated enquiries need to be made regarding these factors. Patients will try banning their pets from the bedroom for a week or two; when there is little change in their symptoms they believe that the pets do not play a role. However, pet antigens can persist for many months before levels drop significantly.

Patients may also be taking medication which they consider innocuous (e.g. beta-blocker eye drops or NSAIDs).

Common associated conditions

Asthmatics commonly have associated conditions that impact on asthma control. The most common and important of these are:

Chronic sinusitis and upper airways allergy

Nasal allergy, congestion and sinusitis can contribute to poor asthma control by a number of mechanisms. These include direct irritation and infection of the lower airways by a postnasal drip, transfer of inflammatory mediators locally and systemically, reflex bronchoconstriction, and alteration in the perception of breathlessness. Treatment of the upper airways is not always easy but should be pursued enthusiastically.

Gastro-oesophageal reflux disease (GORD)

It remains controversial how often GORD contributes to poor asthma control. In the difficult asthmatic, particularly if there is associated obesity, GORD needs to be considered. The reflux may be asymptomatic and can be difficult to diagnose. A trial of high-dose PPI treatment may be the most practical way of assessing this, but even with control of pH reflux may still be present and pH monitoring with manometry may be necessary.

Other conditions associated with severe asthma include obesity, snoring and obstructive sleep apnoea, and psychosocial factors. Obesity can be a particularly difficult problem. The increased work of breathing aggravates the perception of breathlessness. Obesity itself is associated with asthma and many severe asthmatics are committed to long-term or intermittent corticosteroids which may well aggravate their weight problem. This emphasises the fact that medication has to be considered as only one component of the management of the severe asthmatic. These patients should be encouraged to exercise, remain physically fit within their limitations, and pay attention to other general health factors.

With the difficult asthmatic it is particularly important to review the diagnosis and consider referral to a specialist.

Alternative diagnoses

Most respiratory clinics and physicians would have treated patients who presented with clinical features of asthma but had other conditions, e.g. tracheal stenosis or compression of the trachea by mediastinal nodes. With the difficult asthmatic it is particularly important to review the diagnosis and consider referral to a specialist. Careful attention to the history, both past and present, lung function (in particular the flow-volume loop) and chest radiograph will enable an accurate diagnosis to be made in the majority of patients. A list of alternative diagnoses to consider is given in Table III. Particular mention needs to be made of vocal cord dysfunction. This most commonly occurs in asthmatics and can be very difficult to treat. Diagnosis is important in order to avoid unnecessary long-term systemic steroids with their attendant side-effects, as steroids are unhelpful in this condition. Vocal cord dysfunction has recently been reviewed in *Breathe* (2006).[5] The other diagnosis that needs to be considered is dysfunctional breathing.[6] Patients with this condition, while having asthma, tend to develop abnormal breathing patterns – often with hyperventilation and frequent deep sighs. Breathing retraining and exercise conditioning can be helpful in this group.

Table III. Alternative diagnoses in difficult asthma

- COPD
- Bronchiectasis
- Congestive cardiac failure
- Central airway obstruction
- Cystic fibrosis
- Recurrent pulmonary embolism
- Pulmonary hypertension
- Recurrent aspiration
- Vocal cord dysfunction
- Dysfunctional breathing
- Allergic bronchopulmonary aspergillosis
- Churg-Strauss syndrome
- Psychological disorders

Patterns of difficult asthma

There are two main patterns of severe asthma.[7] Some patients have persistently low lung function and significant baseline breathlessness that deteriorates at times of exacerbations. Other patients may have well-preserved lung function but unstable airways and can deteriorate acutely and severely. These patients may be called brittle asthmatics. Type I brittle asthmatics are patients who have marked day-to-day variation in lung function and symptoms despite adequate preventive treatment. Gastro-oesophageal reflux should be actively sought in these patients. Type II brittle asthmatics are patients who develop acute, severe life-threatening attacks that are not necessarily preceded by a general worsening of their asthma. Luckily this is extremely unusual but it is certainly a form of fatal asthma that is particularly difficult to control.

For information on the pathophysiology of severe asthma please refer to Breathe (www.breathe-cme.org).[8]

Recommended investigations

The investigations recommended for the assessment of patients with difficult-to-control asthma will be guided by the clinical assessment. Table IV indicates appropriate baseline investigations before specialist referral.

Treatment

From a therapeutic point of view, once the diagnosis has been confirmed and the aggravating factors documented above have

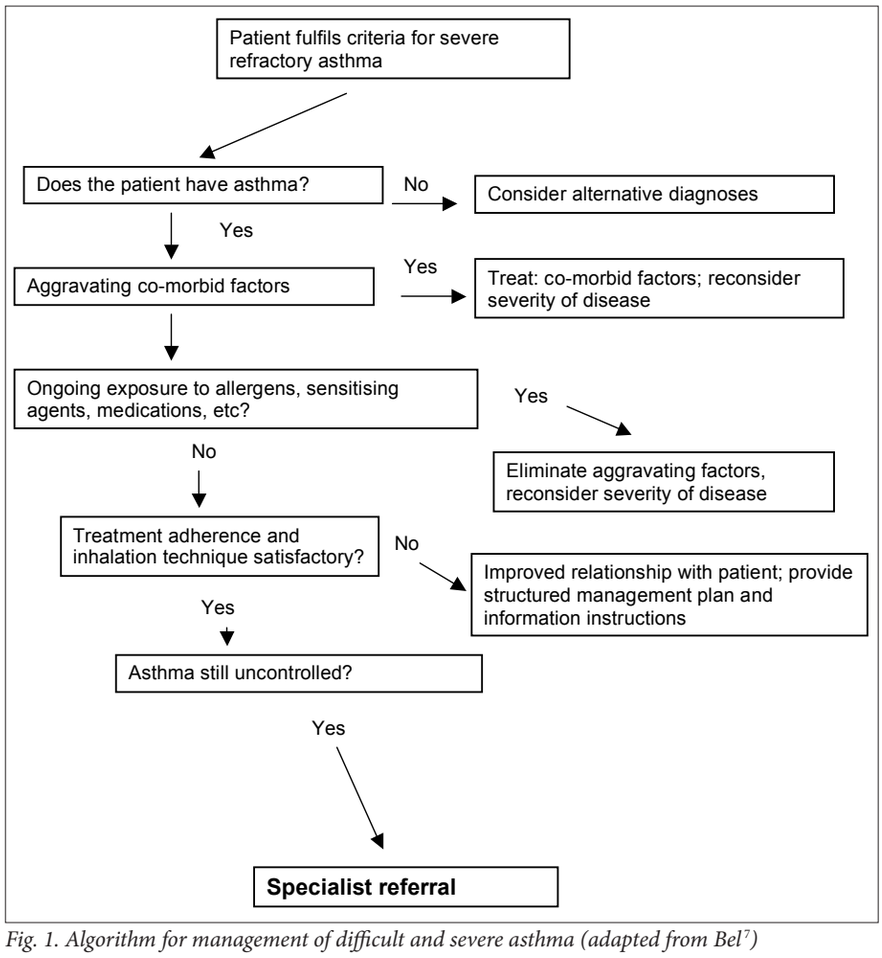

Fig. 1. Algorithm for management of difficult and severe asthma (adapted from Bel[7])

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

Peripheral blood
- Erythrocyte sedimentation rate
- Full blood count (eosinophils)
- Total serum IgE

Lung function
- Spirometry (pre- and post-bronchodilator)

Radiology
- Chest radiography
- Sinus CT

been attended to, the patient needs to be given a treatment plan with regular assessment and modification of the plan as necessary. All patients with difficult asthma need to be on high-dose inhaled corticosteroids. These patients will invariably be on a combination inhaler with a long-acting beta$_2$ agonist. While it is true that the dose response for inhaled steroid is relatively flat many patients will benefit from higher doses of inhaled steroid, particularly those with eosinophilic inflammation. Before adding additional medications it is important to ensure that the dose of inhaled steroid is adequate. If there is a disappointing response to an adequate dose of one inhaled steroid it is reasonable to try a different agent from this class to see if the poor response reflects a general steroid resistance or lack of response to an individual steroid.

When inhaled steroids were first used in cases of asthma they were administered four times a day. Subsequent studies have shown that twice daily administration can achieve the same results in the majority of patients, with the convenience of less frequent dosing. In the difficult asthmatic increasing the dose and frequency of the inhaled steroid is worth trying.

The theophyllines have become second-line asthma medications because of their relatively poor bronchodilator effect and high side-effect profile. This, however, does not mean that they are useless; they may indeed be useful in the difficult asthmatic.

The leukotriene antagonists are usually well tolerated and in some asthmatics can provide significant benefit. The difficult asthmatic justifies a trial of anti-leukotriene therapy before being committed to oral steroids. One needs to avoid adding medications that do not significantly contribute to asthma control. If there is no evidence of benefit from anti-leukotriene medication it should be withdrawn.

Many severe asthmatics will require systemic steroids. If long-term oral corticosteroids are necessary it is important to limit the dosage as far as possible and to reduce side-effects by encouraging exercise and monitoring bone density, blood sugar, etc. If there is doubt with regard to adherence to oral steroids a trial of long-acting intramuscular steroid will help determine steroid responsiveness. Indeed, with long-term steroid use there is some evidence of reduced absorption and occasionally long-term parenteral steroids may be required. This has been shown to be effective, but it is associated with significant side-effects. Some patients show true steroid resistance.[9] Most of these patients are, however, maintained on at least a modest dose of oral corticosteroid.

Monitoring of lung function by home peak flow and FEV_1 devices is essential. Many patients will not be diligent enough to measure the peak flow twice a day but they should be encouraged to be as regular in monitoring their lung function as diabetics are in monitoring their blood sugar level. The lung function can be linked to a treatment action plan. Lung function may start to dip before there is a significant increase in breathlessness. Early intervention with corticosteroids may prevent severe exacerbations and hospitalisation.

Alternative treatment options

For patients on maximum treatment with standard medications who are steroid dependent there are limited alternatives. Methotrexate has been used as a steroid-sparing agent, with varying success. Anti-IgE antibody is now commercially available internationally but is not currently registered in South Africa. Atopic patients with elevated IgE levels may obtain significant benefit but cost constraints limit the use of this product (~ US$1 000.00 per month).

Bronchial thermoplasty[10] is a technique in which radiofrequency probes are used to stimulate the airway and potentially cause retraction of smooth muscle. The first reports suggest that this relatively simple technique may have a limited role in resistant asthma.

Summary

The majority of patients with difficult and severe asthma will achieve adequate control if attention is given to the points described above. In particular, adherence to medication regimes and correct inhaler technique are important. (For assessment algorithm see Fig. 1). If, despite these measures, control remains suboptimal, referral to a pulmonologist is recommend.

The usual aim of asthma control is to achieve absence of symptoms and normal lung function. In cases of severe and difficult asthma one aims to avoid hospitalisation and achieve the best possible control with minimal medication side-effects.

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In a nutshell

- Some asthmatics will have persistent symptoms despite apparently adequate treatment.
- Review possible factors, such as treatment adherence, that lead to poor control before labelling a patient as having resistant asthma.
- Poor adherence to treatment and poor inhaler technique are probably the most common reasons why suboptimal control is achieved.
- Chronic sinusitis and upper airways allergy as well as gastro-oesophageal reflux are also associated with poor asthma control.
- Always refer to a specialist when a patient has resistant asthma in order to rule out alternative diagnoses.
- Some patients have persistently low lung function and significant baseline breathlessness which deteriorates at times of exacerbations.
- Other patients may have well-preserved lung function but unstable airways and can deteriorate acutely and severely. They are called brittle asthmatics.
- All patients with difficult asthma require high-dose inhaled corticosteroids and many severe asthmatics will need oral steroids periodically.

Single Suture

Flu deaths in the family

Although anyone can die of flu, it appears that you are more likely to die of the viral infection if you catch the virus from a blood relative. Lisa Albright and colleagues, from the University of Utah, looked at death certificates and family records dating back 100 years. Nearly 5 000 people had died of flu, 2 000 of them in the 1918 pandemic.

The team found that blood relatives of flu victims were more likely to die than non-relatives, even during different flu outbreaks. The risk increased the more closely related the people were. Siblings were 74% more likely to die of flu than unrelated people and blood uncles and first cousins of flu victims were, respectively, 22% and 16% more likely to die. Victim's spouses were also more likely to die, probably because they lived in the same house, but their relatives were not at higher risk of death.

Researchers are now tracking relatives of people who died recently to see if they too are at increased risk and if a flu vaccine helps.

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