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Management of acute asthma

Acute severe asthma is a major economic and health burden. In 2002, there were over 1400 deaths from asthma in the UK.¹ It is estimated that, on average, one person dies from asthma every 7 hours. However, approximately 75% of admissions to hospital are avoidable and as many as 90% of the deaths from asthma are preventable.² In many countries, asthma mortality increased from the 1960s to the second half of the 1980s, reached a plateau and has subsequently declined.³ This recent downwards trend may reflect increased awareness of the signs and symptoms of acute asthma by patients and healthcare professionals and better management in primary care.

All patients with asthma are at risk of exacerbations, described by terms like 'acute asthma', 'asthma attack' and 'status asthmaticus'. The severity of exacerbations ranges from mild to life threatening. Deterioration usually progresses over hours, days or weeks; however, a few patients have sudden (over minutes) unexpected increases in airway obstruction. Approximately 90% of asthma exacerbations severe enough to warrant hospital admission develop over a period of 6 hours or more.² In one study, over 80% developed over more than 48 hours.² This observation suggests that in many patients there is a window of opportunity for recognition and reversal of this period of deterioration. Although sudden death is infrequent, it is useful practice to assume that every exacerbation is potentially fatal. Morbidity and mortality are most often associated with failure to appreciate the severity of an exacerbation, resulting in inadequate emergency treatment and delay in referring to hospital. Many patients coming to hospital with an acute severe exacerbation of asthma have received little or no treatment and others have only been given extra doses of beta-2 agonists in addition to their usual medication. Most studies of the factors relating to death from asthma have found inadequate treatment to be an important factor and in most patients who die from asthma there is a background of chronic under-treatment for various reasons; inadequate management of the final episode is due about

equally to delay on the part of the patient in seeking help and inadequate treatment from the physician.

Deaths from asthma have been attributed to inappropriate prescribing of medications such as beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), sedatives and even beta-2 agonists. Non-selective beta-blockers can cause bronchospasm and exacerbate asthma in susceptible individuals. Even non-selective beta-blocker ophthalmic solutions can be absorbed systemically and cause bronchospasm. If a patient with asthma requires a beta-blocker, a cardioselective beta-blocker should be chosen (e.g. atenolol, bisoprolol, metoprolol, nebivolol). These beta-blockers have less effect on bronchial beta-2 adrenoceptors and are therefore relatively *cardioselective*; they are, however, not *cardiospecific*. Adults with asthma should be questioned about episodes of bronchospasm associated with ingestion of aspirin or other NSAIDs. If a reaction has occurred, the patient should be warned about the dangers of a fatal exacerbation with use of these drugs. Patients with severe asthma or nasal polyps should also receive counselling about the potential of NSAIDs to cause a fatal exacerbation.^{6,7} Evidence in the medical literature suggests that patients with asthma who take antipsychotics or sedatives are at increased risk of serious complications of their asthma. A number of mechanisms are potentially responsible for this association. Non-causal factors include patient characteristics (e.g. indication for antipsychotic use, non-concordance with asthma therapy, risk-taking behaviour and family dysfunction) and treatment issues (including differential prescribing and the quality of medical care). The main causal mechanism involves depression of the central nervous system and impaired respiratory drive resulting from sedation during an acute asthma attack. Certainly, the use of sedatives in non-intubated patients with asthma is associated with increased mortality and the need for mechanical ventilation.

It has been suggested that cardiac arrhythmias may contribute to some of the observed mortality from asthma. The risk is theoretically increased by hypokalaemia and the prolongation of the QT interval secondary to the administration of beta-2 agonists in high doses.⁶ However, this could be explained by the fact that more severe asthma requires more treatment and is associated with a higher death rate despite treatment, not because of it. Most deaths are not drug induced but are related to the pathology of the disease: patients with fatal asthma almost invariably have extensive airflow limitation and hypoxaemia.

The Risk Factors Focus on page 59 highlights the behavioural and psychosocial factors that have been linked to deaths or near-deaths in



RISK FACTORS FOCUS

Risk factors for near-fatal or fatal asthma²⁻⁵

- Previous near-fatal asthma (e.g. previous ventilation or respiratory acidosis)
- Previous hospital admission for asthma
- Repeated attendances at emergency department for asthma care
- Failure to attend appointments
- Self-discharge from hospital
- Requirement for three or more classes of asthma medication
- Excessive use of inhalers with decreasing response
- Heavy use of beta-2 agonists
- Poor concordance with treatments or monitoring
- Lack of asthma action (self-management) plan
- Refractory (brittle) asthma
- Anxiety and depression, other psychiatric illness or deliberate self-harm
- Obesity
- Learning difficulties
- Social isolation
- Illicit drug use or alcohol abuse
- Disease denial
- Severe domestic, marital or legal stress
- Unemployment
- Shortness of breath that may have developed over hours or days
- Upper respiratory tract infection or exposure to an irritant atmosphere
- Personal or passive smoking

patients with asthma.²⁻⁵ All health professionals must be aware that patients with severe asthma and one or more adverse psychosocial factors are at risk of death.

Mortality and morbidity from asthma exacerbations can be reduced by educating the patient about their condition and treatments, encouraging self-management (see Chapter 8) and improving the organisation of patient care in both primary and secondary care² (see Management Focus, page 60).

Pathology of acute asthma

The pathology of the airways in patients who have died during a severe asthma exacerbation has been described extensively. The pathology suggests two main types of acute asthma exacerbations. The most frequent, at least in asthma deaths, is caused by severe inflammation.



MANAGEMENT FOCUS

Recommended interventions to reduce asthma morbidity and mortality

Many patients with asthma and all patients with severe asthma

- Correct interpretation of warning symptoms at home
- Understanding of an agreed action plan
- Correct treatment at home
- Recognition when medical review or hospital treatment is needed

Primary care physician

- Correct evaluation
- Correct treatment
- Recognition of when referral to hospital is required (any patient with features of acute severe or life-threatening asthma; other factors, such as failure to respond to treatment, social circumstances or concomitant disease may warrant hospital referral)
- Register of patients at high risk of a fatal or a near-fatal attack
- Follow-up of high-risk patients if they do not attend for appointments at asthma clinic
- Avoid prescribing beta-blockers (including eye drops) and non-steroidal anti-inflammatory drugs for patients with asthma

Hospital

- Correct evaluation
- Correct criteria for admission to hospital³
 - Any patient with any feature of a life-threatening or near-fatal attack
 - Any patient with any feature of a severe attack persisting after initial treatment
 - Any patient whose PEF is greater than 75% best or predicted 1 hour after initial treatment but who still has significant symptoms, are non-concordant with medicines, live alone, have psychological problems, physical disability or learning difficulties, previous near-fatal or refractory asthma, present at night or are pregnant should be considered for admission to hospital.
- Patients should be managed in specialist rather than general units. Patients attending hospital with an acute exacerbation of asthma should be reviewed by clinicians with particular expertise in asthma management, preferably within 30 days.
- Correct treatment
- Recognition when transfer to intensive therapy unit is required
- Correct timing of discharge from hospital
- Correct follow-up and modification of treatment: a respiratory specialist should follow up patients admitted with severe asthma for at least 1 year after the admission; patients who have had near-fatal asthma or brittle asthma should remain under specialist supervision indefinitely

Airflow obstruction in these patients is due as much to mucus plugging as to airway smooth muscle spasm. The lungs of such patients are grossly overinflated, mainly because of the presence of plugs obstructing the small and medium airways. These plugs are composed of inflammatory cells, such as eosinophils and neutrophils, together with mucus and exuded plasma. Basophils are also found in increased numbers in fatal disease. The airway smooth muscle is hypertrophied and in a contracted state. The airway wall is grossly thickened, with vasodilated bronchial vessels, oedema and a gross infiltration of inflammatory cells, consisting of eosinophils, neutrophils and lymphocytes. The area of the airway wall in fatal cases has been reported to be increased by 10–100% over that seen in non-fatal disease and by 50–300% over that seen in non-asthmatic control subjects.^{8,9} Thus, patients who have died with acute severe asthma have usually died of asphyxia. The pathology of acute asthma is illustrated in Figure 4.1.

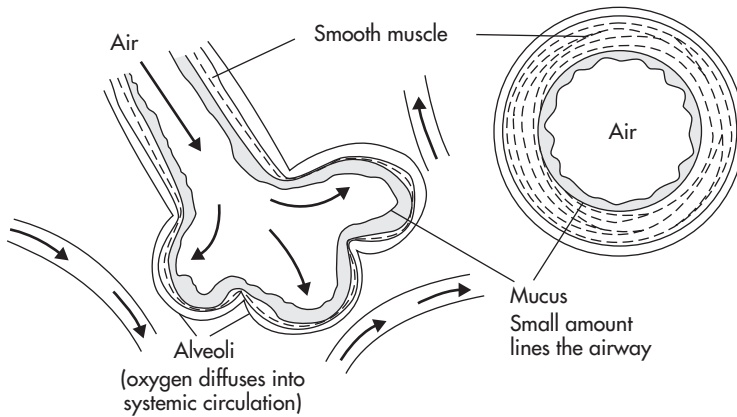
The second main type of acute asthma exacerbation occurs in more patients prone to anaphylaxis. There is relatively little inflammation and most of the obstruction appears to result from airway smooth muscle spasm.

Causes of exacerbations

The cause of an exacerbation of asthma cannot be determined with any degree of certainty in many cases but exacerbations result from a number of factors (see Risk Factors Focus, page 63).

In many cases there is evidence of an upper respiratory tract infection, usually viral, before the exacerbation. Viruses induce an inflammatory response in the airways of patients with asthma. Exposure to allergens can also cause exacerbations in allergic asthmatics. Offending allergens, such as pollens or fungal spores occurring alone or in combination, have been linked to clusters of asthma exacerbations occurring at the time of thunderstorms in the UK.^{10–14} Increased asthma morbidity during thunderstorms has been reported sporadically over the past two decades. On July 6th and 7th, 1983, the number of patients with asthma presenting to the emergency departments of eight Birmingham hospitals averaged 50 over the 2-day period, compared with a usual average of 10.¹² The increase in patient visits was associated with an increase in airborne fungal spores, particularly *Sporobolomyces* and *Didymella* species, and a decrease in pollen. Airborne pollutants represented by smoke and sulphur dioxide were not believed to be unusually elevated. The authors of the report

Cross section of normal lung



Cross section of the lung during an asthma exacerbation

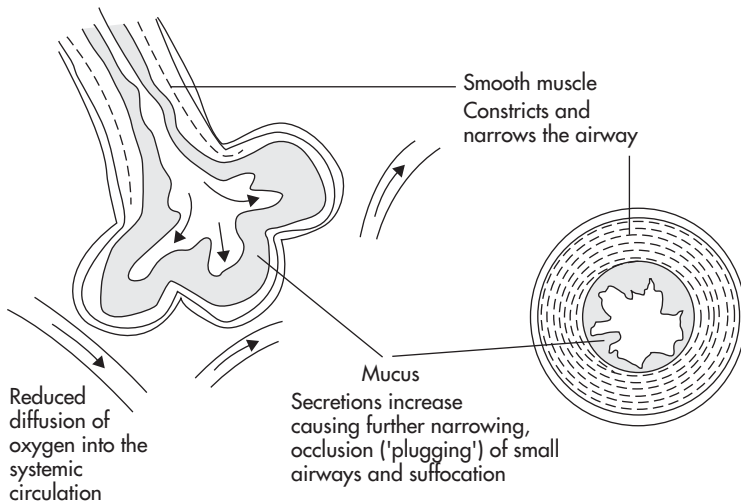


Figure 4.1 Cross-section of a normal healthy lung (top) and the pathological changes that occur in the lung during an acute asthma exacerbation (bottom).

suggested that asthma may have been caused by an increased release of fungal spores during the initial rainfall. During a thunderstorm 11 years later (June 24th and 25, 1994), the number of patients presenting with asthma or other airways diseases to emergency departments in the London area increased 10-fold. 'Out-of-hours' calls to primary care also increased during this time in south and east England.¹³ This thunderstorm was described as unusually large and



RISK FACTORS FOCUS

Causes of acute exacerbations of asthma

- Inhaled allergens
 - Patients often have a history of atopy
 - The severity of asthma has been correlated with the number of positive skin-prick test results
- Viral infection
- Air pollutants (e.g. dust, cigarette smoke, industrial pollutants)
- Medications, such as beta-blockers, aspirin and non-steroidal anti-inflammatory drugs
- Gastro-oesophageal reflux disease
 - Studies indicate that reflux of gastric contents with or without aspiration can trigger asthma in susceptible children and adults
 - Animal studies have shown that the instillation of even minute amounts of acid into the distal oesophagus can result in marked increases in intrathoracic pressure and airway resistance. This response is thought to be due to vagal and sympathetic neural responses.
- Cold temperature
- Exercise

multicentred, and was associated with reduced temperatures and severe wind gusting.^{14,15}

Clinical presentation

Asthmatic patients often have isolated symptoms of asthma that are transient and subside quickly or are easily treated with one or two puffs of their short-acting beta-2 agonist inhaler. However, some patients have recurrent symptoms of asthma that are only partially treated by their reliever medication. Such episodes of poor control are often the prelude to an acute exacerbation of asthma. Acute severe asthma may progress over a period of days, hours or even minutes and can be life-threatening.

Clinically, an exacerbation is characterised by shortness of breath of varying degrees of severity, tachypnoea, chest tightness, wheezing, coughing and inability to speak in full sentences, although no sign or symptom is uniformly present. Dyspnoea is absent in 17–18% of cases¹⁶ and wheezing is absent in 5%.¹⁶ The absence of signs and symptoms does not exclude a severe attack, and wheezing is a poor indicator of functional impairment – it often increases as the obstruction resolves, allowing the flow of air through the airway. A more important

indication of the severity of the asthma exacerbation is the absence of wheezing and/or the nature of the sounds. A silent chest represents a serious attack (see Diagnostic Focus, page 65).

In addition, the distribution of ventilation and perfusion and altered blood gases is abnormal in patients with severe asthma exacerbations. Patients with marked obstruction and significant lung hyperinflation can have electrocardiographic evidence of pulmonary hypertension, right ventricular pressure, reduced cardiac output, hypotension and poor peripheral perfusion. Typical blood gas abnormalities seen in acute asthma consist of a combination of hypoxaemia, hypocapnia and respiratory alkalosis. Measurement of oxygen saturation (SpO_2) with a pulse oximeter is necessary in acute severe asthma to determine the adequacy of oxygen therapy and the need for arterial blood gas (ABG) measurement (patients with $SpO_2 < 92\%$, or other features of life-threatening asthma require ABG measurement). Generally, the more severe the obstruction, the lower the SpO_2 and arterial oxygen tension (PaO_2). During an acute attack, patients generally hyperventilate, causing a reduction in the arterial carbon dioxide tension ($PaCO_2$). As the patient becomes tired and their breathing slows, the $PaCO_2$ starts to normalise, which should be viewed as a sign of impending respiratory failure and treated as such. The majority of patients have respiratory alkalosis although metabolic acidosis may be seen with extreme airflow limitation.

Differential diagnosis

A number of conditions may mimic or complicate the diagnosis of acute asthma. The absence of a history of asthma, particularly in an adult, should be treated with care and an alternative diagnosis considered.

- Congestive heart failure may present with acute shortness of breath accompanied by wheezing.
- The most common and difficult diagnosis is the differentiation of asthma from chronic obstructive pulmonary disease (see Diagnostic Focus p. 28 Chapter 2).
- Laryngeal, tracheal or bronchial obstruction may produce shortness of breath and localised wheezing that often mimics asthma.
- Recurrent small pulmonary emboli may manifest as attacks of shortness of breath and, very rarely, wheezing heard on careful auscultation.
- Recurrent attacks of shortness of breath at rest may be due to the hyperventilation syndrome.


DIAGNOSTIC FOCUS
Severity of acute asthma exacerbations and associated signs and symptoms in adults and children

Nature of asthma	Adults and children over 12 years of age	Children 2–12 years of age
Moderate	Increasing symptoms PEF >50–70% best or predicted No features of acute severe asthma	Increasing symptoms PEF >50–70% best or predicted (attempt to measure PEF in all children over 6 years of age) No features of acute severe asthma
Acute severe	Any one of: <ul style="list-style-type: none"> ● PEF 33–50% ● Respiratory rate ≥ 25 breaths/minute ● Heart rate ≥ 110 beats/minute ● Inability to complete sentences in one breath 	Any one of: <ul style="list-style-type: none"> ● PEF 33–50% ● Respiratory rate: children >5 years of age – >30 breaths/minute; 2–5 years of age – >50 breaths/minute ● Heart rate: children >5 years of age – >120 beats/minute; 2–5 years of age >130 beats/minute ● Inability to complete sentences in one breath or too breathless to talk or feed
Life-threatening	Any one of the following in a patient with severe asthma: <ul style="list-style-type: none"> ● PEF <33% best or predicted ● SpO₂ <92% ● PaO₂ <8 kPa ● Normal PaCO₂ (4.6–6.0 kPa) ● Silent chest ● Cyanosis ● Poor respiratory effort ● Bradycardia ● Dysrhythmia ● Hypotension ● Exhaustion ● Confusion ● Coma 	Any one of the following in a patient with severe asthma: <ul style="list-style-type: none"> ● Silent chest ● Cyanosis ● Poor respiratory effort ● Hypotension ● Exhaustion ● Confusion ● Coma

continued overleaf

<i>Diagnostic Focus continued</i>		
Nature of asthma	Adults and children over 12 years of age	Children 2–12 years of age
Near-fatal	Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures	Fall in heart rate in life-threatening asthma
Refractory (brittle)	<p>Type 1 Wide PEF variability (>40% diurnal variation for >50% of the time over a period of >150 days) despite intense therapy</p> <p>Type 2 Sudden severe attacks on a background of apparently well controlled asthma</p>	
<p>$PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; PEF, peak expiratory flow; SpO_2, oxygen saturation.</p>		

Treatment of acute asthma in adults

The hospital management of acute asthma in adults according to the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma management guideline is illustrated in Figure 4.2.

Aims of treatment

The severity of an asthma exacerbation determines the treatment. The goals of treatment can be summarised as: maintenance of adequate arterial oxygen saturation with supplemental oxygen, relief of airflow obstruction with repetitive administration of rapid-acting inhaled bronchodilators (beta-2 agonists and anticholinergics), reduction of airway inflammation and prevention of future relapses with early administration of systemic corticosteroids.

Oxygen

Hypoxaemia is the most common cause of death in asthma exacerbations. High concentrations of oxygen (usually 40–60%) should be given to correct hypoxaemia. There is little risk of inducing hypercapnia with high-flow oxygen in acute asthma, unlike in patients with chronic

Management of acute severe asthma in adults in hospital

Features of acute severe asthma

- Peak expiratory flow (PEF) 33-50% of best (use % predicted if recent best unknown)
- Can't complete sentences in one breath
- Respirations ≥ 25 breaths/min
- Pulse ≥ 110 beats/min

Life threatening features

- PEF < 33% of best or predicted
- SpO₂ < 92%
- Silent chest, cyanosis, or feeble respiratory effort
- Bradycardia, dysrhythmia, or hypotension
- Exhaustion, confusion, or coma

If a patient has any life threatening features, measure arterial blood gases. No other investigations are needed for immediate management.

Blood gas markers of a life threatening attack:

- Normal (4.6-6 kpa, 35-45 mmHg) PaCO₂
- Severe hypoxia: PaO₂ < 8 kpa (60 mm Hg) Irrespective of treatment with oxygen
- A low pH (or high H⁺)

Caution: Patients with severe or life threatening attacks may not be distressed and may not have all these abnormalities. The presence of any should alert the doctor.

Near fatal asthma

- Raised PaCO₂
- Requiring IPPV with raised inflation pressures

IMMEDIATE TREATMENT

- Oxygen 40-60% (CO₂ retention is not usually aggravated by oxygen therapy in asthma)
- Salbutamol 5 mg or terbutaline 10 mg via an oxygen driven nebuliser
- Ipratropium bromide 0.5 mg via an oxygen driven nebuliser
- Prednisolone tablets 40-50 mg or IV hydrocortisone 100 mg or both if very ill
- No sedatives of any kind
- Chest radiograph only if pneumothorax or consolidation are suspected or patient requires IPPV

IF LIFE THREATENING FEATURES ARE PRESENT:

- Discuss with senior clinician and ICU team
- Add IV magnesium sulphate 1.2-2 g infusion over 20 minutes (unless already given)
- Give nebulised β_2 agonist more frequently e.g. salbutamol 5 mg up to every 15-30 minutes or 10 mg continuously hourly

SUBSEQUENT MANAGEMENT

IF PATIENT IS IMPROVING continue:

- 40-60% oxygen
- Prednisolone 40-50 mg daily or IV hydrocortisone 100 mg 6 hourly
- Nebulised β_2 agonist and ipratropium 4-6 hourly

IF PATIENT NOT IMPROVING AFTER 15-30 MINUTES:

- Continue oxygen and steroids
- Give nebulised β_2 agonist more frequently e.g. salbutamol 5 mg up to every 15-30 minutes or 10 mg continuously hourly
- Continue ipratropium 0.5 mg 4-6 hourly until patient is improving

IF PATIENT IS STILL NOT IMPROVING

- Discuss patient with senior clinician and ICU team
- IV magnesium sulphate 1.2-2 g over 20 minutes (unless already given)
- Senior clinician may consider use of IV β_2 agonist or IV aminophylline or progression to IPPV

MONITORING

- Repeat measurement of PEF 15-30 minutes after starting treatment
- Oximetry: maintain SpO₂ > 92%
- Repeat blood gas measurements within 2 hours of starting treatment if:
 - initial PaO₂ < 8 kPa (60 mm Hg) unless subsequent SpO₂ > 92%
 - PaCO₂ normal or raised
 - Patient deteriorates
- Chart PEF before and after giving β_2 agonists and at least 4 times daily throughout hospital stay

Transfer to ICU accompanied by a doctor prepared to intubate if:

- Deteriorating PEF, worsening or persisting hypoxia, or hypercapnea
- Exhaustion, feeble respirations, confusion or drowsiness
- Coma or respiratory arrest

DISCHARGE

When discharged from hospital patients should have:

- Been on discharge medication for 24 hours and have had inhaler technique checked and recorded
- PEF > 75% of best or predicted and PEF diurnal variability < 25% unless discharge is agreed with respiratory physician
- Treatment with oral and inhaled steroids in addition to bronchodilators
- Own PEF meter and written asthma action plan
- GP follow up arranged within 2 working days
- Follow up appointment in respiratory clinic within 4 weeks

Patients with severe asthma (indicated by need for admission) and adverse behavioural or psychosocial features are at risk of further severe or fatal attacks

- Determine reason(s) for exacerbation and admission
- Send details of admission, discharge and potential best PEF to GP.

Peak expiratory flow in normal adults

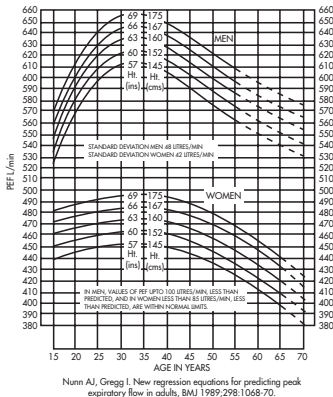


Figure 4.2 Hospital management of acute severe asthma in adults, from the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma management guideline.² (Reproduced with permission from the BMJ Publishing Group.)

obstructive pulmonary disease. Even the nebuliser should be driven using oxygen if possible. Hypercapnia indicates the development of near-fatal asthma and the need for emergency intervention. The goal of treatment should be to maintain SpO₂ at 92% or higher.

Beta-2 agonist bronchodilators

Beta-2 agonists should be given in high doses and as early as possible to relieve bronchospasm. There is no evidence for any differences in efficacy between salbutamol and terbutaline.³ Table 4.1 summarises the prescribing information for adults, children and infants with acute asthma exacerbations.

With regard to use of beta-2 agonists, there are four areas of debate.

1. *Metered-dose inhaler (MDI) with spacer versus nebulised administration.* An MDI and large-volume spacer provide an effective alternative to a nebuliser in mild-to-moderate acute asthma. In acute asthma with life-threatening features, the nebulised route driven by oxygen is the preferred method of administration.
2. *Parenteral versus inhaled therapy.* The inhaled route provides a faster onset of action, fewer adverse effects and is more effective than parenteral routes of administration in the majority of cases (subcutaneous route excluded from meta-analysis).¹⁷ Parenteral beta-2 agonists in addition to inhaled beta-2 agonists may have a role in ventilated patients and patients in extremis in whom nebulised therapy may fail (e.g. patient is coughing excessively), but the evidence base for this is limited.
3. *Doses and intervals of administration.* The BTS/SIGN asthma management guideline recommends the use of high and repeated doses (e.g. salbutamol, 5 mg, in adults), inducing maximal stimulation of beta-2 adrenoceptors with minimal side-effects. However, there is a body of evidence to suggest that administering low doses of beta-2 agonist after the initial high dose is as effective. A study in adults comparing nebulised salbutamol, 5 mg administered every 4 hours, versus salbutamol, 2.5–5 mg, on demand, found that on-demand dosing was associated with reductions in the amount of drug delivered, incidence of adverse effects and possibly length of hospital stay (hospital stay 3.7 days with on-demand dosing versus 4.7 days with regular salbutamol).¹⁸ Another study concluded that there is no advantage to the routine administration of doses of salbutamol higher than 2.5 mg every 20 minutes.¹⁹ This study did not enrol sufficient numbers of patients with severe asthma, so it is

Table 4.1 Prescribing of beta-2 agonists in adults, children and infants with acute asthma exacerbations

	Adults and children over 12 years of age	Children aged 2–12 years	Infants (under 2 years of age)
First-line treatment	Yes	Yes	Consider a trial
Method of administration	<i>Mild/moderate:</i> MDI plus spacer device <i>Severe:</i> as above or via nebuliser <i>Life-threatening:</i> nebuliser driven by oxygen.	<i>Mild/moderate:</i> MDI plus spacer device (children under 3 years are likely to require a facemask connected to the mouthpiece of a spacer) <i>Severe:</i> as above or via nebuliser <i>Life-threatening:</i> Nebuliser driven by oxygen	<i>Mild/moderate:</i> MDI plus spacer and close fitting facemask – as effective if not better than nebulisers for treating mild-to-moderate asthma <i>Severe:</i> via nebuliser <i>Life-threatening:</i> nebuliser driven by oxygen
Dosage	<i>Mild/moderate:</i> salbutamol, 200 micrograms, or terbutaline, 500 micrograms PRN <i>Severe/life-threatening:</i> Initially salbutamol, 5 mg, or terbutaline, 10 mg, nebulised. If the patient is improving, consider salbutamol 2.5 mg, 4–6 hourly or PRN. If the patient is not improving, give beta-2 agonist more frequently (e.g. salbutamol, 5 mg, up to every 10–15 minutes or continuous nebulisation (e.g. salbutamol, 5–10 mg/hour).	<i>Mild:</i> Salbutamol 200–400 micrograms (2–4 puffs), via spacer plus facemask, repeated every 20–30 minutes according to clinical response. Increase dose by 200 micrograms (2 puffs) every 2 minutes up to 1 mg (10 puffs) according to response. If good response, continue up to 10 puffs PRN (not exceeding 4 hourly). <i>Severe:</i> 1 mg (10 puffs) repeated according to clinical response. Consider nebulised administration. <i>Life-threatening:</i> nebulised salbutamol, 2.5 mg, or terbutaline, 5 mg, with oxygen as driving gas. If life-threatening features present, repeat nebulised beta-2 agonist plus bolus intravenous salbutamol, 15 micrograms/kg, of 200 micrograms/ml solution over 10 minutes. Doses above 1–2 micrograms/kg/minute should be given in a paediatric intensive care unit.	<i>Mild/moderate:</i> Salbutamol up to 1 mg (10 puffs) via spacer and facemask <i>Severe/life-threatening:</i> MDI plus spacer ineffective. Nebulised salbutamol, 2.5 mg, or nebulised terbutaline, 5 mg. Repeated according to clinical response.

MDI, metered dose inhaler; PRN, *pro re nata* (as needed).

possible that there may be an advantage in higher doses in patients with the most severe obstruction. In practice, the acute episode should be efficiently controlled using high doses of beta-2 agonists. However, subsequent dose and dosing interval should be individualised using objective measures of lung function as a guide.

4. *Continuous versus intermittent nebulisation.* Continuous nebulisation is thought to be more beneficial than intermittent therapy; however, a meta-analysis of randomised controlled trials of adults with acute asthma found no significant differences between the two methods in terms of improvement in pulmonary function or hospital admission; nevertheless, continuous nebulisation was associated with fewer side-effects.¹⁹ Most patients with acute asthma respond adequately to bolus nebulisation of beta-2 agonists.³ The BTS/SIGN asthma management guideline recommends that continuous nebulisation (salbutamol, 5–10 mg/hour) should be considered in severe asthma (peak expiratory flow [PEF] or forced expiratory volume in 1 second [FEV₁] less than 50% best or predicted) and asthma that is poorly responsive to an initial dose of a beta-2 agonist.

Corticosteroids³

Systemic steroids should be given in adequate doses to all patients with acute asthma. Corticosteroids are not bronchodilators but are extremely effective in reducing the airway inflammation present in virtually all patients with asthma. They reduce mortality, relapses, subsequent hospital admission and requirement for beta-2 agonists. The earlier corticosteroids are given in an acute attack, the better the outcome. Steroid tablets are as effective as parenteral steroids, provided the tablets can be swallowed and retained and there is no problem with absorption. A soluble preparation is available for those unable to swallow tablets. A 5 day course of prednisolone, 40–50 mg daily, is recommended, although in practice the duration of treatment should be adjusted to bring about recovery.

Steroid tablets can be stopped abruptly after recovery from the acute exacerbation; there is no need to taper the dose of steroid, except in rare cases where the patient was previously on a maintenance dose of steroid or the steroid course was longer than 3 weeks.

Inhaled steroids do not provide additional benefit to the management of acute asthma but should be started as soon as possible or continued to be prescribed to ensure that the long-term management plan is adhered to (see Chapter 3).

Ipratropium bromide³

The use of inhaled ipratropium bromide as the initial bronchodilator for adults with acute asthma has been consistently reported to be inferior to the use of beta-2 agonists in improving airflow. However, the existing literature suggests that inhaled anticholinergic agents provide an additional benefit to children and adults with acute asthma who are treated with beta-2 agonists, with minimal side-effects. Ipratropium bromide should be added to nebulised beta-2 agonist treatment for patients with acute severe or life-threatening symptoms and for patients who show a poor response to administration of beta-2 agonist alone. The recommended dose in adults with acute asthma is 500 micrograms every 4–6 hours, reducing the frequency as clinical improvement occurs. The continued prescribing of ipratropium bromide once the condition is stable is not beneficial. Special caution is needed to protect the patient's eyes from the nebulised drug, as it has been reported to cause acute-angle glaucoma (see Chapter 11).

Intravenous magnesium

Magnesium is an intracellular ion that is essential for a wide range of cellular functions, including inhibition of calcium channels. It relaxes smooth muscle *in vitro* and is a weak bronchodilator but probably does not inhibit airway hyperresponsiveness.^{21,22} The idea of using intravenous magnesium in asthma was first reported in 1936. A number of case reports and studies have reported on the role of intravenous magnesium given as a bolus (1.2–2 g over 20 minutes) in the management of acute severe asthma. A systematic review of the literature reported that, overall, there was no significant improvement in either hospital admissions or lung function, although there was a significant improvement in a subgroup analysis of more severely affected patients.²³ Another study showed that magnesium benefited a subgroup of patients presenting to the emergency department with an FEV₁ below 25%, further supporting the idea that magnesium should be administered to patients with life-threatening or near-fatal asthma,²⁴ which is the recommendation of the BTS/SIGN asthma management guideline.² The guideline also suggests that a single dose of intravenous magnesium be considered for patients with acute severe asthma who have not had a good initial response to inhaled bronchodilator therapy. The *Drugs and Therapeutics Bulletin* recently reviewed the evidence for administration of intravenous magnesium in acute severe asthma and, contrary to the

recent BTS/SIGN guideline, concluded that the evidence “is weak and conflicting and does not justify the unlicensed use of this drug.”²⁵

Intravenous aminophylline

The role of aminophylline in the treatment of severe acute asthma has been challenged since the advent of potent selective beta-2 agonists. At therapeutic doses, aminophylline is a weaker bronchodilator than the beta-2 agonists, and it has many undesirable side-effects. Furthermore, intravenous aminophylline may not provide any additional benefit when administered to patients already receiving beta-2 agonists and corticosteroids. The BTS/SIGN asthma management guideline therefore does not recommend the routine use of intravenous aminophylline in the treatment of acute asthma. If the response to standard treatment is poor, individual patients with life-threatening asthma may benefit from intravenous aminophylline. In these cases, a loading dose of 5 mg/kg over 20 minutes (unless on maintenance oral therapy, when no loading dose is given) followed by an infusion of 500–700 micrograms/kg/hour; daily measurement of blood theophylline levels is recommended.

Leukotriene receptor antagonists

Data on the effects of leukotriene receptor antagonists in acute asthma are limited and they are therefore not recommended for managing acute asthma.

Antibiotics

Antibiotics are not an effective treatment for acute asthma, as infections that precipitate an acute attack are usually viral. Routine prescription of antibiotics for all patients with acute asthma is not indicated.²

Heliox

The administration of heliox, a helium–oxygen mixture, reduces turbulent airflow across narrowed airways, which can help to reduce the work of breathing. This, in turn, can improve gas exchange, arterial blood gas levels and clinical symptoms. Some data suggest that nebulised-size particles may be distributed more uniformly in the distal airways when nebulisation treatments are administered via heliox than

with a standard oxygen–nitrogen mixture. The effectiveness of heliox in reducing the density of administered gas and improving laminar airflow depends on the helium concentration of the gas – the higher the helium concentration, the more effective the result; an 80:20 mixture of helium–oxygen is most effective. However, the current evidence is not sufficient to establish the administration of heliox in routine care.²

Other therapies

Inhaled anaesthetic agents (e.g. halothane, isoflurane and enflurane) have been used with varying degrees of success in intubated patients with refractory severe asthma. The mechanism of action is unclear but they may have direct relaxant effects on airway smooth muscle.

Additional management options

Some case reports describe successful use of extracorporeal membrane oxygenation in extreme cases of refractory status asthmaticus in which maximum standard pharmacotherapy and mechanical ventilation was unsuccessful.

Ventilatory assistance can be life saving, and both non-invasive and invasive techniques are available. The decision to intubate a patient with asthma is taken with extreme caution. Positive-pressure ventilation in a patient with asthma is complicated by severe airways obstruction and air trapping, resulting in hyperinflated lungs that may resist further inflation, placing the patient at high risk of barotrauma. Therefore, mechanical ventilation should be undertaken only in the face of continued deterioration despite maximal bronchodilatory therapy. Non-invasive facemask ventilation may offer short-term support for some patients with hypercapnic respiratory failure who are gradually tiring and can cooperate with their care. It is not recommended for use in the place of mechanical ventilation in cases of very acute asthma, as further studies are required.

Management of acute asthma in children

The principles of treating acute asthma in children are the same as in adults but there are differences in dosages of medication and clinical assessment (Figure 4.3).

Management of acute asthma in children in hospital

Age 2-5 years

ASSESS ASTHMA SEVERITY	
<p>Moderate exacerbation</p> <ul style="list-style-type: none"> • SpO₂ ≥ 92% • No clinical features of severe asthma <p>NB: If a patient has signs and symptoms across categories, always treat according to their most severe features</p>	<p>Severe exacerbation</p> <ul style="list-style-type: none"> • SpO₂ < 92% • Too breathless to talk or eat • Silent chest • Poor respiratory effort • Respiratory rate > 50/min • Use of accessory neck muscles <p>Life threatening asthma</p> <ul style="list-style-type: none"> • SpO₂ < 92% • Silent chest • Poor respiratory effort • Altered consciousness • Cyanosis
<p>Oxygen via face masks/nasal prongs to achieve normal saturations</p>	
<p>β₂ agonist 2-4 puffs via spacer</p> <ul style="list-style-type: none"> • Increase β₂ agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response • Consider soluble oral prednisolone 20 mg <p>Reassess within 1 hour</p>	<p>β₂ agonist 10 puffs via spacer ± face mask</p> <ul style="list-style-type: none"> • Nebulised β₂ agonist followed by 2.5 mg or terbutaline 5 mg plus ipratropium bromide 0.25 mg nebulised • Soluble prednisolone 20 mg or IV hydrocortisone 4 mg/kg <p>Repeat β₂ agonist up to every 20-30 minutes according to response</p> <p>If poor response add 0.25 mg nebulised ipratropium bromide</p> <p>Discuss with senior clinician, PCU team or paediatrician</p> <ul style="list-style-type: none"> • Repeat bronchodilators every 20-30 minutes
<p>ASSESS RESPONSE TO TREATMENT</p> <p>Record respiratory rate, heart rate and oxygen saturation every 1-4 hours</p>	
<p>RESPONDING</p> <ul style="list-style-type: none"> • Continue bronchodilators 1-4 hours pm • Discharge when stable on 4 hourly treatment • Continue oral prednisolone for up to 3 days <p>At discharge</p> <ul style="list-style-type: none"> • Ensure stable on 4 hourly inhaled treatment • Review the need for regular treatment and the use of inhaled steroids • Review inhaler technique • Provide a written asthma action plan for treating future attacks • Arrange follow-up according to local policy 	<p>NOT RESPONDING</p> <ul style="list-style-type: none"> • Arrange HDU/ICU transfer • Chest x-ray and blood gases • IV salbutamol 1.5 mcg/kg bolus over 10 minutes • Followed by continuous infusion 1-5 mcg/kg/min (dilute to 200 mcg/ml) • IV aminophylline 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) • Followed by continuous infusion 1 mg/kg/hour

Age >5 years

ASSESS ASTHMA SEVERITY	
<p>Moderate exacerbation</p> <ul style="list-style-type: none"> • SpO₂ ≥ 92% • PEf > 50% best or predicted • No clinical features of severe asthma <p>NB: If a patient has signs and symptoms across categories, always treat according to their most severe features</p>	<p>Severe exacerbation</p> <ul style="list-style-type: none"> • SpO₂ < 92% • PEf < 50% best or predicted • Heart rate > 120/min • Respiratory rate > 30/min • Use of accessory neck muscles <p>Life threatening asthma</p> <ul style="list-style-type: none"> • SpO₂ < 92% • PEf < 33% best or predicted • Silent chest • Poor respiratory effort • Altered consciousness • Cyanosis
<p>Oxygen via face masks/nasal prongs to achieve normal saturations</p>	
<p>β₂ agonist 2-4 puffs via spacer</p> <ul style="list-style-type: none"> • Increase β₂ agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response • Oral prednisolone 30-40 mg <p>Reassess within 1 hour</p>	<p>β₂ agonist 10 puffs via spacer</p> <ul style="list-style-type: none"> • Nebulised β₂ agonist followed by 2.5 mg or terbutaline 5-10 mg • Oral prednisolone 30-40 mg • IV hydrocortisone 4 mg/kg <p>Repeat β₂ agonist and ipratropium bromide 0.25 mg</p> <p>Repeat β₂ agonist and ipratropium up to every 20-30 minutes according to response</p> <p>Discuss with senior clinician, PCU team or paediatrician</p> <ul style="list-style-type: none"> • Repeat bronchodilators every 20-30 minutes
<p>ASSESS RESPONSE TO TREATMENT</p> <p>Record respiratory rate, heart rate and oxygen saturation and PEf/FEV every 1-4 hours</p>	
<p>RESPONDING</p> <ul style="list-style-type: none"> • Continue bronchodilators 1-4 hours pm • Discharge when stable on 4 hourly treatment • Continue oral prednisolone 30-40 mg for up to 3 days <p>At discharge</p> <ul style="list-style-type: none"> • Ensure stable on 4 hourly inhaled treatment • Review the need for regular treatment and the use of inhaled steroids • Review inhaler technique • Provide a written asthma action plan for treating future attacks • Arrange follow-up according to local policy 	<p>NOT RESPONDING</p> <ul style="list-style-type: none"> • Continue 20-30 minutes nebulisers and arrange HDU/ICU transfer • Consider: <ul style="list-style-type: none"> • Chest x-ray and blood gases • Bolus IV salbutamol 1.5 mcg/kg if not already given • Continuous IV salbutamol infusion 1-5 mcg/kg/min (dilute to 200 mcg/ml) • IV aminophylline 5 mg/kg loading dose over 20 minutes followed by continuous infusion 1 mg/kg/hour (omit in those receiving oral theophyllines) • Bolus IV infusion of magnesium sulphate 40 mg/kg (max. 2 g over 20 minutes)

Figure 4.3 Hospital management of acute asthma in children, from the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma management guideline.² (Reproduced with permission from the BMJ Publishing Group.)

Treatment of acute asthma in children over 2 years of age

Beta-2 agonists

In children (2–12 years of age), beta-2 agonists are superior to all other bronchodilators since they work effectively within minutes of administration and should be administered as first-line therapy, usually by inhalation. An MDI with a spacer device provides an effective way to administer the beta-2 agonist to children with mild-to-moderate asthma and is less likely to induce tachycardia and hypoxia than when the same drug is given via a nebuliser.²⁶ Children under 3 years of age are likely to require a facemask connected to the mouthpiece of the spacer device to aid successful drug delivery. It is important that the facemask fits tightly, as inhalation through a facemask 2–3 cm from the face will reduce drug delivery by as much as 85%.²⁷ The dose of inhaled beta-2 agonist required to treat acute asthma in children depends on the severity of the disease and should be adjusted according to the patient's response. For mild asthma exacerbations, 2–4 puffs (i.e. 200–400 micrograms salbutamol) repeated every 20–30 minutes might be sufficient, whereas up to 10 puffs may be required in a severe attack. Continuous nebulised beta-2 agonists are of no greater benefit than frequent as-required doses in the same total hourly dosage.^{28,29} The role of intravenous beta-2 agonists in children remains unclear.

For children with severe acute asthma or in those where there is uncertainty about reliable drug delivery via the inhalation route, the recommendation is to either add a bolus dose of intravenous salbutamol (15 micrograms/kg) to maximal doses of nebulised salbutamol or to start a continuous intravenous infusion.

Corticosteroids

Steroids should be administered as early as possible after initial presentation – prednisolone, 20 mg daily, for children aged 2–5 years; 30–40 mg daily for children over 5 years of age. Oral administration is effective in the majority of children. A soluble preparation can be used for those unable to swallow tablets. Parenteral administration is recommended only if the child is unable to retain oral medication. The inhaled route is not recommended for the treatment of acute symptoms but children who are already using inhaled corticosteroids should continue with their usual maintenance dose. There is insufficient evidence to support increasing the dose of inhaled steroid in an exacerbation. Treatment with oral prednisolone for 3 days is usually sufficient but the length

of course should be tailored to the individual and continued until recovery.²

Anticholinergics

Anticholinergics, such as ipratropium, are recommended for children who respond poorly to beta-2 agonists. Administered alone, ipratropium has no role in the management of acute severe asthma in this age group. However, the combination of a beta-2 agonist and an anticholinergic produces better results than either drug used alone and benefits are more apparent in severe cases. Frequent doses (250 micrograms /dose nebulised up to every 20–30 minutes) should be used in the initial stages of an asthma attack. The dose frequency should be reduced as clinical improvement occurs.

Intravenous aminophylline

As in adults with acute asthma, intravenous aminophylline is not recommended in children with mild-to-moderate acute asthma but should be considered for children with severe or life-threatening bronchospasm that is unresponsive to maximal doses of bronchodilators and steroid tablets.

Other therapies

There is no evidence to support the use of heliox, leukotriene antagonists or routine antibiotics for the treatment of acute asthma in children. Intravenous magnesium is a safe treatment although its place in therapy is not yet established.

Treatment of acute asthma in children under 2 years of age

Management of acute asthma attacks in children under 2 years of age is complicated by differences in lung anatomy and physiology compared with older children and a poorer response to treatments. Several early studies showed no bronchodilator response to beta-2 agonists in children under 2 years of age with asthma, encouraging the debate that infants do not have functioning beta-2-receptors from birth.^{30–32} More recent studies have shown that beta-2-receptors are present and function from birth but that the response to beta-2-receptors can be small and there is marked inter-individual variation.^{33,34} A trial of inhaled beta-2

agonist is recommended for the initial treatment of acute asthma.² For mild-to-moderate acute asthma, an MDI with a spacer device and mask is the preferred method of drug delivery, although a nebuliser can be used if there is doubt or concern about effective drug delivery.

Oral corticosteroid tablets (e.g. 10 mg soluble prednisolone daily for up to 3 days) should be started as early as possible and used in conjunction with beta-2 agonists.²

In severe cases, the addition of ipratropium bromide to the beta-2 agonists and corticosteroids may produce some improvement in clinical symptoms and reduce the need for more intensive treatment.²

Discharge from hospital after an acute attack

A patient can be discharged from hospital when they have recovered sufficiently from an acute attack. There should be good air entry without wheezing and the PEF should be greater than 75% predicted or personal best. Oxygen saturation should be greater than 92% (94% for children) when breathing room air. The patient's requirement for beta-2 agonists should be decreasing and preferably no more than every 4 hours, and they should be taking medication that could easily be continued safely at home.

An acute exacerbation of asthma should be regarded as a failure of long-term asthma care, and ways of helping patients and families to avoid further severe episodes should be considered. The discharge plan should address the following points.

- Check the patient's inhaler technique.
- Consider the need for regular inhaled corticosteroids.
- Provide a written action plan (see Chapter 8).
- Ensure the patient has a full understanding of medications to be taken.
- Ensure the patient is followed up by their general practitioner within 1 week (children) or 2 days (adults).
- Ensure the patient is followed up by a hospital physician within 1–2 months (children) or 1 month (adults).

References

1. The Burden of Lung Disease: A statistics report from the British Thoracic Society, 2001 www.brit-thoracic.co.uk
2. British Thoracic Society/Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. *Thorax* 2003; 58 (Suppl I): S1–S94.

3. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. *Chest* 2004; 125: 1081–1102.
4. Turner MO, Noertjojo K, Vedal S, *et al.* Risk factors for near-fatal asthma: a case-control study in hospitalized patients with asthma. *Am J Respir Crit Care Med* 1998; 157: 1804–1809.
5. Hessel PA, Mitchell I, Tough S, *et al.* Risk factors for death from asthma. *Ann Allergy Asthma Immunol* 1999; 83: 362–368.
6. Abramson MJ, Bailey MJ, Couper FJ, *et al.* Are asthma medications and management related to deaths from asthma? *Am J Respir Crit Care Med* 2001; 163: 12–18.
7. Plaza V, Serrano J, Picado C, *et al.* Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. *Eur Respir J* 2002; 19: 846–852.
8. Carroll N, Carello S, Cooke C, James A. Airway structure and inflammatory cells in fatal attacks of asthma. *Eur Respir J* 1996; 9: 709–715.
9. Carroll N, Elliot J, Motron A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis* 1993; 147: 405–410.
10. Dales RE, Cakmak S, Judek S, *et al.* The role of fungal spores in thunderstorm asthma. *Chest* 2003; 123: 745–750.
11. Marks GB, Colquhoun JR, Girgis ST, *et al.* Thunderstorm outflows preceding epidemics of asthma during spring and summer. *Thorax* 2001; 56: 468–471.
12. Packe GE, Ayres JG. Asthma outbreak during a thunderstorm. *Lancet* 1985; 2: 199–204
13. Higham J, Venables K, Kopek E, *et al.* Asthma and thunderstorms: description of an epidemic in general practice in Britain using data from a doctors' deputising service in the UK. *J Epidemiol Commun Health* 1997; 51: 233–238.
14. Venables KM, Allitt U, Collier CG, *et al.* Thunderstorm-related asthma: the epidemic of 24/25 June 1994. *Clin Exp Allergy* 1997; 27: 725–736.
15. Celenza A, Fothergill J, Kupek E, *et al.* Thunderstorm associated asthma: a detailed analysis of environmental factors. *BMJ* 1996; 312: 604–607.
16. McFadden ER. Acute severe asthma. *Am J Resp Crit Care Med* 2003; 168: 740–759.
17. Travers A, Jones AP, Kelly K, *et al.* Intravenous beta-2 agonists for acute asthma in the emergency department (Cochrane Review) In: *The Cochrane Library*, issue 3. Chichester: John Wiley & Sons, 2001 (www.thecochrane-library.com).
18. Bradding P, Rushby I, Scullion J, *et al.* As required versus regular nebulised salbutamol for the treatment of acute severe asthma. *Eur Respir J* 1999; 13: 290–294.
19. Emerman CL, Cydulka RK, McFadden ER. Comparison of 2.5 mg versus 7.5 mg of inhaled albuterol in the treatment of acute asthma. *Chest* 1999; 115: 92–96.
20. Rodrigo GJ, Rodrigo C. Continuous vs intermittent beta-2 agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. *Chest* 2002; 122: 160–165.

21. Hill JM, Britton J. Effect of intravenous magnesium sulphate on airway calibre and airway reactivity to histamine in asthmatic subjects. *Br J Clin Pharmacol* 1996; 42: 629–631.
22. Hill J, Lewis S, Britton J. Studies of the effects of inhaled magnesium on airway reactivity to histamine and adenosine monophosphate in asthmatic subjects. *Clin Exp Allergy* 1997; 27: 546–551.
23. Rowe BH, Bretzlaff JA, Bourdon C, *et al.* Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature. *Ann Emerg Med* 2000; 36: 181–190.
24. Silverman RA, Osborn H, Runge J, *et al.* IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest* 2002; 122: 489–497.
25. Anonymous. Intravenous magnesium for acute asthma. *Drugs Ther Bull* 2003; 41: 79–80.
26. Cates CJ, Rowe BH, Bara A. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review). *The Cochrane Library*, issue 3. Chichester: John Wiley & Sons, 2001 (www.thecochranelibrary.com).
27. Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. *Arch Dis Child* 1992; 67: 580–585.
28. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulised albuterol for emergency management of asthma. *Acad Emerg Med* 1996; 3: 1019–1024.
29. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulised albuterol for severe status asthmaticus in children. *Crit Care Med* 1993; 21: 1479–1486.
30. Lenney W, Milner AD. At what age do bronchodilator drugs work? *Arch Dis Child* 1978; 53: 532–535.
31. Lenney W, Evans NAP. Nebulised salbutamol and ipratropium bromide in asthmatic children. *Br J Dis Chest* 1986; 80: 59–65.
32. Chavasse RJ, Bastian-Lee Y, Richter H, *et al.* Inhaled salbutamol for wheezy infants: a randomised controlled trial. *Arch Dis Child* 2000; 82: 370–375.
33. Yuksel B, Greenough A. Effect of nebulised salbutamol in preterm infants during the first year of life. *Eur Respir J* 1991; 4: 1088–1092.
34. Wilkie RA, Bryan MH. Effect of bronchodilator on airway resistance in ventilator-dependent neonates with chronic lung disease. *J Paediatr* 1987; 111: 278–282.

