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Asthma

Reprint Collection

The variability of asthma and how to respond to it

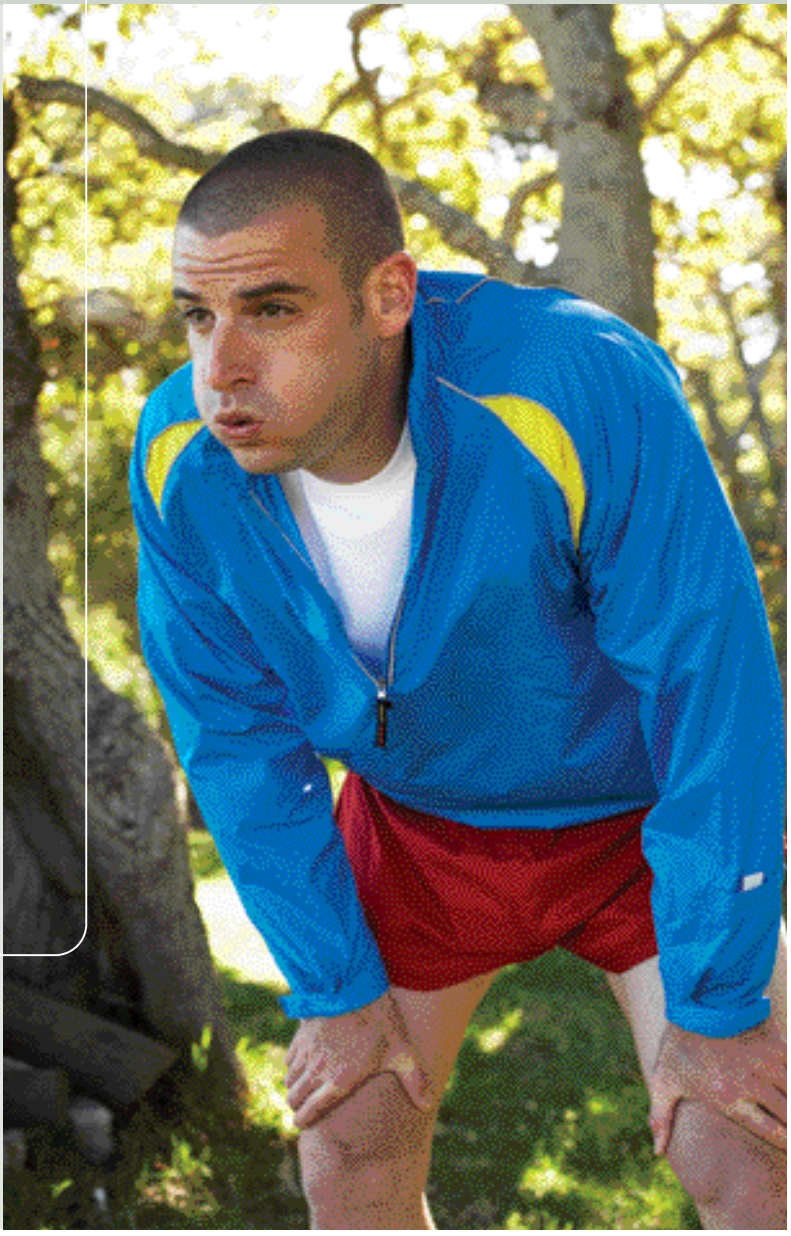
Parents as partners in managing childhood asthma

Difficult to control asthma in children

Difficult to control asthma in adults

Budesonide/eformoterol combination inhaler as maintenance and reliever treatment in asthma

Asthma action plans



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SYDNEY OFFICE
Level 1, 57 Grosvenor Street,
Neutral Bay, NSW 2089
POSTAL ADDRESS
PO Box 1473,
Neutral Bay, NSW 2089
TELEPHONE (02) 9908 8577
FACSIMILE (02) 9908 7488
EMAIL
Editorial enquiries
katemurchison@medicinetoday.com.au
Production enquiries
mariamarmora@medicinetoday.com.au
Advertising sales enquiries
prueanderson@medicinetoday.com.au
General enquiries
reception@medicinetoday.com.au

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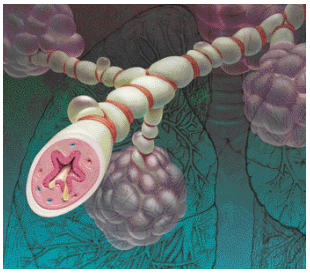

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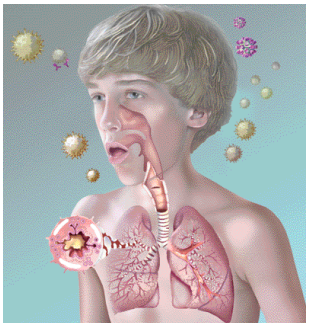

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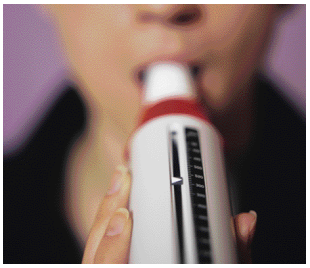

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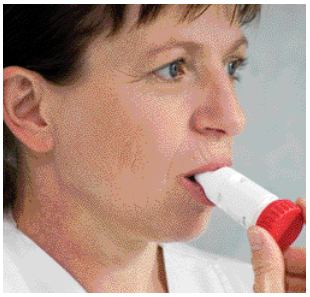

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The variability of asthma
and how to respond to it

Asthma, by its very nature, is a variable disease, and this makes it particularly challenging to manage for both patients and clinicians.

CHRISTINE JENKINS
MD, FRACP

Professor Jenkins is Head, Airways Group, Woolcock Institute of Medical Research, Camperdown, and Senior Staff Specialist, Department of Thoracic Medicine, Concord Hospital, Concord, Sydney, NSW.

The definition of asthma contains within it a clear indication that asthma is a variable disease. 'Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.'[1]

This and other definitions refer to several domains in which variability occurs in people with asthma, including:

- variable symptoms
- variability over time
- variable airflow obstruction
- variable response to treatment
- variable triggers causing asthma.

To this I would add:

- variable prognosis
- variable patterns of asthma, particularly in children.

Unfortunately the variability of asthma makes it a particularly challenging disease to manage for both patients and clinicians.

Variable symptoms

A cardinal feature of asthma is the variability of symptoms. Typically these occur in response to triggers – either nonspecific irritants (such as particulate dusts, cold air, aerosols or strong smells) or, in atopic people, common inhaled allergens (such as house dust, animal furs and moulds). Exercise is another classic trigger, either through exercise-induced asthma or ventilatory limitation due to airway obstruction.

Asthma symptoms are also variable through the day, peak flow readings typically being lowest in the mornings on first waking but also dipping during the night. This diurnal variability relates to changes in air temperature, activity levels, medication effects and circadian rhythm.

Asthma exacerbations represent an extreme end of the spectrum of symptom variability, but are probably qualitatively as well as quantitatively different from within-day and day-to-day symptoms.

IN SUMMARY

- **Asthma is associated with variability in several domains, including symptoms experienced, disease pattern over time, degree of airway obstruction, response to treatment, triggers causing symptoms, and prognosis.**
- **The variability of asthma makes it a particularly challenging disease to manage for both patients and clinicians.**
- **It is essential that patients recognise that typically asthma has a variable pattern and long symptom-free intervals usually do not mean the disease is cured.**
- **The use of standard questions and a peak flow record can help clinicians understand the degree to which patients are sensitive to, or apparently unaware of, the variability of asthma.**
- **Optimal asthma control takes months or even years to achieve in some patients. Fine tuning of medications, identification of triggers, provision of a written action plan and facilitation of self-management education are all crucial in achieving this.**

It is important, therefore, to consider asthma control in relation to both within-day and day-to-day symptom variability, and to review separately the frequency of exacerbations.

Variability over time

The pattern of asthma varies throughout life. The classification of childhood asthma into infrequent episodic, frequent episodic and persistent describes a pattern that contrasts with that of asthma in adults.

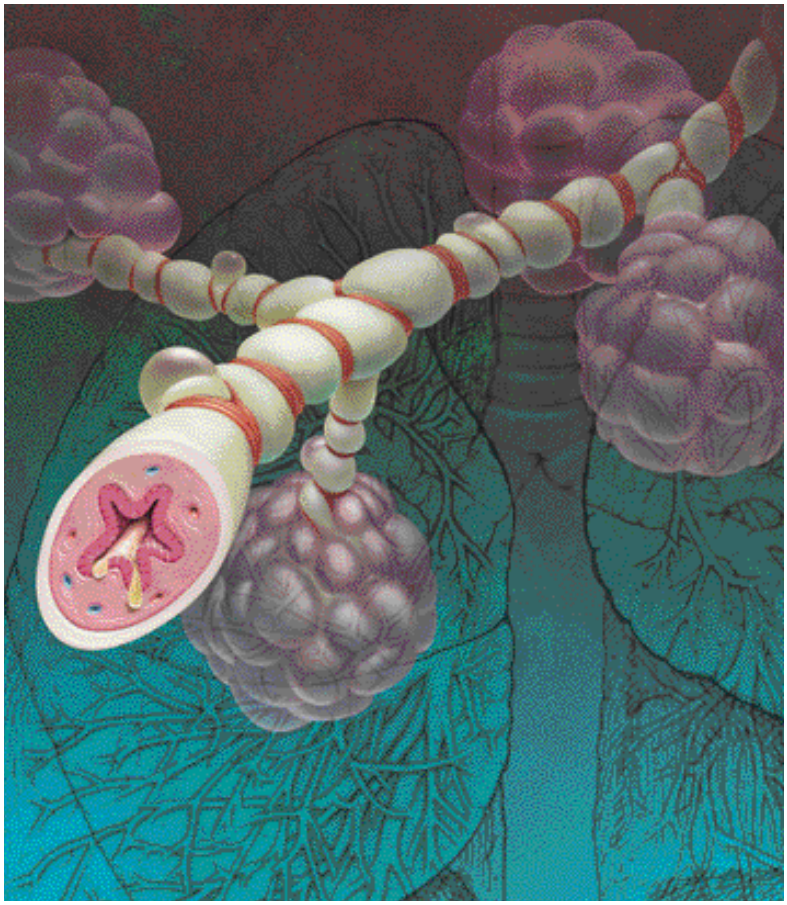
Children with episodic asthma tend to have symptom variability specifically related to upper respiratory tract infections and often have long symptom-free intervals between these episodes.[2,3] Children with persistent asthma may have abnormal lung function and variable symptoms to a range of triggers in addition to viral infections. Although this is the least common pattern of asthma in childhood, it is very important to recognise because it necessitates regular preventer medication and carries a worse prognosis.[4]

As children grow older, the pattern of their asthma may change and the severity of their disease may progressively improve. Hence, the inhaled corticosteroid (ICS) dose should be carefully back titrated and asthma control reviewed regularly. Regular review is essential so that children do not remain on higher ICS doses or are not treated for longer than needed. Acknowledgment that the pattern of childhood asthma invariably changes over time is crucial to prevent overtreatment and enable patients to finally cease medication altogether.

In contrast to the majority of children who have episodic asthma, most adults have persistent asthma. Between exacerbations, symptoms may be mild, but lung function may be abnormal. In adults, poor perception of symptoms can lead patients and their doctors to believe that their asthma is well controlled, when in fact spirometry is abnormal and persistent airway inflammation may be contributing to airway remodelling and a decline in lung function.[4,5]

Variable airway obstruction

Although adults may develop fixed airway obstruction and have minimal variability in lung function, this is usually a feature associated with long standing, often suboptimally treated disease.



PHOTOLIBRARY

Adults with milder asthma may still have variable airway obstruction despite achieving normal post-bronchodilator forced expiratory volume in one second (FEV_1). This may hide a hectic peak flow pattern and wide diurnal variability, and pre-bronchodilator FEV_1 may be more revealing. Childhood asthma is more often associated with long periods of normal lung function interspersed with episodes of worsening symptoms and airflow limitation usually triggered by a viral infection.

The variability of airflow limitation in asthma is reflected in two useful features that assist in making a diagnosis.

- Classically, acute bronchodilator reversibility testing has been used to help make a diagnosis of asthma. Although many patients do not have such reversibility, the presence of an acute bronchodilator response of 12% and 200 mL improvement in FEV_1 and/or forced vital capacity (FVC), along with a consistent clinical picture, enables practitioners to confirm a

diagnosis of asthma.

- Secondly, peak flow monitoring remains a valuable diagnostic and monitoring tool for asthma. As an aid to diagnosis, it can clearly demonstrate whether there is diurnal variability and a response to bronchodilator. Further, it can be used to monitor asthma and indicate whether asthma control is achieved by current treatment, and whether changes in lung function are heralding an exacerbation.

When best lung function is achieved on ICS treatment, patients often have minimal or no spontaneous variability and additional bronchodilator does not result in further significant improvement.

Variable response to treatment

Although asthma management guidelines are based on the observation that most patients respond to the two major components of asthma therapy (bronchodilators and ICS), many studies show that responses to both these classes of drugs can be quite variable among patients. Patients who have relatively fixed airways disease often do not demonstrate marked bronchodilator reversibility and may have a pattern of airway obstruction more suggestive of chronic obstructive pulmonary disease (COPD). It is important to recognise that some patients with asthma do have poorly reversible lung function and may not gain benefit from a change in treatment, such as adding a long-acting beta agonist (LABA) or increasing the dose of ICS. In such patients the change in treatment should not be continued unless there are strong theoretical arguments in favour of doing so.

Several studies have shown that patients with asthma also vary in their response to ICS.[6] Some patients have highly responsive disease and their lung function and symptoms normalise rapidly when taking a low dose of ICS, whereas others show minimal benefit, particularly to low doses. There is evidence suggesting that earlier treatment with ICS results in greater benefits, and that delays in treatment are associated with poorer lung function responses. The benefits of ICS treatment are both short and long term. Even if short-term effects (symptom or lung function improvement) are unimpressive, ICS treatment should be maintained for its beneficial effects in preventing exacerbations, reducing hospital admissions and preventing asthma deaths. Additionally, ICS slow the rate of decline in lung function in patients with asthma. Table 1 lists the expected time to asthma control with ICS treatment.

Other classes of asthma medications appear to benefit only a minority of patients with asthma. In adults this is the case with the leukotriene receptor antagonist montelukast, and in children it is the case with LABAs.

Additional factors affecting response to treatment include coexisting exposure to triggers that maintain airway inflammation and the nature of the underlying inflammation – whether predominantly eosinophilic or neutrophilic. The effect of current smoking in reducing the response to ICS has been well described. It is clear that asthma patients who smoke are less likely to gain benefit from ICS and require higher doses to achieve the same lung function improvement as their nonsmoking counterparts.

Table 1. Expected time to asthma control with inhaled corticosteroids

Timeframe	Asthma control
Days	No nocturnal asthma
1-2 months	Optimal FEV_1
3-4 months	Optimal morning PEF
6 months	Minimal reliever use (no more than once a week)
24 months	Mild or normal airway hyperresponsiveness
24 months	No more than one exacerbation requiring oral corticosteroids

Abbreviations: FEV_1 = forced expiratory volume in one second; PEF = peak expiratory flow.

Variable triggers causing asthma

A wide range of triggers can set off asthma symptoms. Identifying triggers and minimising exposure to these is a crucial aspect of good asthma management, so it is essential that each patient can identify the specific triggers that are associated with his or her symptoms worsening. How a particular trigger affects a patient is not simply a function of whether the patient is atopic. Indeed, even among patients who are atopic, different triggers can have different effects on an individual patient's symptoms.

Responses to nonspecific irritants also vary. Patients often nominate cigarette smoke as a trigger of asthma, although on specific questioning it may largely cause upper respiratory tract symptoms such as nasal and throat irritation. Other irritants that cause asthma symptoms include strong smells (especially perfumes), aerosol sprays (especially bleaches and cleaning agents) and sudden changes in air temperature. The extent to which patients respond to these triggers is highly variable, even day-to-day, suggesting that several factors work together to cause vulnerability to triggers.

Dietary triggers include chemical additives such as metabisulfite, which causes symptoms soon after ingestion of food or drink containing this preservative, and salicylates in foods, which often do not cause immediate symptoms but may

contribute substantially to poor asthma control among the minority of patients who are sensitive to them.

Patients with aspirin sensitivity can experience asthma soon after ingestion of aspirin or a NSAID, and this can vary from a mild increase in symptoms to a catastrophic attack. Most rigorous studies suggest that about 10% of adults with asthma have aspirin sensitivity, although the severity varies.

Variable prognosis

Several studies of the natural history of asthma from childhood to adult life indicate that it is possible to identify patterns of asthma in the population that are most often associated with either a good or a poor prognosis.

- Generally, children who have persistent asthma that develops before the age of 3 years and continues into late childhood are most likely not to 'grow out of it' and to have asthma in adult life.
- At the other end of the spectrum in childhood, infrequent episodic asthma is most often associated with an excellent prognosis and resolution of asthma in late childhood.
- Transient early wheezing, such as that occurring in infants and preschool children associated with viral infection, often resolves by the age of 5 or 6 years and is not associated with persistent asthma, especially in nonatopic children.

Among adults with asthma, prognostication is a little more straightforward. Most adults with persistent asthma retain this pattern of asthma throughout their adult lives. However, very little is known about the change in asthma severity in adult life and whether there are risk factors for adults with relatively mild asthma at one stage developing more severe disease at another stage of their lives. In some adults, the airflow limitation and symptoms of asthma are due partly to airway remodelling, which does not appear to be reversible. Despite retaining some bronchodilator responsiveness, lung function is unlikely ever to return to normal. On the other hand, adults with relatively mild intermittent asthma often retain this pattern throughout their adult lives and do not develop significant airway obstruction or disease that is suboptimally responsive to treatment.

Smokers with asthma constitute a particularly high risk group for developing persisting airway obstruction. Although the evidence is inconclusive, smokers who are atopic are at greatest risk of developing a more rapid decline in lung function.[4,5] Whether this is because they are developing coexisting COPD or whether smoking predisposes them to worse airway inflammation that then contributes to deteriorating lung function has been difficult to establish. As already mentioned, patients with asthma who smoke do not respond optimally to ICS and may need higher doses to achieve best lung function.[7]

Variable patterns of asthma

The patterns of childhood asthma, in particular, differ significantly across the spectrum of severity. It is important to identify these features and determine whether a child has episodic asthma characterised by normal lung function and freedom from symptoms between episodes. Most of these children do not need long-term ICS medication. They can be well managed with written asthma action plans and clear guidance to increase their bronchodilator dose and start oral corticosteroids as soon as symptoms worsen significantly in association with a cold. However, others may require long-term ICS treatment because their episodes, although infrequent, are severe.

Children with persistent asthma are more likely to have abnormal lung function and may have an abnormally rapid decline that can begin from early life. Hence, ICS should be given to children who truly have persistent asthma, even if it is mild. They should be monitored closely to determine their level of asthma control and their minimum effective ICS dose.

As mentioned previously, in children the pattern of asthma may change as they get older and the severity of their disease may progressively improve. Hence, regular review is necessary to prevent overtreatment.

The patterns of asthma among adults have been less well documented. Many adults have intermittent asthma symptoms, only occasionally needing bronchodilators and having a background of normal lung function. They may clearly experience minor and infrequent, short-lived worsening of symptoms, sometimes associated with allergen exposure or colds. However, it is essential that these patients have their lung function checked during symptom-free intervals to ensure that they are not poor perceivers, living with airway obstruction of which they and their clinicians are unaware.

How should clinicians respond to the variability of asthma?

Day-to-day asthma management

GPs and specialists see patients with asthma when they are at different phases of their disease and each needs to consider this in the overall management of these patients. Patients often present to primary care at times of acute deterioration, when they have reached the point of needing help.[8] The GP needs to address the acute symptoms and get the patient through the exacerbation safely, while at the same time urging him or her to return for review during his or her recovery and then again at a more stable phase of the disease. At this point, patients often feel there is no need to return as they are well again. It is for this very reason that the Asthma 3+ Visit Plan was conceived and became a means by which the National Asthma Council's six-step asthma management plan could be implemented in three or more visits.

Evaluation of the program has revealed that patients consider that they do not

Table 2. Features of optimal asthma control

- Absent or minimal symptoms
- Reliever use less than three times a week, excluding that used during exercise
- No nocturnal or early morning symptoms
- Normal or best lung function
- No or minimal exacerbations
- Able to do all usual activities without limitation

need to return regularly for review, and so there is a significant educational challenge in persuading them that this is necessary to achieve optimal asthma control.[9,10] Indeed, the goal of achieving optimal asthma control underpins the 3+ Visit Plan (acknowledging that for some patients only two visits are needed) and is a crucial element in asthma management. It is essential that patients recognise that typically asthma has a variable pattern and that long symptom-free intervals usually do not mean the disease is cured.

In the light of evidence that suggests that patients self-titrate doses, and may cease their preventer medications when they believe they are well, options for variation of treatment could be considered. One option would be very regular medical review and an aggressive, supervised back titration when patients are stable and optimally controlled. Cutting back ICS dose by half did not result in poorer outcomes, health status or more exacerbations in a UK primary care study in which patients were stepped down from >800 µg beclomethasone and followed for a year.[11]

Proactive planning of asthma visits can be helpful in assisting patients to comply with a proposed treatment strategy on the understanding that treatment can be reduced when asthma control is achieved.

Table 3. Helpful strategies to improve patient adherence to asthma management plans[2]

- Educate and advise patients about:
  - asthma as a chronic inflammatory disease that needs long-term management
  - the role of the different categories of asthma medications (preventers, symptom controllers, relievers and combination medications)
  - asthma triggers and how to avoid and manage them
  - correct inhaler use
  - skills for self-management
- Keep treatment simple
- Encourage patients to create useful daily habits regarding medication use tailored to the their lifestyles
- Establish patients' personal goals for asthma management and set targets
- Explain likely side effects of medications and identify and address concerns
- Allow patients time to express concerns and beliefs about medication
- Arrange regular medical review of patients to:
  - identify best lung function
  - achieve optimal asthma control
  - progressively back titrate to the minimum dose required to maintain control
  - optimise self-management skills

By embarking on this process of using objective measures to assess control and back-titrating ICS systematically, you will often reassure patients and help them resist the temptation to reduce or cease their preventive medication.

An alternative approach is to employ a combination of budesonide/eformoterol as maintenance and reliever therapy (Symbicort SMART), which enables a low maintenance dose of budesonide/eformoterol and step up in dose as needed, according to symptoms. With this approach, patients can be reassured that they are taking only a small regular twice daily maintenance dose, either Symbicort 100/6 µg or 200/6 µg twice daily, but can up titrate according to need. They can be reassured that this will minimise their daily ICS use and their intermittent requirements for oral corticosteroids. This approach can be used for well controlled patients who may only require a regular once daily dose.

Patients must be informed that a Symbicort SMART approach places them on the lowest possible daily ICS/LABA dose. However, for benefit in preventing exacerbations, and achieving good control, the as-needed Symbicort must be used in response to increased symptoms. A short-acting beta agonist should not be substituted for as-needed medication in place of budesonide/eformoterol.

Assessment of asthma control

The goal of asthma management is to achieve optimal asthma control (Table 2). It is our role as clinicians to convince patients that this is worthwhile and that although asthma is a chronic disease, it can be so well managed that it barely impacts on their day-to-day lives (Table 3). Patients may be willing to live with suboptimally controlled asthma as a trade-off for less intrusion of medical therapy and doctor visits, but unaware of the real risks of this strategy. Many patients believe that their mild symptoms suggest they may never be troubled

Table 4. Questions to ask patients with asthma at every visit

In the last four weeks:

- How often have you woken at night or in the early morning with wheeze, chest tightness or cough?
- How often has wheeze, chest tightness or cough interfered with your normal daily activities?
- How often have you used your reliever (average number of puffs per week)?
- How much school or work have you missed because of asthma?

Table 5. The Asthma Control Test[13]*

Answers to the questions below are scored on a scale 1 (worst) to 5 (best). A total score of less than 20 indicates poor asthma control.

- In the past four weeks how often did your asthma prevent you from getting as much done at work, school or home?
- During the past four weeks, how often have you had shortness of breath?
- During the past four weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath or chest tightness) wake you up at night or earlier than usual in the morning?
- During the past four weeks, how many times have you used your reliever medication?
- How would you rate your asthma control during the past four weeks?

* These questions relate to the Asthma Control Test for adults and children 12 years and older. For younger children, the test comprises seven questions (refer to reference 13).

by acute severe episodes.[8,12] An important educational goal is to present the evidence indicating that even mild asthma can be associated with life-threatening episodes. Patients' self-assessment of their symptoms can be highly misleading and clinicians are also vulnerable to being too readily reassured that asthma is well controlled when patients state that they have no symptoms.

Optimal asthma control takes months, or even years, to achieve in some patients, and fine tuning of medication, identification of triggers, provision of a written action plan and facilitation of self-management education are all crucial elements in achieving this. It is not good enough to ask patients 'How's your asthma?' We must ask specific questions about recent control because we lack a robust test for retrospective assessment of control – such as an HbA_{1C} test used in diabetes management. Asthma control can be assessed simply and reliably by asking patients standard questions at each visit (Table 4). The retrospective period of time over which these questions can be reliably answered is probably a maximum of four weeks.

A peak flow record over three to four weeks also enables a clinician to gain a quick perspective on recent asthma control, and if these standard questions and the peak flow chart are compared, the clinician can readily appreciate the degree to which patients are sensitive to, or apparently unaware of, the variability of their asthma. This can provide evidence that some patients are poor perceivers and will need to have their lung function objectively monitored to determine treatment needs and asthma control. It is valuable for GPs to have a couple of spare peak flow meters that they can lend to patients for this purpose. Longer term monitoring of peak flow is not necessarily needed, although some patients will choose this once they see the benefits of objective monitoring.

Quick questionnaires that can be completed by patients while waiting to see the doctor have also proven useful and correlate well with physician assessment of asthma control. The Asthma Control Test has five questions (Table 5),[13] and scoring each of these, together with spirometry, enables a rapid assessment of asthma control to be made.

Measurement of exhaled nitric oxide is a newer test that provides an indirect measure of airway inflammation and can help indicate whether recently prescribed ICS doses are adequately controlling the disease. This is a simple breath test that can be performed in most large hospitals, and the results are immediately available to the clinician.

Different treatment regimens suit different patients

Recently, several published studies have used combination therapy in different ways. The combination of fluticasone and salmeterol in one inhaler (Seretide) taken twice daily has been shown to achieve well controlled asthma in over 70% of patients with mild to moderate asthma who were randomised to this treatment. This study involved a six-month step-up phase in treatment, guided by the use of an asthma control score, followed by a six-month treatment period, during which time asthma became well controlled in progressively more patients.[14]

Although patients may experience small benefits in symptoms and lung function when taking combined ICS and LABA therapy, many achieve excellent asthma control taking ICS alone. Additionally, in mild asthma, ICS alone and combined ICS and LABA reduce exacerbation rates to a similar extent. Once good asthma control is achieved, the dosage can

Table 6. Characteristics of high risk asthma patients

- Frequent visits to emergency department with acute asthma
- Requirement for three or more medications
- Need for frequent oral corticosteroids
- A history of admission to intensive care/previous near-fatal attack
- Psychosocial difficulties
- Severe night-time attacks
- Failure to perceive asthma symptoms
- Excessive reliance on short acting bronchodilators

be progressively stepped down to a minimum ICS dose, with or without LABA, that is safe and effective and maintains these benefits in the longer term.

As mentioned above, the combination of budesonide and eformoterol given as maintenance and reliever medication (Symbicort SMART) offers the possibility of a low maintenance ICS/LABA dose and a rapidly effective as-needed top up for breakthrough symptoms. Symbicort SMART has been shown to be highly effective compared with budesonide/eformoterol given at a higher fixed dose and a short-acting beta agonist used as a reliever. Patients in these studies were able to take budesonide/eformoterol also for the relief of acute symptoms. This strategy has resulted in a low exacerbation rate, good asthma control and a lower total dose of oral corticosteroids taken over six and 12 months.[15] Such a strategy enables patients to increase their combination therapy when needed day by day, but necessitates regular medical review to titrate the maintenance dose appropriately.

Recognition of the highly variable or at risk patient

The pattern of asthma in some patients can be quite chaotic despite some periods of stability and apparently good compliance with treatment. It is important to recognise these patterns of asthma and to anticipate and address the risks where possible.

Patients who have a history of sudden deterioration, particularly resulting in severe attacks and hospital presentations, need to be well prepared for such events. In addition to a written action plan clearly specifying when they should seek advice, they should keep a supply of prednisone (Panafcort, Predsone, Sone) or prednisolone (Panafcortelone, Predsolone, Predmix, Redipred, Solone), have reliever bronchodilators available in several different locations and always have spare prescriptions for their medications. Such patients should always be assessed for possible dietary triggers and should be able to recognise the circumstances in which they are most prone to sudden attacks.

High risk patients can be recognised by several features, which are listed in Table 6. These patients may also:

- deny that asthma is a problem
- have poor adherence to treatment or management plans
- have a history of sudden attacks provoked by foods, aspirin or other NSAIDs.

Leading up to severe attacks, such patients have also been shown to have symptoms of poor asthma control, especially the following:

- overuse of short-acting bronchodilators
- night waking from asthma
- persistent morning dips or marked in diurnal variation in PEF (i.e. morning PEF <60% recent best or diurnal variability >25%).

Table 7. Benefits of variations in written action plans[17]

Variation	Efficacy
Action points	
Symptoms versus PEF based	Equivalent
Standard written instruction	Consistently beneficial
Four action points	Not consistently better than fewer than four points
PEF based on personal best	Consistently beneficial
Treatment instruction	
Individualised written action plan using inhaled and oral corticosteroids	Consistently beneficial

Abbreviation: PEF = peak expiratory flow.

Written action plans

A written action plan is a key component of good asthma management. One of the failures of asthma care in Australia at present is the documented fall in ownership of written action plans over the last 10 years; ownership reached a peak in the mid-1990s at about 45% of patients with current asthma.

All patients with asthma, apart from those with the mildest disease and no history of acute episodes, should have a written action plan that clearly indicates the symptoms of deteriorating asthma and the actions needed to deal with these.[16,17] There is evidence from studies of

life-threatening asthma that patients who have written action plans are less likely to die from asthma. An evidence based review has clearly indicated that the provision of a written action plan in the context of optimal self-management education, which includes regular medical review and information about asthma, results in better lung function, fewer days off school or work and fewer unscheduled GP or emergency department visits.[18] A subsequent review of the vital components of written action plans indicates that they:[17]

- must be individualised – i.e. tailored to each person's needs and lifestyle
- should include the use of both inhaled and oral corticosteroids
- should calculate action points for change in treatment according to best peak flow readings or symptoms
- have no more than four action points
- be written clearly and as simply as possible
- should include advice on urgent action (e.g. when and how to call an ambulance).

An educational CD providing step by step guidance for clinicians writing action plans is available.[19] Action plan pads are available for patients taking regular therapy with maintenance ICS or ICS/LABA, and for those on a Symbicort SMART regimen, based on PEF or symptoms. Table 7 lists the benefits of various aspects of written action plans.

Summary

Asthma, by its very nature, is a variable disease; however, this does not prevent the achievement of stability and optimal asthma control in most patients. Recognition of an individual's pattern of variability will help the patient and his or her physician to tailor management appropriately. Particular attention should be paid to the pattern of asthma in childhood to avoid overtreatment and to identify the features that predict a good outcome for most children with asthma.

In all patients, recognition of risk factors and self-management education, including particularly a written action plan, are crucial to success in achieving and maintaining asthma control. MT

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Parents as partners in managing childhood asthma

The effective treatment of childhood asthma relies on a correct diagnosis having been made and optimal communication between physician, patient and parents.

LOUIS I. LANDAU
AO, MD, FRACP

Professor Landau is Professor of Paediatrics, School of Paediatrics and Child Health, The University of Western Australia, Crawley; Director, The Clinical Child Health Research Network, and Chair, Postgraduate Medical Council of Western Australia, WA.

Making a diagnosis

A diagnosis of asthma in children is determined mostly from an accurate history supporting asthma as the cause of wheeze and excluding other diagnoses. Physical examination may help in the assessment of severity and to check for alternative diagnoses. Diagnostic tests are of limited value, although lung function testing is helpful in older children, especially those with moderate to severe symptoms. A chest radiograph may be helpful in younger children, in whom alternative diagnoses are more common.

A diagnosis of asthma is particularly difficult to make in patients during their first year of life. Wheezing associated with respiratory tract infection occurs in more than 30% of infants during this period and has been referred to as wheeze associated respiratory infection (WARI). In many cases, this occurs in a child with smaller airway calibre as a result of factors such as familial predisposition, male gender or maternal smoking during pregnancy. Rarely, the wheeze in infants may be due to conditions such as cystic fibrosis, milk aspiration or congenital structural abnormalities. However, about one-third to one-half of infants who wheeze will have the early onset of asthma. Although these children often have more frequent wheezing and are atopic, they may be difficult to differentiate from those with smaller airways and viral induced wheeze.

Assessing severity

Assessment of asthma severity is based on the pattern of wheeze and breathlessness. Cough is usually associated with these symptoms. Some have argued that people with asthma may present with cough alone and have called this entity 'cough variant asthma'; however, evidence now indicates that cough without wheeze is uncommon in childhood asthma.[1]

The asthma severity of each child should be assessed so that treatment can be individualised. The child and/or parents must be asked specifically if he or she has a cough or wheeze and whether this occurs regularly or intermittently. The first box on page 12 lists some questions for parents that are helpful to determine the severity of asthma in their child.

IN SUMMARY

- **Make sure that the diagnosis of asthma is correct.**
- **Assess the severity of the child's asthma.**
- **Provide effective education to parents and older children on pathology, lifestyle and drug regimens.**
- **Discuss with parents and older children the triggers of asthma, including allergens, pollutants, diet and exercise.**
- **Pharmacotherapy for asthma in children is based on bronchodilators, inhaled corticosteroids and leukotriene modifiers; only occasionally are other drugs used.**
- **Alternative therapies have limited efficacy in the management of asthma in children.**
- **Good control can usually be achieved with the use of medications, without toxicity.**
- **Current understanding on the development of asthma may lead to a future cure.**

Determining asthma severity: questions for parents

- Does your child wake at night because of cough or wheeze?
- Does your child have a cough or wheeze on waking first thing in the morning requiring urgent bronchodilator therapy?
- Is your child's sport or physical activity limited by cough, wheeze or tightness in the chest?
- How frequently does your child need bronchodilator for symptom relief?
- Does a metered-dose inhaler last for less than 4 to 6 weeks (i.e. is it used more than twice daily)?
- Has your child's school attendance been affected by his or her symptoms?

Features of patients at high risk of life-threatening asthma

- Repeated visits to the doctor or emergency department or admissions to a hospital, especially the intensive care unit
- Previous life-threatening attacks
- Poor compliance with treatment, especially in teenagers and young adults
- Poor perception of symptoms
- Persistently abnormal lung function measurements
- Denial of asthma
- Overt psychosocial problems

Information regarding the use of medication should be sought because inappropriate medications such as antibiotics, antihistamines and nonprescription medications may be given for symptoms that are actually caused by asthma.

Poorly controlled asthma will be recognised by the frequent presence of wheeze, excessive use of reliever medication, inadequate length of response to reliever medication, and supporting evidence of abnormal lung function. Patients at high risk for life-threatening asthma may be recognised by the features listed in the second box on this page.

It must be recognised that, although low, there is a risk of dying from asthma in every child with this condition, and each child should be carefully assessed and appropriately managed to minimise that risk.

Educating parents and children

An extensive education program involving the child, the parents, other health professionals and the physician in comanagement is vital to ensure complete understanding of the natural history of the disease and the roles of particular medications. Without this understanding, adherence to medications will be severely compromised.[2] Recent studies have shown that fewer than 50% of patients adhere to medication that is prescribed daily.[3] Written material in the form of action plans with detailed personalised information may be useful to improve adherence, although Cochrane reviews have reported that there are insufficient data to confirm their value in asthma control.[4] Peak flow meters may be of additional value for those with troublesome asthma and poor perception of symptoms, but they are not necessary to improve control of symptoms in most children.[5] Support groups can help in providing information and encouragement.

Use plain language and address concerns

Education should begin with a description in plain language of the pathogenesis of asthma. Emphasis should be placed on how airway inflammation, mucus production and bronchoconstriction can each contribute to airway obstruction. Patients are confused by the multiple terms used to describe asthma, including 'bronchitis', 'asthmatic bronchitis', 'wheezy bronchitis', 'reactive airways disease', 'hyperreactive airways disease', 'attack' and 'exacerbation'.

It is important that health professionals address real concerns of the parents that may not be related purely to the symptoms that the child presents with at consultation. Patients and families really want to know whether asthma will impair or interfere with a normal active life, but they rarely ask this directly. Emphasis on there being a wide spectrum of severity in children and adults with asthma but that most are able to lead active and productive lives sets the right tone and provides motivation for the patient to play an active part in controlling and managing asthma. It is worth pointing out that Olympic athletes with asthma have managed to win gold medals, particularly in swimming.

Set goals and explain how medication works

Goal setting for preventive therapy is also important. Many families do not like the idea of giving their child medicines for long periods of time, particularly if the child seems well. It is important to set the goal of gradually reducing inflammation and, once good control is established, to try to reduce the amount of medication needed to maintain the child in that state.

It is important to be explicit about how the medicines work, how to take them correctly (including the use of spacers), and their potentially harmful effects. Most parents are very concerned about drug toxicity, whether or not they articulate this concern. Some confuse muscle-building or anabolic steroids with anti-inflammatory corticosteroids.

Others have seen patients with considerable facial swelling following systemic doses of corticosteroids and may be terribly worried about the use of these medications.

Parents need to be reassured that the risks of serious asthma far outweigh the side effects of medication, including inhibition of growth, in the conventional inhalation doses of corticosteroids currently recommended. Following an extensive meta-analysis, Allen and colleagues concluded that children treated with inhaled beclomethasone were more likely to reach predicted or normal heights than children whose asthma was not treated with preventive medication.[6] Nevertheless, there is still considerable controversy about the possibility that inhaled corticosteroids may inhibit linear growth. Parents should be reassured that once their child's asthma is well controlled, the inhaled corticosteroid dosage will be reduced. The physician's task is to recommend a regimen that maximises good control while using the least amount of medication in the long term. The strategy of aggressive early treatment of asthma may, in fact, lead to a lower total cumulative dose of medication given in the long term.

Provide an action plan in case of deterioration

The physician should provide patients with a plan of action in case of deterioration, and especially in an emergency. Deterioration may be expected when patients catch a cold. It is important to emphasise that the first sign of a cold refers to the earliest signs, such as a runny nose or scratchy throat, rather than full blown signs and symptoms, such as thick nasal mucoid discharge, prominent cough or wheeze. Bronchodilators should be started at the earliest signs of a cold and can be given up to every four hours. They should be continued until two to seven days after the cough or wheeze has resolved.

Recommend several visits

Several (three or more) visits will probably be needed to develop a long term plan and teach the patient or family to follow it. These visits provide the opportunity to obtain patient feedback, provide additional health education, adjust the pharmacological regimen and correct any misunderstandings. The aim is for the patient to be as symptom free and physically active as possible.

Avoiding triggers

Continued exposure to allergens and other triggers may be associated with worsening of asthma, and thus it is important to discuss with children and their parents the specific triggers that make their asthma worse. Avoidance of triggers should be considered at all times to maximise the potential for asthma improvement.

In utero sensitisation

Sensitisation *in utero* appears to occur, but most studies do not show any benefit from restrictive diets during pregnancy and severe restriction can be detrimental to the mother and the fetus. At present, apart from avoidance of maternal smoking, there are no other proven strategies for prenatal avoidance.

Dietary triggers

Some foods and additives may trigger asthma. Because there is no single food that affects all people with asthma, the role of food needs to be considered individually for each patient. A common trigger is the preservative, sodium metabisulfite, which is often present in dried fruits, sausages, wines, and other drinks. This preservative releases sulfur dioxide, especially in the presence of acidic drinks. Cold drinks have been shown to lead to increased airway responsiveness, especially in Asian children. There are anecdotal reports of asthma attacks caused by monosodium glutamate and tartrazine, but no consistent findings. Occasionally, foods such as nuts, shellfish, strawberries, eggs and cow's milk produce an acute response, but this is usually associated with generalised anaphylaxis and clearly recognised as such. Attempts have been made to influence the induction of asthma in early childhood by dietary modification; however, results are inconsistent.[7,8]

Aeroallergens

Most people with asthma develop long term sensitisation to aeroallergens, which is associated with persistence of symptoms. However, a direct causal relation is not always clear, and further studies must be carried out to clarify this association. Exposure to animals such as dogs and cattle during the prenatal period and early postnatal life is associated with reduced asthma and atopy. However, it may be reasonable to exclude furry pets such as cats from the homes of those people who are already sensitised. The fur of cats is often coated with saliva containing enzymes that assist the passage of allergen across epithelial surfaces.

House dust mites

Although house dust mite sensitisation is one of the more common associations with continuing asthma,[9] avoidance measures have rarely proved successful. Extreme measures such as admitting patients to hospital or living in alpine environments does appear to be associated with a decrease in sensitisation to house dust mite and improvement in symptoms and lung function. Less extreme measures do not often work, although Murray and Ferguson found that pillows encased with thick plastic or replaced regularly, mattresses encased with thick plastic, bedding washed in warm water, and humidity kept below 50% were beneficial.[10] The removal of carpets and use of high-grade filters, acaricides and special vacuum cleaners have not consistently shown significant benefit. A recent Cochrane review concluded that chemical and physical

Figure. Exercise may trigger asthma but need not be avoided.

methods aimed at reducing exposure to house dust mite allergens could not be recommended.[11]

Tobacco smoke

Exposure to environmental tobacco smoke is associated with increased asthma symptoms. Maternal smoking has been shown to be associated with increased wheeze in infancy, decreased lung function and increased airway responsiveness, and to be responsible for up to 20% of acute attacks of asthma and an increase in emergency room visits.[12,13] An improvement in symptom severity has been noted in children whose parents cease smoking.[14]

Active smoking is an important trigger for progression of symptoms and should be discussed with all children from about the age of 10 years.

External pollutants

Although external atmospheric pollutants are important triggers of lower respiratory symptoms, particularly bronchitis, and asthma symptoms in those who already have asthma, they have not been shown to be a major factor in the primary development of asthma. The use of filters and ionisers has not been shown to have any clinically significant benefit in patients with asthma.

Paints and other fumes can usually be avoided.

Medications

Medications are not a common cause of asthma attacks in children. Aspirin and other NSAIDs and some complementary medicines very occasionally cause symptoms in younger children. Beta blockers, either orally or as eye drops, should be avoided or used cautiously in children with asthma as they can cause severe asthma.

Other conditions

Gastro-oesophageal reflux, obstructive sleep apnoea and rhinitis have been associated with increased asthma symptoms in adults, but this does not seem to be a common clinical issue in children. It is recommended that people with chronic asthma receive influenza vaccination; however, the benefits for this in children with asthma have not been confirmed. The association of asthma with obesity, particularly in adolescent girls, may justify consideration of dietary advice, but adequate trials to document benefit have not been conducted.

Exercise

Exercise may be a trigger of asthma but need not be avoided (Figure). With appropriate warm-up sprints to induce tachyphylaxis and, if necessary, premedication with beta$_2$ agonists or sodium cromoglycate, a more sustained period of exercise will not cause significant symptoms. Approximately 30-second sprints every two minutes for 10 to 20 minutes have been shown to be a useful warm-up.[15] Physical training improves cardiopulmonary fitness, but has little impact on lung function. It is likely that improved fitness will lead to better quality of life.

Treatment

Treatment is based on the pattern of asthma symptoms, which can be classified as:

- infrequent episodic (occurring in 75% of children with asthma)
- frequent episodic (20%)
- persistent (5%).

Criteria for this classification are shown in Table 1. Persistent asthma can be further classified as:

- mild persistent
- moderate persistent
- severe persistent.

The goals of treatment are shown in the box on page 15.[16]

Pharmacotherapy

Current concepts on the use of drugs in asthma are based on the treatment of the underlying inflammatory disease as well as prevention and treatment of acute attacks of asthma associated with environmental triggers. Asthma attacks may be treated with reliever medications such

as beta$_2$ agonists, ipratropium bromide and, rarely, theophylline (Nuelin). The underlying disease process is generally controlled with inhaled corticosteroids, leukotriene modifiers or, now rarely, sodium cromoglycate. Maximum efficacy and safety is usually achieved by the use of inhaled medications.

Inhaler devices

Inhaler devices for children include metered dose inhalers (MDIs) with or without a spacer, dry powder inhalers (DPIs), and nebulisers (Table 2). Clear instructions on their use are essential. Children must be observed repeatedly using these devices to ensure that their technique is satisfactory; they will often revert to bad habits despite careful instructions. Most children over the age of 7 years can use a MDI, DPI or breath-activated autohaler. Some may be helped by using a large volume (750 mL) spacer, which will improve deposition and may, in some cases, allow larger doses to be given to have an effect similar to that of using a nebuliser during an acute attack. Some children will need to use a nebuliser if they have severe acute attacks of asthma or troublesome chronic asthma.

Children aged from 4 to 7 years can use a MDI with a large volume spacer. The medication can be inhaled through the mouth as a single breath or with panting tidal manoeuvres, both being equally effective. Only one to two actuations at a time should be used; any larger number allows significant deposition and reduces the available respirable particles.[17] Spacers should be washed with detergent and left to air-dry, not wiped, to minimise electrostatic forces that cause increased aerosol fallout. Some children of this age can use a DPI, but deposition is unreliable in those aged under 5 years,[18] especially during symptomatic periods when inspiratory flow rates are low. For many DPI devices, a rate of at least 30 L/min is required for optimal de-aggregation and appropriate deposition of particles. It is not clear whether the breath-actuated autohaler is of significant benefit in this age group.

In children aged under 4 years, MDIs with a small volume spacer and face mask can provide adequate deposition and similar therapeutic response to that seen with nebulisers.[19,20] In some societies, access to and cost of these devices are a particular problem, and a large plastic coffee cup or the bottom half of a one litre plastic drink bottle may be modified to produce a reasonable spacer device.

Goals of asthma treatment in children*

Immediate aims

- Ensure the correct diagnosis has been made
- Abolish symptoms
- Maximise lung function

Long-term aims

- Maintain the child symptom free
- Maintain best lung function at all times†
- Avoid the need for extra bronchodilators
- Prevent the restriction of normal childhood activities
- Prevent the development of irreversible airway obstruction
- Reduce the risk of death from acute attacks of asthma
- Avoid unnecessary side effects from medications

* The Global Initiative for Asthma[16] and State and Territory Asthma Foundations provide guidelines to management.
† Children with persistent asthma should have spirometry at each consultation. Those with troublesome symptoms may regularly measure their peak flow at home. The aim is to ensure that lung function remains within normal limits for each individual and diurnal variation in peak flow is less than 10%.

Table 1. Classification of asthma by pattern of symptoms

Pattern of asthma	Infrequent episodic	Frequent episodic	Persistent
Wheeze, tightness, cough or symptoms on exercising	Occasionally (e.g. with viral infection)	Most days	Every day
Nocturnal asthma	Usually absent	Less than once per 4-6 weeks	More than once per week
Asthma on waking	Usually absent	Less than once per 4-6 weeks	More than once per week
Hospital admission in past year	No	Usually not	Usually
Previous life-threatening attack	No	Usually not	May have a history
Bronchodilator use	Infrequent	Needed most weeks	Needed most days
FEV_1 (% predicted)	Normal	Normal/low	Usually low
Mean peak flow variability over 2 weeks*	10-20%	20-30%	>30%

* Mean peak flow variability % = (highest - lowest) / highest x 100.

Nebulisers are effective because large doses can be administered and breathing pattern does not have as significant an effect on deposition. They can be used with oxygen if needed, but they are bulky, expensive and not necessary for most children with asthma. Use of a MDI and spacer with up to 10 puffs of $beta_2$ agonist will produce the same or better result than a nebuliser in an attack of asthma.[21] Nebulisers with a venturi design to drive air or oxygen through the fluid and with a separate expiratory valve provide a better dose of drug.

Use of novel incentive spacer devices, such as the 'Funhaler', appear to be associated with improved adherence and likely efficacy.[22]

Affect of genetic polymorphism

It is being shown increasingly that many different genetic polymorphisms can contribute to asthma susceptibility and severity. These polymorphisms also influence the variability in the patient's response to drugs, both therapeutic and adverse (pharmacogenetics). Polymorphisms can impact on drug metabolism, target receptors or unintended targets, and research in this area is providing enticing data on their future potential. Polymorphisms in the $beta_2$ adrenergic receptor, particularly the 16th and 27th amino acid positions, may affect response to beta agonists so that patients who are good responders or those who may have adverse effects with regular use could be identified. Polymorphisms on leukotriene C4 synthase or 5-lipoxygenase enzyme sites may identify variation in response to leukotriene modifiers. Genetic variation is known to affect patients' responses to corticosteroids and adverse events experienced, such as decreased bone density.

Nonpharmacological therapies

Physiotherapy has a specific role in the management of patients with asthma. Those with mucus plugging and subsequent atelectasis will benefit from physiotherapy as well as adequate pharmacological treatment of their asthma. This group often needs corticosteroids to reduce the mucus hypersecretion. Physiotherapists have an important role also in educating children on useful exercises and correct techniques in the use of aerosol devices.

There are reports that antioxidant supplementation is associated with both a reduction in asthma symptoms and improved lung function in people with asthma exposed to pollutants.[23] Some, but not all reports note reduced development of asthma in atopic people who take *Lactobacillus*[24] or omega-3 fatty acid supplements. Further studies are needed to confirm the role of these dietary interventions.

Many people with asthma resort to alternative health therapies,[25] most of which have not been found to be effective in controlled trials. Ionisers and acupuncture have been shown to be ineffective in controlled trials.[26,27] Most studies of chiropractic, herbal medicines, homeopathy, yoga, specific breathing exercises and hypnosis have also been disappointing, although they suggest that some individuals may gain nonspecific benefit. The evidence available is too limited to make recommendations on the use of most of these alternative therapies.

The role of immunotherapy in asthma continues to be debated. At present, avoidance of known triggers and pharmacotherapy are more appropriate initial approaches to management, providing good control without significant side effects. The efficacy of immunotherapy is mild and less than that obtained with anti-inflammatory agents, and it is associated with more side effects, including death. It is considered occasionally in highly selected children who are sensitive to a specific single allergen, such as grass pollen, mites or *Alternaria*, and when it can be performed safely under specialist supervision. Usually it must be given for at least three years. Some argue that it may reduce the number of children who progress from rhinoconjunctivitis to asthma.

Treatment of an acute attack

For a child having an acute attack, treatment will usually be initiated at home with a beta agonist. If the child's asthma is not responding to standard treatment at home, he or she should be given the $beta_2$ agonist repeatedly while medical attention is sought. An alternative diagnosis such as an inhaled foreign body should be considered in patients who fail to respond to treatment. However, if asthma is suspected, the patient should be taken

Table 2. Recommended delivery device according to age*

Delivery device	Under 4 years	4 to 6 years	7 years and older
Nebuliser	Yes	Yes	Yes
MDI/small volume spacer/mask	Yes	–	–
MDI/large volume spacer	–	Yes	Yes
DPI	–	Sometimes	Yes
MDI	–	–	Yes

* Always assess compliance and delivery technique when symptom control or response to medication is poor.
Abbreviations: MDI = metered dose inhaler; DPI = dry powder inhaler.

to the emergency room or doctor's office where $beta_2$ agonist may be given with oxygen if necessary.

Mild to moderate episodes of asthma can be treated with beta agonists given by a MDI and spacer, using six to 10 puffs, administered as two actuations every 30 seconds. Some centres would use additional ipratropium bromide, which may result in a 10% increase in, and a greater duration of, response.

If the child responds to the treatment above, he or she should be observed for one to four hours and then sent home with instructions to continue treatment. If the child does not respond optimally, corticosteroids will be added to the regimen. There is some evidence that in the emergency room high dose inhaled corticosteroids may be equally effective to oral corticosteroids in selected patients with mild asthma, but a combination of inhaled and oral corticosteroids does not provide additional benefit.[28]

Those children not responding to treatment over one to four hours should be admitted to hospital. Admission criteria are based on duration and severity of clinical signs, peak flow, arterial oxygen saturation and lack of response to bronchodilator, but admission is often influenced by social circumstances, past history and comorbidities.

Long-term management

Successful long-term asthma management is achieved by adherence to a treatment strategy based on recently published guidelines. These provide algorithms that recommend currently agreed-upon good clinical practice. However, treatment must be individualised; choice provides an opportunity to find the most suitable regimen for each child based on initial assessment and then to move up or down the protocol depending on response.

Infrequent episodic asthma

Children with infrequent episodic asthma (75% of children with asthma) will usually require only intermittent treatment with inhaled short-acting $beta_2$ agonists. Parents should be aware of early signs that indicate an attack, such as runny nose, itchy throat, or cough, so that treatment can be instituted early. Treatment is usually continued until the child has been free of symptoms for at least 48 hours.

Frequent episodic asthma

Children with symptoms at least every two months but with no symptoms in between (20% of children with asthma) should be given regular preventive therapy. This may be low dose inhaled corticosteroid, leukotriene modifier or sodium cromoglycate. Choice will depend on the pattern of asthma and patient preferences. Low dose inhaled corticosteroids are the most useful medication and are effective within one to two weeks and should then be continued. If episodes are mild or experienced only with exercise, other agents with demonstrated efficacy may be considered.

Persistent asthma

Children with troublesome symptoms on most days (5% of children with asthma) will require inhaled corticosteroids once or twice daily with bronchodilator added as required. The starting dosage of the inhaled corticosteroids will depend on asthma severity. If symptoms are not well controlled, regular peak flow measurements may be needed to monitor response to additional treatments. Additional treatments include long-acting $beta_2$ agonist and, less commonly, higher dose inhaled corticosteroids, oral corticosteroids, leukotriene-receptor antagonists, ipratropium bromide and theophylline.

Children taking inhaled corticosteroids should use a spacer device if they have a MDI, or rinse out their mouth if they have a dry powder device.

There is evidence that exhaled nitric oxide monitoring may be useful in reflecting eosinophilic inflammation and may be used to optimise inhaled corticosteroid treatment in selected children with persistent symptoms.[29]

Combination therapy

Combination of inhaled corticosteroid and long-acting beta agonist therapy has been shown to be safe and effective in children.[30,31] Long-acting beta agonists should always be used with inhaled corticosteroids and not as monotherapy. A fixed dose combination (inhaled corticosteroid and long-acting beta agonist) is indicated for the regular treatment of asthma where the combination is appropriate in adults and older children (usually those aged over 12 years, but from 4 years in some countries). Standard fixed dose combinations are thought to be less effective in children than adults, but an adjustable dose regimen, budesonide/eformoterol (Symbicort Turbuhaler) as maintenance and reliever therapy (SMART), appears equally effective in appropriate children as in adults.[32,33] This replaces the need for a short-acting $beta_2$ agonist, as unlike other long-acting beta agonists, eformoterol has a rapid onset of action allowing it to be used for reliever activity.

Using the Symbicort SMART approach in appropriate patients resulted in fewer exacerbations, prolonged time to first exacerbation, decreased waking and higher FEV_1 than a fixed combination plus short-acting beta agonist as reliever or a higher dose inhaled corticosteroid plus short-acting beta agonist as reliever. Overall, there was a lower cumulative corticosteroid use with the Symbicort SMART approach.[32] This regimen is not necessary for those well controlled on low dose inhaled corticosteroid, but is effective in selected patients whose asthma is not well controlled. Its effectiveness may be related to the timing of administration of the extra reliever doses of the budesonide/eformoterol early in an exacerbation.

Mediator specific therapy

Viruses may lead to increased airway responsiveness associated with mucosal

damage and the presence of cysteinyl leukotrienes in airway secretions. Leukotriene modifiers have been shown to produce some symptomatic relief in infants and toddlers with viral induced wheeze.[34] The availability of leukotriene-receptor antagonists (montelukast [Singulair], indicated for children 2 years and above, and zafirlukast [Accolate] for children over 12 years) provides new mediator-specific therapy for asthma. Their specific role is not yet clear. They have been shown to block airway response to challenge, including exercise, and, in chronic asthma, to lead to improved lung function, reduced symptoms, and some steroid sparing. They are well tolerated but appear to be less effective than corticosteroids, with 17% of an asthmatic cohort showing increased FEV_1 with the use of both inhaled corticosteroids and leukotriene modifiers, 23% increased FEV_1 with inhaled corticosteroids only and 5% increased FEV_1 with leukotriene-receptor antagonist only.[35,36]

Specific recommendations on the use of these newer agents cannot yet be made, and inhaled corticosteroids remain first line therapy for most children with persistent asthma. The leukotriene modifiers may prove useful in mild asthma if an oral preparation is required, as an alternative to inhaled corticosteroids and long acting beta agonists and, possibly, in those in whom corticosteroid reduction is sought.

Omalizumab (Xolair) is a recombinant humanised monoclonal antibody directed against IgE to inhibit the immune response to allergen exposure. It prevents free serum IgE from attaching to mast cells and other effector cells and prevents IgE-mediated inflammatory changes.

A Cochrane review reported that omalizumab is significantly more effective than placebo in enabling patients to reduce or withdraw inhaled corticosteroids,[37] but its clinical value is debatable. It is approved for use in children aged 12 years and older who have evidence of asthma and atopy not controlled by inhaled corticosteroids. Omalizumab is administered by regular subcutaneous injection, is well tolerated and reduces asthma exacerbations. However, it is expensive, and further assessment is necessary.

When to refer

Specialist referral should be considered for any child who has a life-threatening attack of asthma, frequent hospital admissions, poor parental management, or poor response to regular treatment or in whom the diagnosis is uncertain. The natural history of childhood asthma is usually for improvement, and the possibility of a decrease in drug treatment or cessation of therapy should be considered every six months.

Outlook

Although asthma cannot be cured at present, it can be well controlled. The increasing understanding of the development of asthma symptoms in early childhood may mean that early intervention in the future will lead to a cure. MT

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DECLARATION OF INTEREST: Professor Landau has received honoraria in the past from GlaxoSmithKline and AstraZeneca for presentations at scientific meetings.

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Difficult to control asthma in children

Asthma is one of the most common paediatric presentations to general practice. Some children demonstrate persistent symptoms despite appropriate use of medications. This review provides a user-friendly clinical approach to managing difficult to control asthma in children.

ANDREW TAI
MB BS
JOHN MASSIE
MB BS, PhD, FRACP

Dr Tai is Fellow, Department of Respiratory Medicine, Royal Children's Hospital, and Associate Professor Massie is Paediatric Respiratory Physician, Department of Respiratory Medicine, Royal Children's Hospital, Melbourne, Vic.

Asthma is an airway disorder associated with reversible airflow obstruction. Patients with asthma typically complain of recurrent wheeze, breathlessness, chest tightness or cough, and these symptoms are usually responsive to treatment with a short acting bronchodilator.

In 2004 to 2005, the prevalence rate of asthma in Australia in children aged 0 to 14 years, as reported by the Australia Bureau of Statistics, was approximately 12%, which is relatively high by international standards.[1,2] Approximately 90% of children have episodic asthma (infrequent or frequent) and about 10% have persistent symptoms.[3] In most of these children the asthma is well controlled with appropriate medications. The proportion of children with difficult to control asthma accounts for fewer than about 2% of all children with asthma;[4] however, these children and adolescents with difficult to control asthma use significant medical resources.

Australian guidelines indicate that patients with well controlled asthma require rescue therapy with bronchodilators less than twice per week, but the guidelines do not formally define difficult to control asthma.[1] The European Respiratory Society defines difficult to control asthma as the presence of chronic symptoms with episodic exacerbations, persistent and variable airway obstruction and continued requirement of short acting beta agonist despite treatment with 800 µg/day or more of budesonide or its equivalent (e.g. 500 µg/day or more of fluticasone).[5] Difficult to control asthma in children may be considered as that requiring bronchodilators more than three times a week or resulting in school absence of more than five days a term.

Children with difficult to control asthma should undergo a careful evaluation that includes review of the diagnosis and medications, and assessment of drug delivery techniques and medication adherence. Also, the child's home environment and psychosocial factors should be assessed for potential precipitants.

Confirming the diagnosis

It is necessary when addressing children with difficult to control asthma to reconfirm the diagnosis of asthma. A history should be taken of asthma symptoms. A normal physical examination will help to exclude important differential diagnoses. Well performed measures of lung

IN SUMMARY

- **Difficult to control asthma carries significant morbidity to children and their families.**
- **It is important to ensure that the diagnosis of asthma is correct.**
- **Patients' medications, drug delivery method, adherence to treatment, home environment and psychosocial factors should be assessed. Precipitating factors, particularly exposure to tobacco smoke, should be minimised.**
- **Inhaled corticosteroids are the cornerstone of therapy. The dose should be titrated to control symptoms, maximise efficacy and minimise adverse effects.**
- **GP's should regularly review patients and establish a partnership of care.**

function (in children older than 6 years of age) and chest imaging (i.e. chest x-ray) are essential in the diagnostic work up.

History

Wheeze

Wheeze is an important symptom of asthma, but can have other causes (see the box on page 22). The description of wheeze (an expiratory noise emanating from intrathoracic airways) can be variable and is not necessarily discriminating. Wheeze is a very common symptom in children, with reports indicating that up to 40% of children have at least one episode of wheeze during childhood.[6] There is less than a 50% agreement between parents' and clinicians' reports of wheeze.[7] Patients and parents may confuse stridor (an inspiratory noise emanating from extrathoracic airways) with wheeze. It is useful to ask the child or family members to demonstrate the sounds or to demonstrate wheezing yourself.

Cough

When cough is due to asthma, it is usually dry and accompanied by wheezing, chest tightness or shortness of breath and there is a clear response to bronchodilator therapy. Cough in the absence of wheeze is unlikely to be due to asthma. Postviral cough generally occurs after an upper respiratory tract infection and resolves in two to four weeks. Chronic nonspecific cough during childhood may resemble asthma as it is dry, mostly nocturnal and may last for months, but it is usually not associated with other asthma symptoms and does not respond to a bronchodilator. If the cough is moist and worse on waking, consider suppurative lung disease.

Shortness of breath

Shortness of breath may accompany the wheeze and cough associated with asthma. If exertional shortness of breath is due to asthma, it is generally responsive to bronchodilator therapy or is prevented by use of bronchodilator before exertion. Exercise-induced dypsnoea can be confused with asthma, but is unresponsive to bronchodilator treatment.

Asthma precipitants

A detailed history should explore asthma precipitants, in particular viral respiratory infections and allergies and a personal or family history of atopy (e.g. eczema or hayfever).

Difficult to control asthma in children

The prevalence rate of asthma in Australian children is about 12%, which is relatively high by international standards. In most of these children the asthma is well controlled with appropriate medications; however, some children demonstrate persistent symptoms that are difficult to control.

Investigations

Inspection of the respiratory system for underlying chronic changes is the focus of investigations. In particular, the following signs should be assessed:

- nutrition and growth percentiles
- respiratory effort
- digital clubbing
- chest shape (e.g. hyperinflation, pectus carinatum, Harrison's sulcus – an inward deformity of the ribcage along the insertion of the diaphragm)

Differential diagnoses of wheeze in children

Transient infant wheeze

Onset in infancy. There is no associated atopy and no response to bronchodilator therapy. Spontaneous regression occurs by 3 to 6 years of age. Maternal smoking is a risk factor.

Suppurative lung disease (e.g. cystic fibrosis)

About 95% of individuals with cystic fibrosis are diagnosed through newborn screening. The missed 5% present with moist cough, recurrent wheeze and/or failure to thrive.

Foreign body aspiration

History of sudden onset coughing and choking that is often followed by wheeze and cough. Up to 50% of events are unwitnessed. On auscultation, there may be unilateral signs of reduced air entry or wheeze.

Congenital malformation causing narrowing of the intrathoracic airways (e.g. tracheobronchomalacia)

Symptoms such as a barking cough, increased work of breathing, poor feeding and wheeze may be present from birth or within a few weeks of life.

Recurrent aspiration

Choking and coughing during feeds particularly with fluids. Children with developmental delay are at increased risk. If associated with symptoms of vomiting and wheeze occurs at night when lying down to sleep, consider gastro-oesophageal reflux.

Cardiac failure

Underlying congenital heart disease may cause wheeze when pulmonary oedema is present. Physical examination is likely to reveal a heart murmur and hepatomegaly.

Vocal cord dysfunction

Symptoms include wheeze, stridor or breathlessness. Occurs only when awake and may be induced by exercise.

- auscultatory signs of air entry and added sounds (e.g. wheeze or crackles).

Tests of lung function

Lung function testing can be useful in supporting the diagnosis of asthma, monitoring progress or excluding other conditions. Spirometry can be attempted in children aged 6 years and over. It is important to remember that spirometry may be normal despite the presence of difficult to control asthma symptoms. Although spirometry carried out in an office is to be encouraged, in children with difficult to control asthma, spirometry with flow–volume loops (to assess for asthma or other differential diagnoses) and body plethysmography (to measure absolute lung volumes) should be performed in a specialist laboratory in conjunction with a respiratory specialist. A typical flow–volume loop in a patient with asthma is shown in the box on page 23.

Children who demonstrate features of airway obstruction should trial a bronchodilator to assess for reversibility. The lack of a response to bronchodilator therapy in the presence of airway obstruction does not exclude a diagnosis of asthma, but does indicate the need for specialist referral. Assessment of airway reactivity is sometimes helpful. In children, bronchial provocation tests are restricted to exercise challenge tests or, more recently, the dry powder mannitol test.[8] Histamine and methacholine challenges can be dangerous and are rarely used with children.

Using peak flow meters

Peak flow meters are not used for diagnosis and rarely used for monitoring asthma in children. The measurement of peak flow using mini peak flow meters (at home or in the office) does not equate to spirometry.[9] Peak flow meters are effort-dependent and predisposed to error in children under 8 years of age. In older children, peak flow meter recordings provide only an approximate guide to asthma severity and are open to manipulation; values obtained should, therefore, be interpreted cautiously. Finally, there is no advantage of peak flow meter based monitoring over symptom monitoring alone.[10]

Chest imaging

It is worth investigating whether the child with difficult to control asthma has previously had a chest x-ray. This is to exclude differential diagnoses as described above. However, repeat chest x-rays are not indicated as routine surveillance. CT imaging might show bronchiolitis obliterans or bronchiectasis, but these conditions should be considered with the advice of a paediatric respiratory physician.

Monitoring airway inflammation

Although measurements of exhaled nitric oxide and sputum testing for eosinophil products are of interest to researchers, these have not been used in clinical practice to diagnose asthma or monitor therapy in children.

Management

The key factors in managing children with asthma include review of medications, assessment of drug delivery technique and adherence to medication, identification and avoidance of precipitating factors and evaluation of the home environment and psychosocial factors. The goals of asthma therapy are to maintain control of symptoms, prevent exacerbations, attain the best possible lung function and minimise side effects.[1]

Reviewing medications

Inhaled corticosteroids

Inflammation is a critical feature in the pathogenesis of asthma and consequently inhaled corticosteroids (ICS) are the mainstay of treatment of difficult to control asthma in children. Randomised controlled trials clearly demonstrate that ICS reduce asthma symptoms, improve lung function, reduce the frequency of acute exacerbations and improve airway hyper-responsiveness.[11] In approximately 90% of children, therapeutic benefit of ICS is achieved with a total daily dose of 200 µg/day fluticasone (Flixotide) or the equivalent doses of budesonide (Pulmicort; 400 µg/day) or ciclesonide (Alvesco; 160 µg/day). The maximum effect is achieved with a dose of about 500 µg/day fluticasone (about 800 µg/day budesonide or 320 µg/day ciclesonide).[12]

Children taking long term high dose ICS should undergo monitoring for adverse effects. This includes assessment of growth, cataracts, osteoporosis and adrenal suppression. It is our practice to measure early morning cortisol level to screen for adrenal insufficiency in children regularly taking more than 500 µg/day fluticasone, or its equivalent. Patients with low cortisol levels should have definitive testing for adrenal sufficiency.

Combination therapy (ICS and long-acting beta$_2$ agonist)

Patients with inadequately controlled asthma and taking 200 µg/day fluticasone (or its equivalent) should have a long-acting beta$_2$ agonist (LABA), such as salmeterol (Serevent Accuhaler) or eformoterol (Foradile, Oxis Turbuhaler), added to their regimen. (From 1 May 2008, salmeterol metered dose inhaler was removed from the PBS due to manufacturer's discontinuation of the product.)

LABAs should not be used as monotherapy. The patient should be reviewed to assess the success of LABA addition before combination inhalers are used.

Spirometry: flow–volume loops

Spirometric testing in a child with difficult to control asthma can support the diagnosis of asthma. In the flow–volume loops shown, the convexity of the expiratory flow–volume curve (buff line above x axis) represents airway obstruction. Comparison of the flow–volume loops before and after bronchodilator (buff and green lines) shows a significant bronchodilator response, indicating reversible airway obstruction consistent with asthma. The flow–volume loop during normal tidal breathing is also shown (blue line).

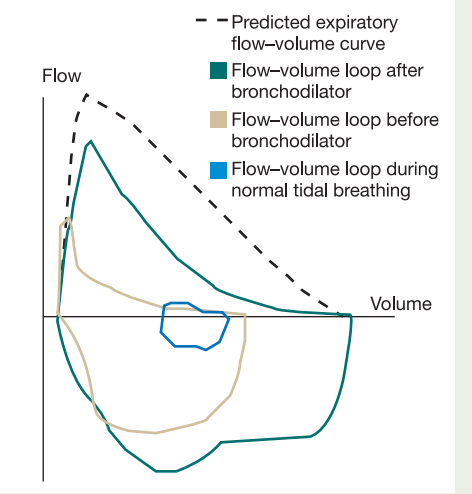

Figure. Flow–volume loops in a patient with asthma.

There are limited studies assessing the efficacy of combination treatment in children under the age of 5 years and this group of children should be referred for specialist paediatric advice.

Symbicort maintenance and reliever therapy

A combination inhaler containing budesonide/eformoterol (Symbicort Turbuhaler) may be used for both maintenance and rescue therapy in children over 12 years of age. The manufacturer of Symbicort refers to this regimen as Symbicort maintenance and reliever therapy (Symbicort SMART).

In the study by Rabe et al[13] the use of budesonide/eformoterol as both maintenance and reliever therapy was superior to budesonide/eformoterol maintenance plus eformoterol or terbutaline as-needed therapy in prolonging the time to first severe exacerbation in patients aged 12 years or older with moderate to severe asthma.

Another study by Rabe et al[14] also showed that budesonide/eformoterol as both maintenance and reliever therapy was superior to budesonide maintenance plus terbutaline as-needed therapy in reducing the risk of a severe exacerbation and hospitalisation/emergency department treatments due to asthma in patients aged 12 years or older with mild to moderate asthma.

One study has shown that budesonide/eformoterol as both maintenance and reliever therapy prolonged the time to first severe exacerbation and reduced the exacerbation rate in children as young as 4 years of age when compared with budesonide maintenance plus as-needed terbutaline and budesonide/eformoterol maintenance plus as-needed terbutaline.[15]

These findings have not been demonstrated with the use of the combination inhaler fluticasone/salmeterol (Seretide) because of the slower onset of action of salmeterol (20 minutes) compared with eformoterol (one to three minutes).

Symbicort SMART is not currently indicated for use in children under 12 years of age in Australia. For children over the age of 12 years, one to two inhalations twice daily or two inhalations once daily of budesonide 100 µg/

eformoterol 6 μg (Symbicort 100/6) or budesonide 200 μg/eformoterol 6 μg (Symbicort 200/6) can be used as maintenance therapy plus additional doses for reliever therapy up to a maximum of eight doses in a day.[1] (However, a total daily dose of up to 12 inhalations can be used temporarily.)

Leukotriene receptor antagonists

Montelukast (Singulair), a leukotriene receptor antagonist, may be used for the treatment of mild persistent asthma in children but there are limited studies of its use as an anti-inflammatory agent for difficult to control asthma. A randomised study with montelukast added to budesonide in children with persistent asthma did not show a clinically significant benefit.[16] A recent trial in adults also suggested that there is no benefit in adding montelukast to ICS alone or in combination with LABAs for patients with difficult to control asthma.[17] Despite the lack of supportive evidence, a trial investigating the effects of montelukast should be considered as it may benefit some patients. Montelukast can sometimes be helpful for children with exercise-induced asthma.

Theophylline

In recent years, theophylline (Nuelin) has not been widely used due to its adverse effects and reduced efficacy when compared with ICS. A study did not demonstrate benefit with the addition of theophylline to ICS for the management of moderate childhood asthma.[18] Nevertheless, because of its anti-inflammatory properties, some individual patients may benefit and it can be tried as adjunct therapy in those who are not well controlled on combination therapy. This use should be supervised by a paediatric respiratory physician.

Prednisolone

Some children with difficult to control asthma may initially require two to four weeks of treatment with prednisolone to achieve control of symptoms and normalise lung function. Specialist paediatric advice is required, and also weaning to the lowest dose.

Other medications

Second-line medications such as methotrexate (Methoblastin), cyclosporin (Cicloral, Cysporin, Neoral, Sandimmun) and high dose immunoglobulins have occasionally been used as corticosteroid-sparing agents for difficult to control asthma in children. These are not disease modifying and the limited data suggest a modest effect.[19-21]

Omalizumab (Xolair), a recombinant humanised anti-immunoglobulin E antibody, has been used in patients with poorly controlled allergic asthma and elevated serum immunoglobulin E levels. However, data in children are limited. Omalizumab is extremely expensive and only effective while patients are maintained on treatment. Paediatric respiratory advice is required.

Managing and preventing exacerbations

In children, acute exacerbations should be managed with prednisolone (1 mg/kg/day to a maximum dose of 50 mg/day) and regular use of bronchodilators. Recommended doses of salbutamol in children under 6 years of age are 100 μg per puff, six puffs via a small volume spacer, and in children aged 6 years and over, 100 μg per puff, 12 puffs via a large volume spacer. Terbutaline (Bricanyl) can be used in children aged over 8 years at a dose of 500 μg per puff, six puffs. It is usual to prescribe prednisolone for three to five days but this may depend on the patient's history and level of control prior to exacerbation. Doubling the dose of ICS has no effect in managing acute exacerbations.

An annual influenza vaccine is recommended for all patients with difficult to control asthma. The vaccine is safe (egg allergy is the main contraindication), although the data to support improved asthma control or reduced exacerbations is poor.

Assessing drug delivery technique and adherence to medication

Invariably, patients who do not respond to appropriate medication doses need to be evaluated for both technique of inhalant administration and adherence to medication.

Patients should be instructed to bring their inhalers to appointments and clinicians should view and/or demonstrate correct inhaler technique. Adherence should be assessed and barriers explored. Some reasons for poor adherence include patient (or parental) concerns about the safety of corticosteroid use, lack of education about asthma or difficulty using inhalers correctly. Forgetfulness or disorganisation are common problems that require practical solutions. GPs have an important role in reviewing patients and empowering them to maintain adherence with therapy. Decisions regarding preventer therapy should start with the patient's choice of the preferred delivery system. Wherever possible, appropriate medications should be selected to suit the chosen delivery system appropriate for the child's age (Table). The use of inhalers once a day (suitable for ciclesonide or budesonide) may promote adherence to treatment and determine which medication is selected.

Identifying and avoiding precipitating factors

Many children with difficult to control asthma have underlying atopy. Potential precipitants in their surrounding environment include:

- tobacco smoke (active and passive)
- inhaled allergens (e.g. house dust mite, pollens and animal danders)
- respiratory infections
- drugs (e.g. NSAIDs and beta blockers)
- occupational exposures from parents' occupation or from part time jobs.

A thorough clinical history is the best way to detect clinically relevant allergies.

Table. Asthma therapy: suitability of drug delivery systems according to a child's age

	Age of child			
Drug delivery systems	**Under 2 years**	**2 to 6 years**	**6 to 8 years**	**8 years and older**
Metered dose inhaler plus small volume spacer and mask	Yes	Yes. Mask not necessary from 4 years of age	No	No
Metered dose inhaler plus large volume spacer	No	No	Yes	Yes
Metered dose inhaler alone	No	No	No	Only for bronchodilator therapy
Turbuhaler	No	No	In some children	Yes
Accuhaler	No	No	In some children	Yes
Autohaler	No	No	No	Yes
Tablet	No	Yes	Yes	Yes

Sensitisation to inhaled allergens and food can be tested by skin prick tests or radioallergoabsorbent tests. Identifying allergens may be helpful in defining an atopic child but the allergens may not be causally associated with asthma.

Allergen avoidance may be difficult. If a child develops wheeze after exposure to specific animals, such exposure can usually be avoided. Avoiding house dust mite can be more problematic – measures to reduce dust mite exposure are costly, and there is also no evidence that reduced exposure improves asthma symptoms. Desensitisation programs for inhaled allergens have no role for the treatment of asthma in children. Children with difficult to control asthma may also have allergic rhinitis and treatment with intranasal corticosteroids may have additional benefits with regard to asthma control.

Evaluating the home environment

Active and passive tobacco smoking are strongly associated with difficult to control asthma.[22] In individuals with asthma, tobacco smoke accelerates the decline of lung function, increases asthma severity and lessens the response to inhaled and systemic corticosteroids. Therefore, it is important to identify members of the household and visitors who smoke within a child's home environment. GPs are well placed to promote smoking cessation within the family unit.

Family dysfunction and peer pressure can exacerbate therapy nonadherence issues in adolescents. Feelings of anxiety and asthma symptoms can be closely linked. These issues require careful assessment and the involvement of a clinical psychologist may be helpful.

Providing a written asthma management plan

Every child with asthma should be provided with a written asthma action plan that is easy to read, concise and individualised to the patient. It should reinforce advice given by the treating physician, provide a written reminder of maintenance therapy and give information about the management of acute episodes. The plan should be reviewed and updated regularly.

For children with difficult to control asthma, it is crucial to implement a strategy of regular assessments. This assists in developing an effective partnership

Checklist for managing difficult to control asthma in children

Step 1. Check the diagnosis of asthma is correct. Consider other possible diagnoses

Step 2. Review medications and dosages, and titrate accordingly

Step 3. Assess inhaler technique. If suboptimal, re-educate patient and family

Step 4. Assess medication adherence. If suboptimal, use positive reinforcement

Step 5. Clarify allergic status. Promote allergen avoidance if appropriate

Step 6. Evaluate home environment (tobacco smoke exposure) and psychosocial factors

Step 7. Prevent exacerbations. Manage them should they occur

Step 8. Refer patient to a specialist

among patients, their carers and the GP, and promotes long term control.

Referring patients

Referral to a paediatrician or respiratory paediatrician should be considered for children who have any of the following:

- uncertain diagnosis
- poor response to treatment
- significant school absence
- frequent hospitalisations or a life-threatening episode
- persistent lung function abnormalities
- requirement for high dose ICS to maintain control (i.e. 500 µg/day fluticasone or equivalent, with or without LABA)
- frequent courses of oral corticosteroids
- other complicating medical or psychosocial issues.

Conclusion

Difficult to control asthma in children is uncommon but carries a significant burden to the child and the family. Management involves a clear assessment of the diagnosis and systematic evaluation of medications, drug delivery technique, adherence to medications and atopic status. It also involves elimination of exposure to tobacco smoke and modification of the home and psychological factors as needed (see the box on page 25). ICS are the cornerstones of therapy and should be titrated to the correct dose maximising efficacy and minimising adverse effects. GPs have an important role in regularly reviewing patients and establishing a partnership of care with them and their family, thus promoting successful mana - gement of these children. Useful online asthma resources can be found on page 33 in the article 'Difficult to control asthma in adults' (originally published in *Medicine Today*, June 2007).[23] MT

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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.

JAMES BARTLETT
MB BS, DTM&H

JO DOUGLASS
MD, FRACP

Dr Bartlett is Allergy & Asthma Registrar, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, and Dr Douglass is Associate Professor, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital and Monash University, Melbourne, Vic.

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).[4] 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.[5] The current Australian recommendations for care are summarised in the box on page 29.

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 (reliever medication or oral corticosteroids) 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 of the patient 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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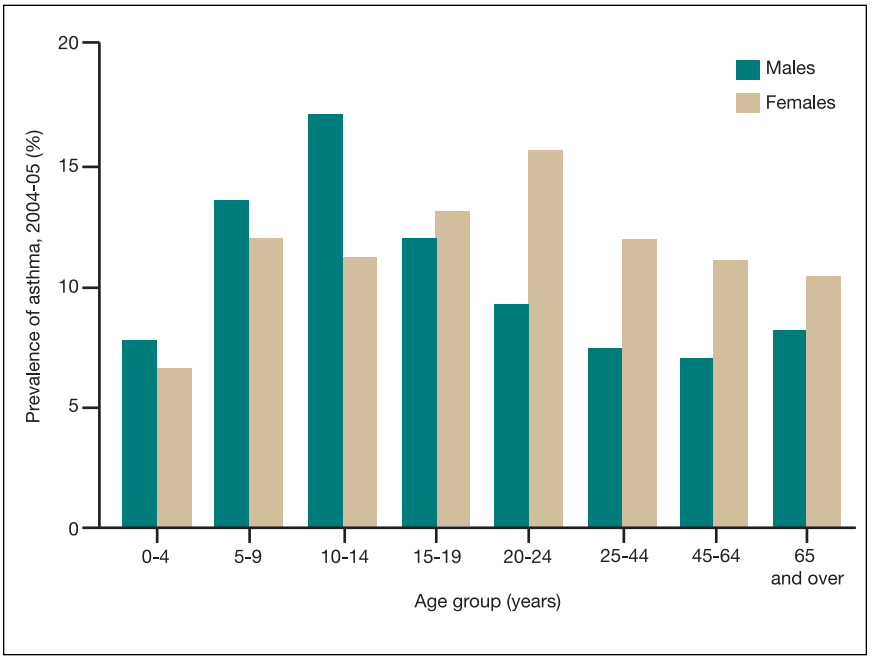

Figure 1. The prevalence of asthma between 2004 and 2005. Prevalence in adults is approximately 10%, with a significant proportion of adults over the age of 64 years old being affected. (Source of data: Australian Bureau of Statistics 2004–05 National Health Survey, cat. no. 4364.0. Figure reproduced 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 beta$_2$ agonist (LABA) or theophylline treatment, or that requires oral corticosteroids in the 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 noncorticosteroid therapy is desired.
- **Step 2. Moderate persistent asthma with persistent symptoms or poor lung function on inhaled corticosteroid alone**
  Add long-acting beta$_2$ 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$_2$ 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$_2$ 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 EpiPen 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 of the patient 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 pulmonary disease (COPD) indicates that the airway obstruction is not fully

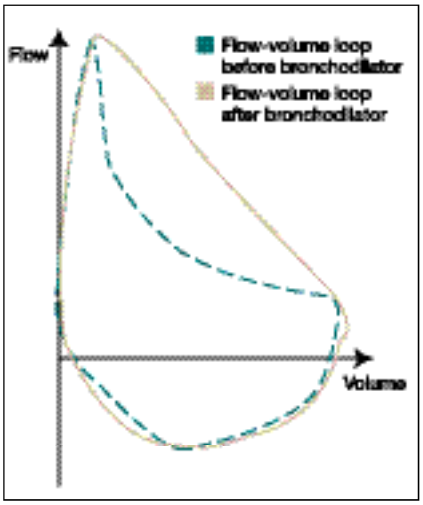

Figure 3. Typical flow–volume loops in asthma, where the forced vital capacity is within normal limits but the forced expiratory volume in 1 second (FEV_1) is reduced. Characteristic of the reduction in FEV_1 is the reduced airflow at low lung volumes giving a scalloped shape to the flow–volume curve before bronchodilator (dashed green 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 buff line), although often not as completely as in this example.

reversible. This 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 of the patient to a specialist for identification of a cause and ongoing management advice. Management involves referral to a physiotherapist to aid clearance of secretions and the exclusion of underlying systemic causes.

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 Accuhaler), 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]

The use of salmeterol without inhaled corticosteroids may be associated with increased asthma-related death or life-threatening experiences. Events were rare and not statistically significant. These data suggest that LABA should only be used with concurrent inhaled corticosteroid therapy.[20]

Single inhaler therapy

In moderate to severe, persistent asthma, the combination therapy budesonide/eformoterol (Symbicort Turbuhaler) can be used as both maintenance (budesonide 200 μg, eformoterol 6 μg [Symbicort 200/6], one or two puffs twice daily) and reliever medication (as needed) – Symbicort SMART. Studies suggest that such a regimen is clinically effective in moderate to severe asthma and may offer an advantage in reducing severe exacerbations without increasing the cumulative inhaled corticosteroid dose. The use of combined inhaled corticosteroid/LABA therapy as a single maintenance and reliever inhaler is only indicated with eformoterol/budesonide due to the rapid onset of action of eformoterol enabling its use as an effective reliever treatment. Salmeterol/fluticasone (Seretide) is not indicated for this treatment regimen.

The introduction of single inhaler therapy as both maintenance and reliever medication needs to accompanied by appropriate education regarding the necessity of maintaining regular maintenance treatment, and the provision of a written asthma action plan including the use of the Symbicort inhaler.

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 2 to 14 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, 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.[21,22]

The more selective biological immunosuppressive agents etanercept (Enbrel) and omalizumab (Xolair) 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[23,24] has led to etanercept, 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.

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 these 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.

Etanercept administered subcutaneously has been shown to reduce airway hyper-responsiveness 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 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.[25,26]

The cost of omalizumab is generally prohibitive but it may be cost effective for patients who have more than five asthma exacerbations or two admissions to hospital with asthma per year despite maximal conventional therapy.[27]

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.[28] 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. Varenicline (Champix) or bupropion (Clorprax, Prexaton, Zyban SR) are therapeutic alternatives available on the PBS.[29] Nicotine replacement therapy is also available through pharmacies. The recent increase in numbers of smoking cessation clinics, which specialise in the therapeutic use of pharmaceutical agents to improve smoking cessation rates together with appropriate counselling and support, can only be of benefit to patients with asthma who smoke.

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 coordination 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 types of inhaler devices are described in the box on this page.

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.[30]

Written asthma management plans

A written asthma management plan is essential for all people with asthma, regardless of the underlying severity. Written plans empower patients, are protective against asthma-induced death and improve the outcomes of self-management education.[31] 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 are usually 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 corticosteroids can improve symptom control and reduce exacerbation rates.

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

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/ClinicalInformation/Asthma/tabid/81/Default.aspx
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).

Gastro-oesophageal reflux disease

Up to 75% of people who have difficult to control asthma also have reflux detectable on oesophageal pH monitoring.[32] 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.[32]

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.[33]

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, although it lacks the precision of spirometry.

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 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.[34] 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.[35-37]

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, which appears unlikely to respond to corticosteroids.[38]

Conclusion

Difficult to control asthma presents a significant problem for the clinician. 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 page 33. MT

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Budesonide/eformoterol combination inhaler as maintenance and reliever treatment in asthma

MATTHEW PETERS MD, FRACP

There is now convincing evidence that the combination inhaler (budesonide/eformoterol) can be used as both maintenance and reliever therapy in patients with asthma, improving symptom control and lung function and reducing the risk of severe exacerbations.

Although asthma management has changed considerably since the 1960s, it has always included a maintenance treatment for long-term control (a preventer inhaler) and a separate reliever treatment (a bronchodilator inhaler) to treat short-term breakthrough symptoms.[1] The maintenance dose is adjusted based on the patient achieving the goals of treatment. For patients with moderate and severe asthma, data published over the past decade support the use of a combination inhaler with a corticosteroid and a long-acting beta$_2$ agonist as maintenance treatment with a short-acting beta$_2$ agonist to relieve symptoms.

The combination therapy budesonide/eformoterol (Symbicort Turbuhaler) can now be used as single inhaler maintenance and reliever treatment (Symbicort SMART) in patients with asthma.[2] This replaces the need for a short-acting beta$_2$ agonist reliever therapy,[3] as eformoterol has a quick onset of action giving it the properties of an acute bronchodilator. This allows the convenience of all treatment being delivered by one inhaler. The other available combination therapy fluticasone/salmeterol (Seretide) cannot be used in this way as salmeterol has a slow onset of bronchodilator effect.[4]

Substituting budesonide/eformoterol for a standard reliever should address breakthrough symptoms. In turn, the dose and timing of treatment that best produces control will be shaped to fit fluctuating levels of asthma severity without complex monitoring.[5]

In theory, an increase in budesonide/eformoterol treatment during the period before a severe exacerbation (as symptoms and reliever use are increasing) may prevent the severe exacerbation from occurring or reduce its severity. The use of budesonide/eformoterol in both maintenance and preventer roles is not so much a revolution in asthma management but rather the latest in a long line of maintenance and reliever combinations.

Simplicity in any novel asthma treatment approach is intrinsically valuable but to have real merit it must achieve good control (few or no symptoms), a minimal need for reliever use, maintenance of good lung function and the avoidance of episodes of poor control, involving emergency care, hospitalisation or the need for oral corticosteroids. There is now convincing evidence that the Symbicort SMART approach can achieve this with a reduced treatment burden.

Evidence of effectiveness

The efficacy and safety of budesonide/eformoterol as maintenance and reliever in patients with asthma has been evaluated in a series of large, randomised, fully blinded studies.[6-10] Compared with the use of a higher fixed dose of an inhaled corticosteroid (budesonide) with a short-acting beta$_2$ agonist as needed, patients using budesonide/eformoterol as maintenance and reliever had substantially improved symptom control and lung function and a reduced risk of severe exacerbations.[6-8]

When compared with higher fixed maintenance doses of budesonide/eformoterol or fluticasone/salmeterol and a short-acting bronchodilator as needed, budesonide/eformoterol as maintenance and reliever produced identical lung function and symptom improvement and also reduced the risk of severe exacerbations and decreased the number of days that oral corticosteroids were required.[9,10] The total dose of inhaled corticosteroids used by patients taking budesonide/eformoterol as maintenance and reliever was 25% lower than in those using conventional approaches,[11] which also makes this approach a cost-effective regimen.[9,10]

Patients using budesonide/eformoterol as reliever used about one dose per day on average[11] and the use of reliever declined with time as asthma control improved.

Dr Peters is a Senior Staff Specialist, Department of Thoracic Medicine at Concord Hospital, Sydney, NSW.

Days of high reliever use were infrequent.[9] During times of worsening asthma, the risk of a severe exacerbation developing during the four weeks after eight or more reliever doses are needed in one day is halved with this new approach.[11] This supports the existence of a 'window of opportunity' during which this approach is effective at reducing severe exacerbations.

There are some concerns that symptom-driven use of asthma therapy might endorse a lower standard of asthma control than that advocated as total control. The achievement of total control was not specifically measured in any study, but in both trials and clinical practice, some patients using budesonide/eformoterol as maintenance and reliever have a surprisingly rapid reduction in the use of reliever and remain well with minimal need for extra doses of budesonide/eformoterol. Overall, trends in lung function, reliever use and exacerbations clearly suggest that neither higher fixed dose maintenance treatment strategy is more likely than the Symbicort SMART strategy to achieve total control.

Implementation into clinical practice

The outcomes of the studies on using budesonide/eformoterol as maintenance and reliever represent such an improvement that practice should change.[11] For the expected benefits to be delivered there are a number of preconditions that need to be taken in account:

- asthma should be the correct diagnosis; in most circumstances, patients should have a diagnosis of asthma confirmed with lung function testing rather than just a suggestive symptom complex such as persistent cough
- patients whose major respiratory illness is smoking-related chronic obstructive pulmonary disease, even if they have acute reversibility more typical of asthma, should be otherwise managed according to guidelines
- asthma should be the cause of symptoms for which a patient might use reliever. This excludes those patients who use reliever frequently because of anxiety, vocal cord dysfunction or predictable exercise-related breathlessness associated with unfitness or obesity
- patients should be suitably educated on the use of budesonide/eformoterol.

These conditions should apply for any patient considered for any asthma treatment.

Who is most suitable?

PBS requirements for use of budesonide/eformoterol as maintenance and reliever therapy are that the patient must experience frequent asthma symptoms while receiving treatment with oral or inhaled corticosteroids or a combination of an inhaled corticosteroid and a long-acting $beta_2$ agonist. This should not be the initial treatment for asthma nor is it necessary in a patient with mild asthma. If asthma control is, or has been in the past, unsatisfactory on one of the above treatments, budesonide/eformoterol should generally be recommended as maintenance and reliever, unless a patient is deemed unsuitable for some of the reasons discussed below. Budesonide/eformoterol should not be commenced during an asthma exacerbation as a treatment of that event.

Although there are benefits of using budesonide/eformoterol as maintenance and reliever for all patients with asthma, these are greater in patients with severe asthma, those who use reliever frequently and/or those with a greater than average risk of exacerbations. Smoking impairs lung function and reduces treatment response to inhaled corticosteroids;[12] therefore, converting a patient with asthma who smokes to the symbicort SMART strategy without addressing smoking itself is poor practice. Patients who are poor perceivers of asthma symptoms or are reluctant to use their reliever in response to symptoms may not benefit from the Symbicort SMART approach. A higher maintenance dose strategy may be preferable for these patients.

Selecting a maintenance dose

In Australia, high doses of inhaled corticosteroids are used in the treatment of asthma and the Symbicort SMART strategy presents an opportunity to address this. Budesonide 200 µg/eformoterol 6 µg (Symbicort 200/6) twice daily and as needed should be considered the usual dose. A higher maintenance dose, budesonide/eformoterol 200/6 two puffs morning and night, should be reserved for patients with very severe asthma or if there is particular anxiety associated with a maintenance dose reduction. Budesonide 100 µg/eformoterol 6 µg (Symbicort 100/6) can be used for patients with less severe asthma. The maintenance dose should not be increased after a single exacerbation.

SMART studies have shown that spreading treatment throughout the day is superior to increasing morning and/or evening dosing.[9,10] Patients who are using Symbicort SMART as reliever once per day should not have the maintenance dose increased unless there are other concerns such as suboptimal lung function. The higher dose budesonide 400 µg/eformoterol 12 µg (Symbicort 400/12) preparation is not suitable for reliever treatment but could be used as the maintenance component if budesonide/eformoterol 200/6 is used on an as-needed basis as the reliever. This can be cost effective for the patient at the expense of losing the convenience of single-inhaler treatment.

Back titration of maintenance treatment in stable patients

Back titration of maintenance treatment may prove to be useful for patients using budesonide/eformoterol as maintenance and reliever. For example, a patient who is well controlled on budesonide/eformoterol 400/12 twice daily and is infrequently using terbutaline as needed, could be commenced on budesonide/eformoterol 200/6 twice daily and as needed. During

such down titration, clinicians may have concerns of an emergence of symptoms and the conversion of a stable patient into one who is at an increased risk of exacerbation. Budesonide/eformoterol as needed will address symptoms and a patient destined for an exacerbation will have that risk at least halved if the reliever used is budesonide/eformoterol rather than a short-acting bronchodilator.[8,11]

For patients established on budesonide/eformoterol as maintenance and reliever, a reduction in the maintenance component should be considered when symptoms and lung function are well controlled and reliever use is infrequent. For a patient stable on budesonide/eformoterol 200/6 twice daily and as needed, a preferable reduction in maintenance dose would be budesonide/eformoterol 100/6 twice daily rather than 200/6 in a once daily dose. The latter is associated with an increase in daily symptoms and use of reliever but not an increase in the risk of exacerbation.[13]

Exercise-induced asthma

Exercise-induced wheeze or breathlessness can persist after other aspects of asthma have resolved. Budesonide/eformoterol is as effective as other beta-adrenergic agonists in preventing exercise-induced asthma. Assuming that all other aspects of asthma management are addressed, the use of budesonide/eformoterol prior to exercise is reasonable and the extra reliever doses of budesonide/eformoterol rather than salbutamol or other short-acting bronchodilators may contribute to improved asthma control. In one clinical study that permitted use of budesonide/eformoterol to prevent symptoms, about half of the doses were used for this reason.[13]

Use of a pre-exercise bronchodilator more than once daily is a reasonable threshold for concern. When lung function is optimal, symptoms are infrequent at other times and clinical judgment is that the use of a bronchodilator prior to exercise is largely habitual, it may be preferable for the patient to use salbutamol before exercise while retaining budesonide/eformoterol as the reliever in other settings. Advice on this important clinical area will be uncertain until specific research is conducted.

Paediatric asthma

Using budesonide/eformoterol as maintenance and reliever is approved in Australia for children aged 12 years and over. There are some data indicating effectiveness in children 4 to 11 years[8,13] and the use of budesonide/eformoterol in children of these ages is permitted in New Zealand. If the approach is to be used off-label, the budesonide/eformoterol 100/6 strength should be used, and there is reason to restrict usage to specialty clinics. In an asthma emergency, for example in a school setting, decisions may need to be made by individuals with limited knowledge of asthma who are guided only by the child's asthma care plan. This plan must therefore clearly permit the use of salbutamol if budesonide/eformoterol is unavailable.

Patient education and asthma action plans

If the Symbicort SMART approach is implemented in the appropriate patients, they will already have previous experience with the use of a maintenance inhaler and a reliever inhaler for asthma; the only change is that one inhaler will be serving both functions. Stressing the simplicity of this change is fundamental. Patients should react intuitively with the use of budesonide/eformoterol as reliever therapy the same as they did before with salbutamol or other short-acting bronchodilators. Reliever use should not be rationed as symptoms increase nor should clinicians attempt to guide patients towards a specific pattern of use. Advice for patients using budesonide/eformoterol as maintenance and reliever therapy is listed in the box on page 40.

When lung function is abnormal during the time of treatment change to the Symbicort SMART approach, using the opportunity and time to demonstrate an acute bronchodilator response to budesonide/eformoterol can be useful and may address any fears that the new inhaler will not work as well as the 'old' one.

Asthma action plans are effective but have their problems, one of which is that they are not being used.[14] The action points listed are also unclear. The changes in symptoms and lung function that are seen several days before a typical exacerbation are also seen at other times, resolving in most cases without intervention.[15] The most commonly prescribed intervention, doubling the inhaled corticosteroid dose, has been proven ineffective at reducing the risk of an exacerbation.[16] Quadrupling the dose of an inhaled corticosteroid[17] or combination treatment[18] may be effective but requires onerous monitoring to determine the action point for this intervention. None of the current plans are compatible with Symbicort SMART because they require detection of an event followed by a prescribed action – usually a change in maintenance treatment or dose.

With the Symbicort SMART approach patients simply use their budesonide/eformoterol maintenance treatment, with the action determined by the frequency of use of as-needed doses. This approach reduces the frequency of severe exacerbations but does not prevent them all, nor does it treat an exacerbation of a severity warranting oral corticosteroid treatment. Two Asthma Action Plans specifically for Symbicort SMART have been endorsed by the National Asthma Council.[19] They describe a state of usual asthma control and treatment, a state of some decline in control in which ongoing treatment with vigilance is required, and an emergency situation with necessary responses. One plan is based on symptoms alone and the other uses peak flow measurements during periods of increased symptoms to

Advice for patients using budesonide/eformoterol as maintenance and reliever treatment

- It is important to stress the simplicity of the change from conventional therapy to the budesonide/eformoterol as maintenance and reliever regimen.
- Patients should take their regular maintenance treatment every day, even if they have no symptoms.
- Patients should react intuitively with the use of budesonide/eformoterol as reliever therapy when needed.
- Patients should not use more than six inhalations on a single occasion and no more than 12 inhalations per day. If more than 12 inhalations are needed per day, patients must see their doctor.
- When the red mark appears on the inhaler it needs to be replaced. An alternative reliever, salbutamol or terbutaline, should only be used if the patient's usual inhaler is unavailable.
- Patients should keep track of how often they use the inhaler for relief of symptoms and consult their asthma action plan when more inhalations are needed than usual.

guide self management. Either written plan can be administered in three minutes and its creation provides an opportunity to reiterate to the patient the key principles of treatment and the key actions needed to maximise benefit.

Summary

For patients with significant asthma, the use of budesonide/eformoterol as both maintenance and reliever treatment is similarly effective to other management strategies in the achievement of good asthma control, while also reducing episodes of poor control and lessening overall treatment burden. The evidence suggests that the management of asthma should change unless there is an identifiable contraindication.[11] Education, emphasising the simplicity of this change in treatment, is critical to delivering the benefits. An opportunity is presented to widen the use of written asthma action plans. MT

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DECLARATION OF INTEREST: Dr Peters has served on the Advisory Board for AstraZeneca and received honoraria for lectures and presentations.