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Difficult to control asthma in adults

Asthma continues to be a significant disease burden in Australia and remains a common reason for patients to consult primary care providers. Most people with asthma are adequately controlled with inhaled agents but a few continue to suffer symptoms that are difficult to control.

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The 2004 to 2005 National Health Survey estimated a 10% prevalence rate for asthma in Australia, as reported by the Australian Centre for Asthma Monitoring and the Australian Bureau of Statistics (Figure 1).[1,2] Australia now ranks second out of 41 countries in terms of prevalence of self-reported wheeze in the last 12 months in adults aged 20 to 44 years, according to the 2004 Global Initiative for Asthma (GINA) report, *'The Global Burden of Asthma'*.[3] The prevalence of 10% manifests as 37,461 hospital presentations, of which half are in adults, and an increased proportion of time (days) away from work or study (10% compared with 7% for people without asthma).[2] In 2004, asthma was implicated as the primary cause of death of 313 individuals and played a significant role in a further 895 deaths. Patients aged over 55 years have the highest risk of experiencing an asthma-related death, especially during winter.

Aims of treatment

The aims of asthma treatment are to control symptoms, prevent exacerbations and normalise lung function while preventing permanent airflow limitation and minimising treatment side effects. Lung function measurements (spirometry or peak flow readings) and symptom severity monitoring are essential requirements for optimal care (Figure 2). Although asthma guidelines have traditionally focused on titrating treatments according to disease severity, international guidelines are now focusing on controlling symptoms using medical treatments.[2] The current Australian recommendations for care are summarised in the box on page 23.

Recent Australian and international guidelines suggest that asthma is well controlled when as-needed therapy is required less than twice a week.[3,4] However, in the Gaining Optimal Asthma Control (GOAL) study, where inhaled combination therapy

IN SUMMARY

- **Some 5 to 10% of asthma cases are severe and difficult to treat.**
- **Frequent use of rescue medication (oral corticosteroid) should prompt review of the patient's asthma management plan.**
- **Alarming features of ongoing deterioration in lung function or corticosteroid dependence should prompt early referral to a specialist centre.**
- **Basic blood tests and spirometry may suggest an alternative diagnosis in the individual with difficult to control asthma.**
- **Difficult to control asthma is both physically and emotionally draining. Psychological support remains an important task for the primary care physician.**

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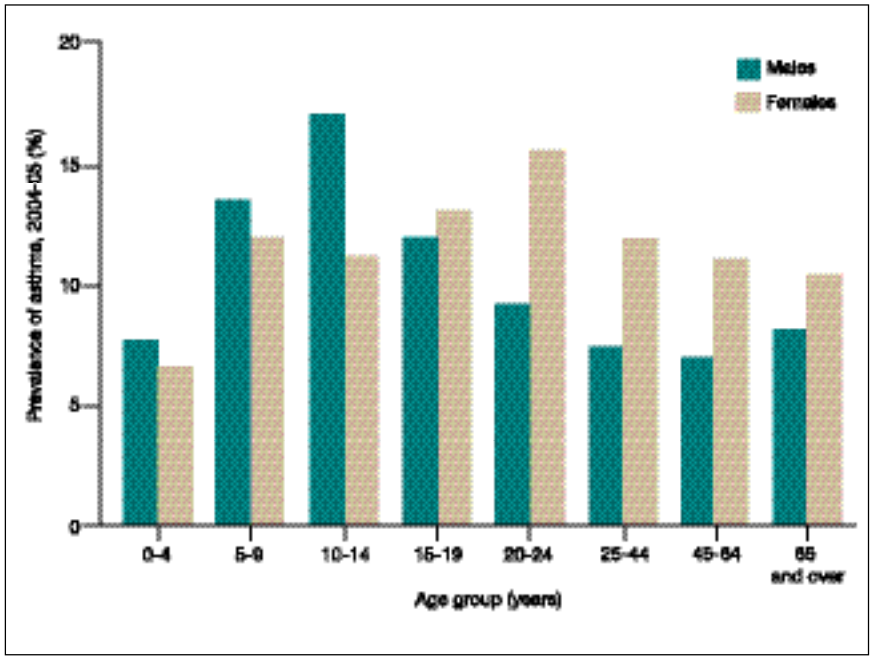
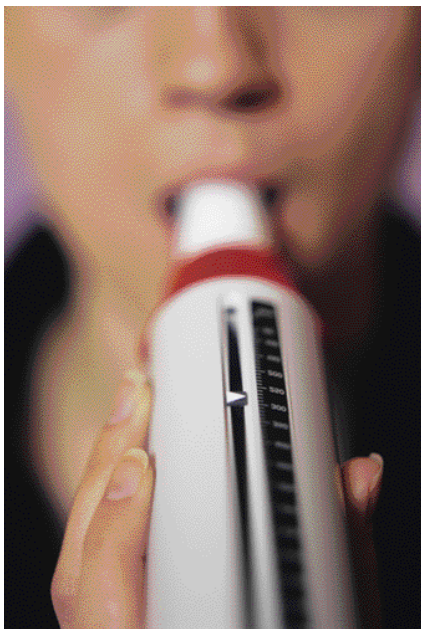


Figure 1. The prevalence of asthma between 2004 and 2005. Prevalence in adults is approximately 10%, with a significant proportion of adults over the age of 64 years old being affected. (Source of data: Australian Bureau of Statistics 2004–05 National Health Survey, cat. no. 4364.0. Figure reproduced with permission from *Asthma in Australia: A Snapshot, 2004-05*; ABS cat. no. 4819.0.55.001; 2006; www.abs.gov.au)[2]



PHOTOLIBRARY

Figure 2. Early intervention in declining asthma control is aided by patients monitoring their own peak expiratory flow rates.

was escalated to maximal doses, 20% of individuals failed to achieve well controlled asthma on daily doses of fluticasone 1000 μg and salmeterol 100 μg.[5] These results suggest that not all patients will achieve good control of their asthma symptoms. In these individuals, lung function measurement and other methods of assessing airway inflammatory processes then guide treatment decisions. Other studies suggest that about 5% of individuals meet the criteria for severe asthma despite maximal prescription of medication according to established guidelines.[6]

Difficult to control asthma

One definition for asthma that is difficult to control is asthma that remains symptomatic despite maximum recommended doses of conventional inhaled corticosteroid therapy and long acting β_2-agonist (LABA) or theophylline treatment, or that requires oral corticosteroids long term to control symptoms. However, other patterns can be recognised. Some patients experience frequent exacerbations despite preventive treatment. Other patients experience significant variability in airflow obstruction despite apparently optimal inhaled preventive asthma treatment – this type of variability might be found in patients who experience exacerbations of asthma premenstrually, or in those with concomitant allergic disease.

Specific triggers for asthma (such as occupational causes, exercise, aspirin use and food allergies) should also be considered when taking a history in patients whose asthma is difficult to control.

High risk asthma patients

Studies have identified patients who are at particular risk of death and hospital admission because of their asthma. Such patients are those with severe asthma and those with previous intensive care admissions or a hospital admission within the past year for their asthma.

Social demographics may play a role in magnifying the risk in certain individuals. In particular, those with poor access to care (whether due to physical or financial constraints or to comorbid conditions) are more likely to have adverse asthma outcomes.

There is good evidence that inhaled corticosteroid treatments are associated with a reduced risk of severe asthma attacks and death. Patients who are unable or unwilling to take preventive asthma treatments are missing an opportunity to improve their prognosis. Furthermore, written asthma management plans have been associated with a reduced risk of asthma death, although the rates of ownership of these plans are declining.

Patients with concomitant food allergy have also been identified as being at high risk of death from asthma. When anaphylaxis occurs, the risk of death is much greater in patients who have asthma than in those without it. Food allergy, along with exercise induced anaphylaxis, is a

Treatment according to disease severity

The care to be delivered according to asthma severity can be considered as a progression through treatment steps, as recommended in the National Asthma Council of Australia's *Asthma Management Handbook 2006*.[4] The steps are made every six to 12 weeks. Patients should continue to take reliever medication on an as-needed basis.

- **Step 1. Mild persistent asthma**
  Inhaled corticosteroid alone (200 µg beclomethasone dipropionate daily or equivalent). Leukotriene antagonists can be used as an alternative to low dose inhaled corticosteroid when a non-corticosteroid therapy is desired.
- **Step 2. Moderate persistent asthma with persistent symptoms or poor lung function on inhaled corticosteroid alone**
  Add long acting beta agonist to inhaled corticosteroid.
- **Step 3. Severe persistent asthma with persistent symptoms or poor lung function on inhaled corticosteroid alone (200 µg beclomethasone dipropionate or equivalent daily) plus long acting beta agonist**
  Increase inhaled corticosteroid dose to 400 to 500 µg beclomethasone dipropionate or equivalent daily.
- **Step 4. Well controlled asthma**
  Consider reducing inhaled corticosteroid dose by 25 to 50%.
- **Step 5. Well controlled asthma**
  Consider ceasing long acting beta agonist.

cause of truly brittle asthma where lung function can deteriorate rapidly from normal levels. In these individuals, optimal management of the allergic disease is critical and should include an anaphylaxis management plan, the provision of an Epi-Pen and appropriate education on avoiding triggers for anaphylaxis.

Confirming the diagnosis

Confirmation of a diagnosis of asthma is critical to enable the correct treatment to be prescribed. The diagnosis is based on the patients' history of symptoms and signs and confirmed by respiratory function testing, ideally spirometry. Asthma symptoms include wheeze, shortness of breath and waking at night due to a cough or wheeze.

Spirometry should confirm an obstructive ventilatory defect (Figure 3). The presence of significant reversibility of lung function is diagnostic of asthma. As asthma is an episodic illness, the presence of normal lung function does not exclude an asthma diagnosis. Nevertheless, normal lung function in patients taking high doses of medication should prompt questions about whether the high doses are justified or whether the diagnosis is correct. Bronchial provocation testing may be of value in these circumstances, and specialist referral may also be indicated. Recently the use of standardised questions or asthma control scores have been used to quantify the control of asthma symptoms in a systematic manner.[7]

Common differential diagnoses

Diagnoses other than asthma should be considered where there is dissonance between lung function tests and symptoms, or where apparently adequate treatments do not appear to be helping.

Chronic obstructive airways disease

A diagnosis of chronic obstructive airways disease (COPD) indicates that the airway obstruction is not fully reversible. This

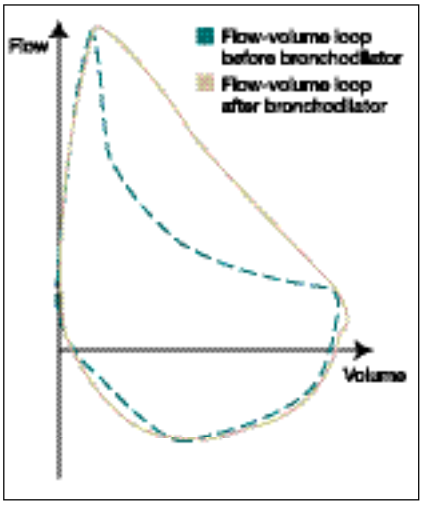


Figure 3. Typical flow–volume loops in asthma, where the forced vital capacity is within normal limits but the forced expiratory volume in 1 second (FEV_1) is reduced. Characteristic of the reduction in FEV_1 is the reduced airflow at low lung volumes giving a scalloped shape to the flow–volume curve before bronchodilator (dotted line). Typically in asthma, this defect responds to treatment with a short acting bronchodilator, an improvement of 12% or 200 mL in FEV_1 being suggestive of significant reversibility. The flow–volume loop may also normalise (solid line), although often not as completely as in this example.

is often seen in people who are smokers, although recent studies suggest that up to 10% of individuals who satisfy COPD diagnostic criteria have never smoked.[8] Patients newly diagnosed with COPD should have a trial of corticosteroid therapy (inhaled or oral) followed by spirometry to ensure their airway obstruction is not fully reversible. Although significant reversibility of airway obstruction can be seen in COPD patients on bronchodilator therapy, the spirometry tests will fail to show a complete reversal of airway obstruction compared with asthma.[9] In these COPD patients, anticholinergic therapies can often improve symptomatic dyspnoea while pulmonary rehabilitation can improve functional status.

The following factors may suggest a

diagnosis of COPD:

- cigarette smoking
- age over 45 years
- prominent wheeze and breathlessness
- bullous parenchymal abnormality and hyperinflation revealed on x-ray
- slowly progressive decline in lung function despite maximal therapy.

Vocal cord dysfunction

In some patients with asthma, the upper airways contribute to airflow obstruction. In some of these patients, it seems that a physiological reflex causes a narrowing of the larynx.[10] In others, upper airway narrowing appears to be the major site of airflow obstruction, causing a markedly audible wheeze and respiratory distress. Oxygen desaturation may occur in these patients, although arterial blood gases may also reveal hyperventilation. Some of these patients may find wheezing difficult to maintain while lying supine.

Features of vocal cord dysfunction include:

- resistant 'asthma'
- exacerbations associated with psychological stressors or anxiety
- erratic peak flow rates
- fluttering on inspiration and a saw-tooth pattern on expiration in lung function tests.

Hyperventilation

Hyperventilation syndromes may present as asthma in some individuals. Normal lung function, other symptoms of hyperventilation and the absence of clinical signs of asthma may alert the physician to this diagnosis. Addressing psychosocial issues and teaching relaxed breathing techniques (often undertaken by a physiotherapist) can help these patients.

Obesity

Airway impingement from oropharyngeal fat can result in wheeze. When combined with poor physical fitness, patients can display symptoms resembling asthma that is unresponsive to corticosteroids. Obesity frequently coincides with difficult to control asthma that is secondary to corticosteroid use and dyspnoea. Recent data confirms that obesity may be associated with wheeze and dyspnoea in the absence of airway hyper-responsiveness.[11]

Less common differential diagnoses

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis – an allergic reaction of the large airways caused by *Aspergillus fumigatus* – may worsen asthma severity. Clinically, this condition is accompanied by worsening symptoms of bronchospasm, fevers and sputum plugging. If untreated, it may trigger inflammation, leading to central bronchiectasis. Typically, patients with allergic bronchopulmonary aspergillosis have recurrent fevers and persistently produce purulent sputum. Investigations reveal an eosinophilia, a highly elevated immunoglobulin E levels and a positive blood specific immunoglobulin E test to *Aspergillus*. Being allergic to *Aspergillus* is a prerequisite for the diagnosis.[12]

Churg-Strauss syndrome

Churg-Strauss syndrome is a systemic vasculitis that is characterised by peripheral blood eosinophilia, asthma and the extravasation of eosinophils. This leads to inflammation, particularly of the skin, peripheral nerves and cardiac tissue. The disease is often unmasked by the withdrawal of oral corticosteroids, and has been associated with the introduction of leukotriene antagonists.[13]

Bronchiectasis

Bronchiectasis is due to irreversibly dilated bronchi with impaired sputum clearance. The clinical features include breathlessness and occasional haemoptysis; spirometry testing shows an obstructive pattern (with reduced forced expiratory volume in 1 second [FEV_1] compared with forced vital capacity [FVC]) and some bronchodilator response may occur.[14] A high resolution CT scan will provide a definitive diagnosis.

A diagnosis of bronchiectasis should trigger referral to a specialist for identification of a cause and ongoing management advice. Management involves referral to a physiotherapist to aid clearance of secretions.

Pulmonary hypertension

Pulmonary hypertension (mean pulmonary arterial pressure above 25 mmHg) is often determined by a transthoracic echocardiogram. Unfortunately, the symptoms of pulmonary hypertension are often a vague dyspnoea and an inability to undertake exertion. Diagnosis of pulmonary hypertension is often delayed or mistaken for another pulmonary condition, even hyperventilation. It is frequently diagnosed late in the course of the disease when patients present with dyspnoea, near syncope and exertional angina due to reduced cardiac output. This condition should be suspected when spirometry is normal despite ongoing dyspnoea and particularly if measurements of gas transfer are reduced.

Patients with scleroderma, CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia), systemic lupus erythematosus or a history of venous thromboembolism are especially at risk of developing pulmonary hypertension.[15]

Medications for severe asthma

Inhaled corticosteroids

High doses of inhaled corticosteroids are the cornerstone of management for patients whose asthma is difficult to control. Nevertheless, there is evidence of a plateau effect in efficacy with doses of budesonide (Pulmicort) above 800 µg/day, fluticasone (Flixotide) above 500 µg/day, beclomethasone (Qvar) above 400 to 800 µg/day or ciclesonide (Alvesco) above 320 µg/day.[16] Most patients achieve optimal results on between 100 and 250 µg/day

of inhaled fluticasone. Although a dose–response curve does exist for fluticasone and some studies report favourable responses at very high doses in corticosteroid-dependent patients,[17] doses beyond usual levels should only be required in exceptional circumstances.

Even though the side effects of inhaled corticosteroids appear to be modest, high dose inhaled corticosteroids have been linked to adrenal suppression and concerns regarding osteopenia.[18] Consequently, it is important to maintain people with asthma on the lowest effective dose. Ciclesonide, a recently developed inhaled corticosteroid, is activated within the lung and appears to cause fewer local side effects, such as voice change, than the other inhaled corticosteroids.

Inhaled long acting beta agonists

Inhaled LABAs such as eformoterol (Foradile, Oxis Turbuhaler) and salmeterol (Serevent), provide superior symptom control and improve lung function in patients who are taking moderate and high dose inhaled corticosteroids. These medications should be used before increasing inhaled corticosteroid doses beyond their plateau effect dosage.[19]

Oral corticosteroids

Oral corticosteroids (prednisone and prednisolone) are effective for acute asthma exacerbations at doses of 0.5 to 1.0 mg/kg for up to 10 days without tapering. In patients with difficult to control asthma, the frequent nature of exacerbations can impede cessation of oral corticosteroids. The help of a respiratory physician may be required to wean patients off oral corticosteroids over a period of weeks. Some patients require ongoing oral corticosteroids to prevent asthma deterioration. These patients should be referred for specialist assessment and consideration of alternative therapies.

Leukotriene antagonists

Leukotriene antagonists are efficacious in asthma. In clinical trials in patients with refractory asthma, their use appears additive to high dose inhaled corticosteroids. Even though leukotriene antagonists seem to have a low side effect profile, the cost of the medication in Australia is frequently prohibitive. Zafirlukast (Accolate), suitable for patients aged 12 years and over, is not PBS listed, and montelukast (Singulair) is PBS listed only for children aged 6 to 12 years, and then only as a single preventer asthma medication.

Theophylline

Evidence shows that theophylline (Nuelin) and its derivatives can be of benefit in patients with severe asthma, although the low therapeutic ratio of these medications, coupled with gastrointestinal side effects, renders them a less commonly used therapy.

Immunosuppressive medications

Many immunosuppressive agents have been used as second line therapies for asthma refractory to the usual treatments. These include cyclosporin (Cicloral, Cysporin, Neoral, Sandimmun), azathioprine, cyclophosphamide (Cycloblastin, Endoxan) and high dose human immunoglobulin. While these agents may provide a corticosteroid sparing effect, their use is accompanied by considerable morbidity, which precludes their application in the wider asthma population. Meta-analyses revealed that although these anti-inflammatory treatments may have some efficacy as corticosteroid sparing agents, the improvements noted were not generally sufficient to justify the side effects.[20,21]

The more selective biological immunosuppressive agents etanercept and omalizumab have shown promise in refractory asthma in recent studies.

Etanercept

The finding that tumour necrosis factor α (TNFα is upregulated in peripheral blood monocytes as well as in the bronchoalveolar lavage fluid of patients with asthma[22,23] has led to etanercept (Enbrel), a TNFα blocking agent, being trialled in patients with refractory asthma. TNFα is associated with cell mediated immune responses to increase neutrophil recruitment, a feature often seen in severe asthma. Etanercept, administered subcutaneously, has been shown to reduce airway hyperresponsiveness and asthma symptoms and to improve lung function. Adverse effects include injection site reactions, infections (serious bacterial or latent viral infections, or tuberculosis reactivation), thrombocytopenia and leucopenia, lymphoproliferative disease, lupus-like autoimmune disease, exacerbation of multiple sclerosis and cardiac failure. Anaphylaxis is rare.

Omalizumab

The recombinant humanised anti-immunoglobulin E antibody omalizumab (Xolair) obstructs the allergic cascade by binding to immunoglobulin and neutralising its capacity to bind allergen. When administered subcutaneously every two to four weeks, omalizumab has been shown to prevent severe asthma attacks. Trials in patients with allergic asthma demonstrate improved lung function and asthma related quality of life.[24,25] The cost of omalizumab is generally prohibitive but it may be cost effective for patients who have more than five asthma exacerbations or 20 days in hospital due to asthma per year despite maximal conventional therapy.[26] Adverse reactions include injection site reactions and, rarely, anaphylaxis.

Other treatment

Bronchial thermoplasty

Applying thermal energy to bronchial walls to reduce the amount of smooth muscle has been shown to reduce bronchoconstriction and reliever medication use in limited human studies.[27] Evidence for safety in the long term is lacking, and this approach cannot currently be recommended in other than trial circumstances.

Management considerations

Smoking cessation

Current tobacco smoking in patients with asthma is associated with more frequent asthma exacerbations and poorer symptom control compared with not smoking. The greater decline in lung function in individuals who have asthma and continue to smoke, together with a reduced response to inhaled corticosteroids, makes cessation of cigarette smoking a major treatment goal. Nicotine replacement therapy, with counselling offers the greatest chance of success.

Inhaler technique

Using the correct technique for inhaled medication devices can dramatically improve drug delivery. Common errors in technique include:

- not timing the inhalation with the release of the spray
- using inhaled medications without a spacer device
- failing to cleanse the mouth and throat after corticosteroid inhalation, which can lead to oral candidiasis.

Patients should be educated about device use at every opportunity. This is particularly important in older or disabled patients whose arthritis or poor co-ordination may present significant obstacles to inhaler use. Allied health personnel, such as asthma educators, can also provide education regarding correct device use. Improved asthma outcomes have been demonstrated with both asthma nurse educators and pharmacists who have provided education on asthma treatments. The available inhaler devices are described in the box on page 28.

Medication adherence

Adherence to medication regimens is rarely perfect, especially when continued use of the medication abolishes the symptoms, as in asthma. It is important to check patients' adherence before escalating their treatment. Poor adherence to medication may result in an unwarranted increase in prescriptions for higher doses of medication. Clinicians should ask patients about medication adherence and perceived barriers to using the medication. Enquiries as to when a patient does not take his or her medication is more likely to elicit a truthful answer than enquiries that assume the medication is being taken. Although not all barriers are surmountable, optimal adherence seems to be achieved when patients and doctors work in partnership, addressing patients' concerns and setting mutual goals for treatment outcomes. It is evident, however, that despite the subsidy to pharmaceutical costs available in Australia, many patients (especially those with comorbidities) find the cost of medications prohibitive and ration their use accordingly.[28]

Written asthma management plans

A written asthma management plan is essential for all people

continued

Inhaler devices for asthma

Metered dose inhalers

Metered dose inhalers may be flow triggered to simplify co-ordination. Deposition in the lungs is between 10 and 25% with these devices when a spacer is not used. The canister requires shaking and may provide lower doses until the metered chamber is primed. Wasting the first few doses should prime the chamber.

Dry powder inhalers

The powder is aerosolised on full inhalation and therefore assists the co-ordination of inhalation with powder release. Greater lung deposition is obtained with longer, stronger inhalation. Moisture in the device can cause the powder to clump and not be inhaled. Patients using dry powder inhalers should have sufficient inspiratory flow to enable good deposition, so such devices may not be suitable for individuals with poor lung function.

Spacers

Spacer devices improve delivery to the lungs and reduce upper airway deposition. Deposition on the device is reduced with detergent washing followed by air-drying to remove the static charge.

Nebulisers

Nebulisers are considered to provide similar dosing to a metered dose inhaler. Patients often favour these devices because of the noise and feel. Spacers used with other devices provide equivalent lung deposition to nebulisers in most instances so nebulisers are now used less frequently.

with asthma, regardless of the underlying severity. Written plans empower patients, protect them against asthma-induced death and improve the outcomes of self-management education.[29] In patients with difficult to control asthma, the rapid recognition and response to symptom exacerbation afforded by these plans may circumvent acute exacerbations and may even prove to be lifesaving.

Key components of a written asthma management plan are clear instructions for when to commence prednisolone therapy (based on asthma symptom severity and/or the peak expiratory flow rate [PEFR] reading) and for when to seek treatment from a doctor or emergency department.

Managing comorbidities

Allergens

Taking a careful history of allergen exposure and undertaking confirmatory tests such

as the skin prick or serum allergen-specific immunoglobulin E tests can identify allergens that contribute to asthma symptoms. Common allergens include house dust mite, grass pollens and household pets. Allergen avoidance or immunotherapy can help patients with allergy related asthma. Because of the risk of adverse reactions to the injections, allergen immunotherapy should only be considered in patients whose asthma is well controlled and whose FEV_1 is greater than 70% of the predicted value. Courses of up to three years may be required. The development of better delivery methods may improve immunotherapy as a treatment option.

Rhinosinusitis

Rhinitis, with or without nasal polyps, is found in about 80% of patients with asthma. Appropriate treatments, pharmacological or allergy based, can significantly improve asthma outcomes. In particular, nasal glucocorticoids can improve symptom control and reduce exacerbation rates.

Gastro-oesophageal reflux disease

Up to 75% of people who have difficult to control asthma also have reflux detectable on oesophageal pH monitoring.[19] Reflux disease is often suspected in patients with nocturnal asthma but individuals can be symptom free. It should be excluded in patients who have refractory asthma. Clinical suspicion can be confirmed with oesophageal pH testing, or possibly with a trial of proton pump inhibition and bed-head elevation. However, proton pump inhibitors are not always effective, and surgical correction with fundoplication has been used to obtain control.[30]

Vaccination

Vaccinating adults against influenza and *Streptococcus pneumoniae* infections may help reduce morbidity and the severity of exacerbation in patients with difficult to control asthma, although the evidence for benefit is modest.[31]

Lung function testing

Lung function testing is currently the major objective indicator of treatment outcomes in severe asthma. Reversibility in airflow obstruction highlights room for improvement. Continued decline or a fixed obstructive defect in lung function may signify an alternative diagnosis, poor medication adherence or a need for treatment escalation. Adequately performed PEFR measurement is a readily available method for monitoring respiratory function. Patients can also monitor their own PEFR, which should help in the early detection of a decline in asthma control and enable early intervention. Persistent symptoms despite

continued

Useful online asthma resources

www.nationalasthma.org.au
National Asthma Council of Australia: for the *Australian Asthma Management Handbook 2006*, information sheets and asthma management plans.

www.asthma.org.au
Asthma Foundation of Victoria: for patient information sheets.

www.ginasthma.com
Global Initiative for Asthma (GINA): for resources such as evidence-based guidelines for asthma management and also statistics (including the *Global burden of asthma report, 2004*).

www.brit-thoracic.org.uk/asthma-guideline-download.html
British Thoracic Society: for asthma guideline downloads.

www.asthmascore.com.au
Asthma Score, a site owned and operated by GlaxoSmithKline Australia in partnership with the National Asthma Council Australia, the Asthma Foundations of Australia, the Pharmacy Guild of Australia and the Pharmaceutical Society of Australia: for asthma score calculators, including some suitable for patients.

www.allergy.org.au
Australasian Society of Clinical Immunology and Allergy: for professional and patient information on allergic diseases.

www.asthmamonitoring.org
Australian Centre for Asthma Monitoring: for *Asthma in Australia: findings from the 2004-05 National Health Survey* (Cat no. ACM 10. Canberra: Australian Institute of Health and Welfare, 2007).

www.abs.gov.au
Australian Bureau of Statistics: for *Asthma in Australia: a snapshot, 2004-05* (Cat no. 4819.0.55.001).

Table. When to refer patients with asthma

- Doubt remains regarding the diagnosis
- The asthma appears severe, with multiple or serious exacerbations
- Symptoms remain constant rather than responding to therapy
- It is difficult to wean patients off oral corticosteroids, or frequent courses of oral corticosteroids are required (more than three per year)
- Lung function abnormality fails to improve with treatment
- There are atypical clinical features:
  - crackles, stridor or unilateral signs
  - weight loss
  - persistent sputum production or pneumonia
  - chest pain

normal spirometry results can be further investigated with bronchoprovocation testing (e.g. the mannitol test).

Referring patients

Instances when patients should be referred to a respiratory physician are listed in the table.

The future: improved airway inflammation monitoring

Increasing evidence supports the use of noninvasive ways of observing airway inflammation to improve asthma management, especially in patients who are not optimally controlled on standard doses of readily available medications. Sputum eosinophil monitoring and measurement of exhaled nitric oxide and of other inflammatory mediators in exhaled breath condensate are promising methods that are currently being investigated. Although not yet available outside research centres, these methods promise greater precision in the initial diagnosis of asthma and appear to reduce exacerbation rates when used in day-to-day management.[32] The development of office-based techniques for undertaking these measurements will improve the ability of clinicians to identify the underlying inflammatory basis of airways disease and titrate treatments accordingly.[33–35]

Of growing interest is a newly recognised group of patients with noneosinophilic asthma, as seen on sputum cell counts. Research is currently under way to evaluate the severity and treatment response profile of this asthma variant.[35]

Conclusion

Difficult to control asthma presents a significant problem for the clinician but, with an understanding of the appropriate investigation, management and referral strategies, the condition need not remain a mystery. A careful history to identify possible contributing factors and alternative diagnoses should always be the first step in such patients, followed by objective measurement of lung function. In patients who still fail to respond optimally, and certainly in those with a persisting abnormality in lung function, specialist referral is indicated. Some asthma resources are listed in the box on this page. MT

A list of references is available on request to the editorial office.

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