

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.

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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 18). 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.

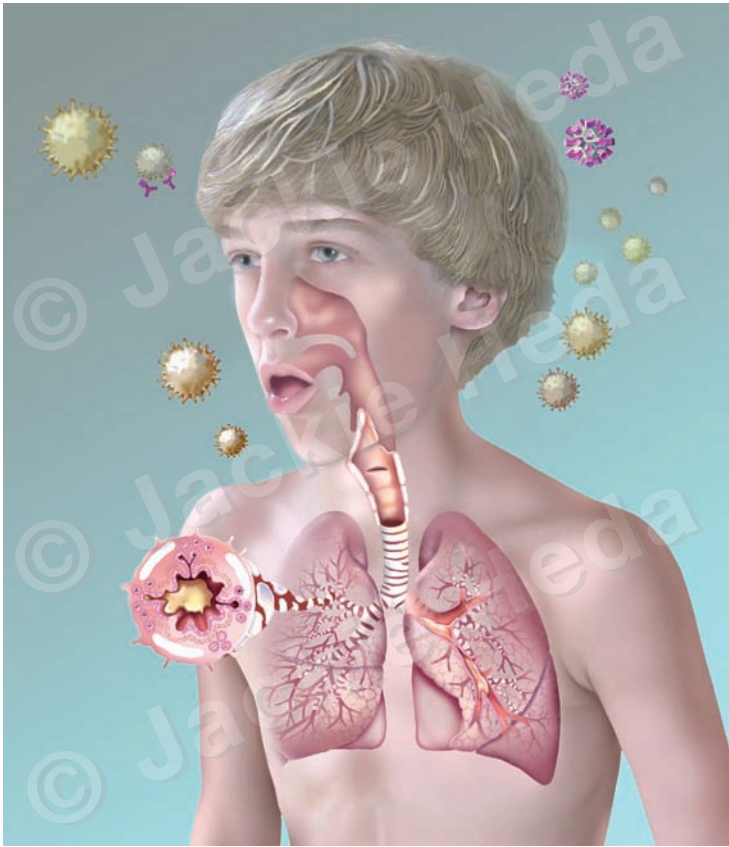
Shortness of breath

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 dyspnoea 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

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The illustration shows a child's head and torso with a semi-transparent view of the respiratory system, including the trachea, bronchi, and lungs. Various allergens, represented by colorful, spiky particles, are shown floating around the child's head and entering the respiratory tract. A large, detailed view of a bronchus is shown in the foreground, illustrating the narrowing of the airway due to inflammation and constriction of the smooth muscle, which is characteristic of asthma.

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.

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allergies and a personal or family history of atopy (e.g. eczema or hayfever).

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 diagnosis 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 19.

Children who demonstrate features of airway obstruction should trial a bron-

chodilator 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 7 to 8 years of age. In older children, peak flow meter recordings provide only an approximate guide to asthma severity and are open to manipulation;

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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

Spirometry: flow-volume loops

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 agonist)

Patients with inadequately controlled asthma and taking 200 µg/day fluticasone (or its equivalent) should have a long acting beta agonist (LABA), such as salmeterol (Serevent) or eformoterol (Foradile, Oxis Turbuhaler), added to their regimen. LABAs should not be used as monotherapy. The PBS requires that LABAs are added as a separate inhaler initially. The patient should be reviewed to assess the success of LABA addition before combination inhalers are used.

A combination inhaler containing eformoterol and budesonide (Symbicort Turbuhaler) may be used for both maintenance and rescue therapy in adolescents. This approach has been shown to reduce exacerbations and improve asthma control.¹³⁻¹⁵ These findings have not been demonstrated with the use of fluticasone and salmeterol (Seretide) combination inhalers because of the slower onset of action of salmeterol (20 minutes) compared with eformoterol (one to three minutes). There are limited studies assessing the efficacy of combination treatment in children under the

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 (yellow line above x axis) represents airway obstruction. Comparison of the flow-volume loops before and after bronchodilator (yellow 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).

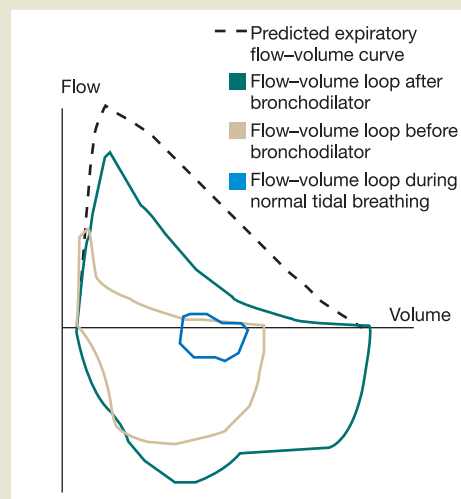


Figure. Flow-volume loops in a patient with asthma.

age of 5 years and this group of children should be referred for specialist paediatric advice.

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 (Cicloal, 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

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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, 6 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. Sensitisation to inhaled allergens and food can be tested by skin prick tests or radio-allergoabsorbent 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.

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

Drug delivery systems	Age of child			
	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

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

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

ological factors as needed (see the box on this page). 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 management of these children. Useful online asthma resources can be found in the article 'Difficult to control asthma in adults' published in *Medicine Today*, June 2007.²³ **MT**

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

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 long acting beta agonist)
- 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 psy-

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

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