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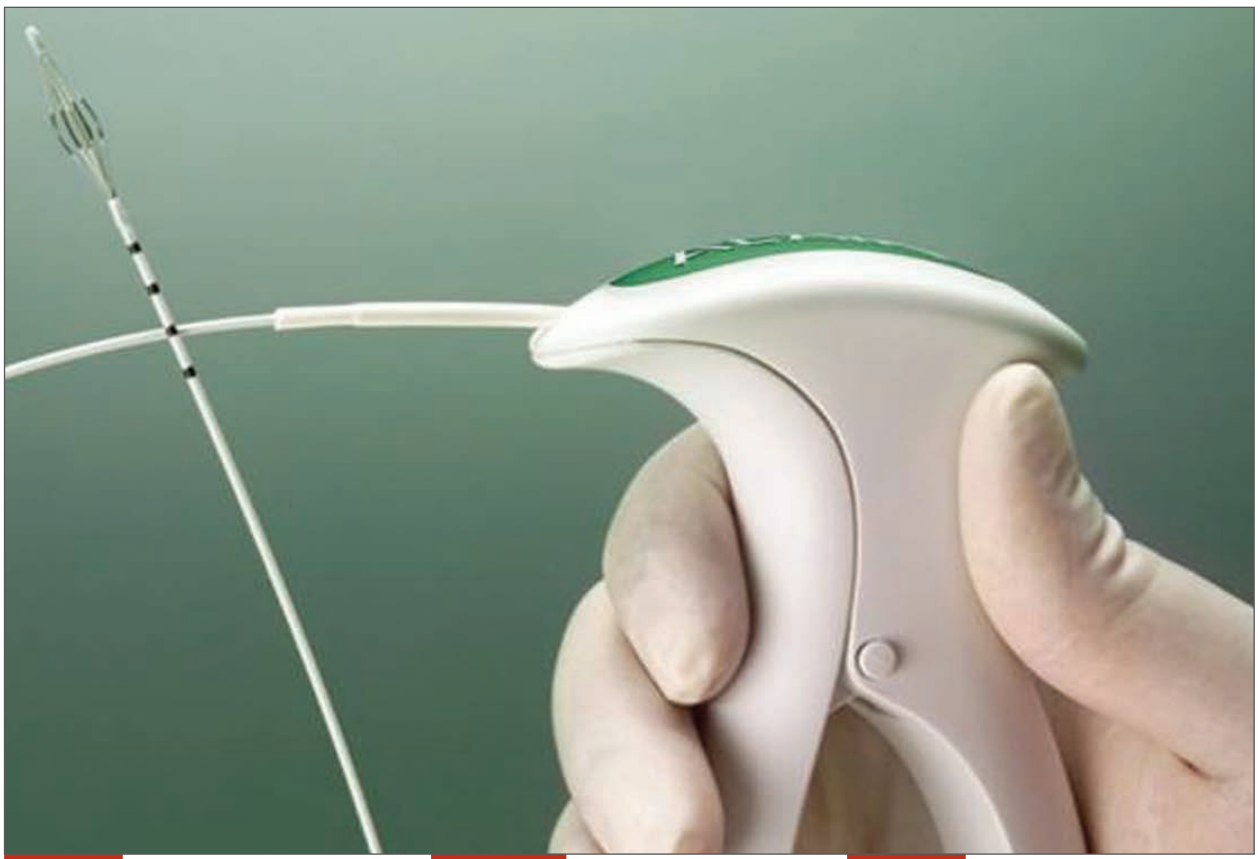


FIGURE 1
Bronchial thermoplasty for severe asthma: the procedure aims to reduce the small airways smooth muscle mass, thereby decreasing the airways' ability to constrict. It is carried out under sedation or general anaesthetic and involves inserting a catheter into the bronchial tree and administering radiofrequency energy to the airway walls

What are the underlying causes of difficult asthma?

ASTHMA AFFECTS 5.4 MILLION PEOPLE IN THE UK,[1] APPROXIMATELY 1 IN 12 OF THE POPULATION.

Most of these patients are successfully managed in primary care. However, 5-10% of asthma (depending on the definition used) is categorised as difficult asthma, a term which generally refers to patients who continue to experience symptoms and frequent exacerbations despite the prescription of high-dose asthma therapy.[2] In the UK this equates to those who remain symptomatic while receiving BTS/SIGN step 4 or step 5 treatments.[2]

Although they represent a minority of those with asthma, these patients will feature on most practice lists and be familiar to GPs as managing these patients is tricky, time-consuming and potentially expensive.

Which patients are at increased risk of death?

Difficult asthma is an indication for specialist review by an appropriate respiratory physician, but close liaison between primary, secondary and tertiary care is critical and it is therefore important that primary care healthcare professionals should be aware of the principles of management.

'Difficult asthma is an indication for specialist review by a respiratory physician'

What are the management approaches?

This article outlines the management of difficult to treat asthma, taking for granted that basic measures such as ensuring good inhaler technique and smoking avoidance are in place; and that, as in milder asthma, patients are offered self-management education which should include a personalised asthma management plan.

CONTRIBUTING FACTORS

Poor adherence

One of the most important questions to ask is whether the individual with difficult asthma is taking their treatment. UK studies in specialist clinics for difficult asthma have documented high levels »

Table 1

Adverse behavioural and psychosocial features associated with severe asthma in patients at risk of developing fatal or near-fatal asthma[4]

- Non-adherence with treatment or monitoring
- Failure to attend GP appointments
- Fewer GP contacts
- Frequent home visits
- Self-discharged from hospital
- Psychosis, depression, other psychiatric illness or self-harm
- Current or recent major tranquilliser use
- Denial
- Alcohol or drug use
- Obesity
- Learning difficulties
- Employment problems
- Income problems
- Social isolation
- Childhood abuse
- Severe domestic, marital or legal stress

of poor adherence.[3] Identifying this, however, is not easy.

Direct questioning may be revealing but more often it is necessary to acquire objective evidence. GPs could assess prescription uptake, looking for low use of preventers and excess use of short-acting bronchodilators. In some parts of the country it is possible to look at filled pharmacy prescriptions.

'Look for low use of preventers and excess use of short-acting bronchodilators'

Newer means of assessing adherence have been developed. Inhaler devices that can monitor completion and timing of actuations have been produced, but are not in general use.

Meters that measure fractional exhaled nitric oxide (FeNO) are available now, although currently used in few practices. High FeNO levels are suggestive of undertreatment, including poor adherence. For those on regular oral corticosteroids, prednisolone levels can be measured although at present the number of laboratories offering this is limited.

Once identified, strategies to improve adherence will need to be based on the individual circumstances of the patient, working around the particular reasons for their non-adherence.

AT-RISK PATIENTS

People with severe asthma and one or more adverse psychological factors, see table 1, above, are at increased risk of death.

The National Review of Asthma Deaths showed that behavioural and adverse psychological factors were recorded in the majority of patients who died from asthma,[4] that they tended to miss appointments and to have less GP contact or fewer home visits as well as poor treatment adherence. These behavioural patterns and the associated psychological factors can be identified in primary care.

Despite the close association between asthma exacerbations and psychological factors, there is a lack of evidence that interventions specifically targeting psychological morbidity are of benefit in asthma.

A meta-analysis of psychoeducational interventions in adults and children with difficult asthma concluded that although there was some evidence for reduced rates of hospital admission in adults and improved symptom control in children, many of the studies were of poor quality and provide insufficient evidence to support major changes in clinical practice.[5]

A more pragmatic approach is to develop a risk register for each practice, as described in a recent UK study.[6] In those deemed to be at risk (not only those with difficult asthma, but encompassing them) electronic prompts were used to alert practice staff with the aim of improving access and encouraging opportunistic asthma intervention. Hospitalisation and A&E attendance were reduced. This is a single study and further assessment of risk registers would be useful, but this seems to us to be an eminently sensible system with the potential to improve asthma care significantly.

'Behavioural and psychological factors were recorded in most patients who died from asthma'

ALTERNATIVE DIAGNOSES

A recent UK study found that 12 out of 100 patients referred for difficult asthma did not have reversible airflow obstruction or a history suggestive of asthma.[7]

Diagnoses included COPD, cystic fibrosis, cardiomyopathy, respiratory muscle dysfunction and severe anxiety with vocal cord dysfunction.

Observational studies have also identified a high number of patients with difficult asthma who were diagnosed with dysfunctional breathing as an alternative or concomitant diagnosis to asthma.[7,8]

These alternative diagnoses can be difficult to establish within the confines of a primary care appointment, but specialist referral for review of patients with asthma who do not respond to treatment should generate a review of the diagnosis.

'Obesity may have a direct adverse effect on the inflammatory processes of asthma'

HIGH BMI

A significant number of patients with difficult asthma have a high BMI. This will increase breathlessness for obvious mechanical reasons, but there is also some evidence that obesity may have a direct adverse effect on the inflammatory processes of asthma.

In a recent study, bariatric surgery not only improved lung function and quality of life measures, but also reduced systemic inflammatory markers.[9] Clearly surgery is not appropriate in all cases, but weight loss should be actively promoted in patients with a high BMI and difficult asthma.

key points

SELECTED BY
Dr Peter Savill
GP Hampshire

Asthma affects 5.4 million people in the UK, around 1 in 12 of the population. Between 5 and 10% of asthma (depending on the definition used) is categorised as difficult asthma, a term which generally refers to patients who continue to experience symptoms and frequent exacerbations despite the prescription of high-dose asthma therapy.

Difficult asthma is an indication for specialist review by an appropriate respiratory physician, but close liaison between primary, secondary and tertiary care is critical and it is therefore important that primary care healthcare professionals should be aware of the principles of management.

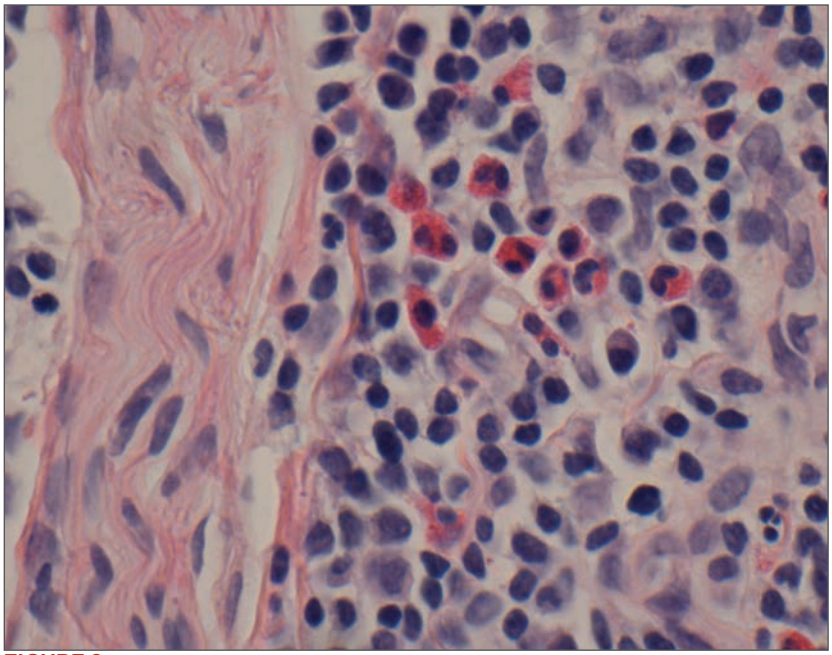
One of the most important questions to ask is whether the individual with difficult asthma is taking their treatment. Identifying this, however, is not easy. GPs could assess prescription uptake, looking for low use of preventers and excess use of short-acting bronchodilators. Newer means of assessing adherence have been developed. Inhaler devices that can monitor completion and timing of actuations have been produced. Meters that measure fractional exhaled nitric oxide (FeNO) are available.

A recent UK study found that 12 out of 100 patients referred for difficult asthma did not have reversible airflow obstruction or a history suggestive of asthma. Diagnoses included COPD, cystic fibrosis, cardiomyopathy, respiratory muscle dysfunction and severe anxiety with vocal cord dysfunction.

Oral corticosteroids will provide control in the vast majority, but the well known side effects demand that other forms of treatment should be considered. Omalizumab is a monoclonal antibody against native IgE. In patients with confirmed IgE-dependent allergic asthma, uncontrolled despite optimal pharmacological treatment and with IgE levels 30-700 IU/ml, a trial of omalizumab is appropriate. In patients who require daily oral steroids, methotrexate can be used as a steroid-sparing agent. It should only be used in specialist centres because of safety concerns and the need for monitoring.

Bronchial thermoplasty in severe asthma is used to reduce the small airways smooth muscle mass, thereby decreasing the airways' ability to constrict. The procedure is carried out under sedation or general anaesthetic and involves inserting a catheter into the bronchial tree and administering radiofrequency energy to the airway walls.

There is debate about the role of FeNO in routine monitoring. A NICE diagnostic appraisal suggested that it should have a role, but a recent international guideline did not recommend it. The authors believe that it is useful particularly in those who are symptomatic at review.



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FIGURE 2
Sputum eosinophil counts may be helpful in guiding treatment

MANAGEMENT

Drug therapy

Checking adherence and looking for concomitant diagnoses will negate the need for high levels of asthma therapy in many patients.

In others, however, the underlying airway inflammation will be severe, and treatment at steps 4 or 5 of the BTS/SIGN guideline will be necessary. Oral corticosteroids will provide control in the vast majority, but the well known side effects demand that other forms of treatment should be considered.

Patients with this degree of asthma should be under joint supervision by primary and secondary care; some of the newer treatments require input from regional difficult asthma teams.

Omalizumab: This is a monoclonal antibody against native IgE. In patients with confirmed IgE-dependent allergic asthma, uncontrolled despite optimal pharmacological treatment and with IgE levels 30-700 IU/ml, a trial of omalizumab is appropriate.[10,11]

Patients should be monitored for improvements in symptom control, reduction in exacerbations and reduced hospital admissions. If a patient does not respond within four months the medication should be discontinued.

Methotrexate: In patients who require daily oral steroids, methotrexate can be used as a steroid-sparing agent. It should only be used in specialist centres because of safety concerns and the need for monitoring.[10]

Azithromycin: Macrolide antibiotics are known to have anti-inflammatory and immune modulatory actions which reduce airways reactivity and inflammation. They are used with good effect in other airways diseases including COPD and bronchiectasis. One study of low-dose azithromycin suggested benefit in non-eosinophilic asthma, but the role of macrolides is not firmly established.[12]

Triazoles: Antifungal treatments are only recommended for patients with asthma who develop allergic bronchopulmonary aspergillosis (ABPA).[10] However, there is some data showing benefit in patients without the complete picture of ABPA, but with severe asthma and evidence of fungal sensitisation.

Again, further studies are required before this treatment can be recommended, particularly given that triazoles can cause significant liver and cardiac toxicity.

Other monoclonal antibodies: A number of agents which block specific modulators of the airway inflammation of asthma are in development. Their use is likely to be governed by NHS England's specialised commissioning arrangements, and by NICE appraisal, and detailed consideration here is premature. »

The furthest advanced is mepoluzimab, an IL5 antagonist, which is currently being appraised and is scheduled to appear in mid-2016.

Bronchial thermoplasty

This novel technique has been approved for the treatment of patients with severe asthma.[13] The aim of bronchial thermoplasty in severe asthma is to reduce the small airways smooth muscle mass, thereby decreasing the airways' ability to constrict.

The procedure is carried out under sedation or general anaesthetic and involves inserting a catheter into the bronchial tree and administering radiofrequency energy to the airway walls, see figure 1, p21.

Studies to date show an improvement in symptoms and quality of life, reduced exacerbations and hospital admissions.[13] The long-term benefits and risks from this procedure are not yet known.

'FeNO monitoring is useful particularly in those who are symptomatic at review'

MONITORING RESPONSE TO TREATMENT

There is considerable interest in the use of objective monitoring to guide adjustment of asthma treatment, as opposed to the traditional symptom-driven management. The potential advantage is that this may forestall deterioration of asthma, and is clearly of great potential value in those with severe asthma and frequent asthma attacks.

One well conducted study used sputum eosinophil counts to guide treatment and proved superior to the conventional control arm,[14] see figure 2, p23.

However, this approach is not recommended for children and is restricted to adults who can produce induced sputum samples. It is only performed in specialist centres and has not yet been sufficiently standardised to be widely available.

There is debate about the role of FeNO in routine monitoring. A NICE diagnostic appraisal suggested that it should have a role,[15] but a recent international guideline did not recommend it.[10] We believe that it is useful particularly in those who are symptomatic at review.

Patients on long-term steroids should have annual eye examinations to assess for cataracts, bone density measurement every 1-3 years and glucose and cholesterol monitoring. Children on long-term corticosteroids should have their growth monitored.

CONCLUSION

Difficult asthma accounts for a small proportion of all patients with asthma. It is important to be aware of the factors that contribute to difficult to treat asthma and identify patients who continue to experience symptoms and exacerbations despite high doses of corticosteroids.

These patients are at risk of fatal or near-fatal asthma exacerbations and should be referred for specialist review. There is a range of treatment options available which must be tailored to the individual patient. This is a complex population of patients and requires input from a multidisciplinary team to provide holistic care.

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Useful information

Asthma UK
www.asthma.org.uk

BTS/SIGN guidelines
www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline

We welcome your feedback

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