

## REVIEW SERIES

## Asthma exacerbations · 5: Assessment and management of severe asthma in adults in hospital

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It is difficult to understand why there is such a huge discrepancy between the management of severe asthma recommended by evidence-based guidelines and that observed in clinical practice. The recommendations are relatively straightforward and have been widely promoted both in guidelines and reviews. Specialist physicians need to be more proactive in their implementation of such guidelines through the use of locally derived protocols and assessment sheets, reinforced by audit. The common occurrence of severe asthma and its considerable burden to the community would support such an approach.

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Over the last two decades, British guidelines on the management of asthma have provided evidence-based recommendations for the assessment and management of severe asthma in hospitals.<sup>1–3</sup> Practical assessment and management algorithms have been provided, supported by clear advice regarding their implementation. Despite their availability and widespread promotion, repeated audits have indicated that there is a major discrepancy between the standard of current medical management of severe asthma in hospitals and that recommended in the guidelines.<sup>4–6</sup> Common problems include inadequate assessment and recognition of severity, confusion over the use and interpretation of investigations, insufficient use of systemic steroids, over-reliance on bronchodilators, delayed specialist or intensivist referral and poor follow-up arrangements including communication with the general practitioner (GP) (table 1).

Recognition of these problems provides a good basis for determining priorities for the hospital care of patients with severe asthma (table 2). In this review we focus on these issues and the clinical approaches that might be used to improve the management of severe asthma in adults in hospital. We also highlight the use of assessment sheets and treatment protocols in the emergency department to illustrate how the guidelines can be implemented in a simple and practical manner. The review also raises issues of clinical uncertainty that need to be considered in updated versions of the guidelines and where further research is required.

**HISTORY**

A brief history can be obtained while the patient is being initially examined as part of the clinical assessment. The priority is to identify quickly the

patient at increased risk of serious morbidity and mortality from asthma, and this can be achieved by asking a few questions to determine the background chronic asthma severity and the severity of the acute attack (table 3). Among the markers of an increased baseline risk of death that have been identified, a hospital admission in the previous 12 months is the most reliable and easily ascertained, with the occurrence of multiple hospital admissions for asthma signifying a greatly increased risk.<sup>7–9</sup> The amount of  $\beta$ -agonist regularly used by the patient is also informative, based on epidemiological evidence that increasing use is associated with a progressively greater likelihood of a hospital admission and/or risk of death.<sup>10</sup> For example, the Saskatchewan study reported that the risk of death increased markedly with the use of more than two  $\beta$ -agonist inhalers per month.<sup>10</sup> The factor which identifies patients at greatest long-term risk of death is a previous life-threatening attack (ever), which is most easily documented by obtaining a history of a previous intensive care unit (ICU) admission for asthma.<sup>11</sup>

The amount of inhaled  $\beta$ -agonist self-administered during the exacerbation is a good marker of the severity of the acute attack and risk of a poor outcome. It also gives the attending doctor an indication of the likelihood of a response to further inhaled  $\beta$ -agonist treatment and requirement for systemic steroid treatment. In a study of adult patients admitted to hospital with severe asthma,<sup>12</sup> about half had used at least 30 doses from their  $\beta$ -agonist inhaler in the 24 h before presentation and about 20% had used over 60 doses. Most patients who had access to both an inhaler and nebuliser had used the nebuliser more than four times, as well as at least 20 doses of their inhaler during the 24 h period before admission. The likely poor response to further inhaled bronchodilator and the requirement for hospital admission and systemic steroid treatment could be predicted from such heavy prior  $\beta$ -agonist use.

For those patients who have monitored their peak flow during the attack, marked variability in peak flow with falls of >50% from baseline is a marker of risk of sudden death.<sup>13 14</sup>

The perceived speed of onset of the attack is also informative for recognising asthmatic patients

**Abbreviations:** CPAP, continuous positive airway pressure; FEV<sub>1</sub>, forced expiratory volume in 1 s; HDU, high dependency unit; ICU, intensive care unit; NIPPV, non-invasive positive pressure ventilation; PaO<sub>2</sub>, PaCO<sub>2</sub>, arterial oxygen and carbon dioxide tension; PEF, peak expiratory flow; PVCD, paradoxical vocal cord dysfunction; SpO<sub>2</sub>, oxygen saturation

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**Table 1** Hospital management of severe asthma: the problems

Poor assessment with resulting lack of recognition of life-threatening asthma	<ul style="list-style-type: none"> <li>• Inadequate history and examination</li> <li>• Lack of lung function measurements</li> <li>• Misuse and misinterpretation of arterial blood gas measurements and chest radiographs</li> </ul>
Poor management with suboptimal outcome	<ul style="list-style-type: none"> <li>• Insufficient use of systemic steroids</li> <li>• Over-reliance on inhaled bronchodilators</li> <li>• Misuse of intravenous bronchodilators</li> </ul>
Poor follow-up	<ul style="list-style-type: none"> <li>• Long-term management not addressed</li> <li>• Poor communication with GP</li> <li>• Inadequate follow-up arrangements</li> </ul>

**Table 2** Hospital management of severe asthma: the priorities

Practical assessment and management protocols Objective measurement of severity and identification of life-threatening attack Management determined by level of severity Measurement of the response to treatment Decision regarding admission/discharge; general/respiratory; ward/high dependency unit (HDU)/intensive care unit (ICU) admission Medical follow-up arranged and long-term management addressed prior to discharge
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with “precipitate attacks” who are likely to present with more severe asthma but have a greater improvement with treatment.<sup>15-17</sup> Overall precipitate attacks are uncommon, representing around one in eight presentations at the emergency department when defined as an onset of symptoms within 3 h of presentation. The more common presentation is that of a gradual deterioration over many days before a more rapid worsening just before presentation.

Additional history will be required, including markers of poor long-term control (such as nocturnal waking) and precipitating factors, of which viral upper respiratory tract infections are most common. In cases of precipitate asthma, allergen exposure, use of non-steroidal anti-inflammatory drugs and psychological stress are important factors to consider.<sup>15-17</sup> In addition to documentation of the routine medications (including compliance with inhaled corticosteroid therapy), consideration of other issues such as continuity of primary care, adverse behavioural or psychosocial problems and the presence of comorbid conditions is required.<sup>18</sup>

It is also informative to ask the patient to describe the sequence of events in the 24 h period before admission to establish if there was a significant delay in the recognition of the severity of the attack and whether earlier medical review

**Table 3** Markers of risk of an adverse outcome in asthma

Baseline severity	Recent hospital admission Three or more regular medications Frequent “after hours” GP visits Psychosocial problems Previous ICU admission (ever)
Acute severity	Heavy use of $\beta_2$ -agonist Precipitate asthma Marked (>50%) reduction or variation in peak flow

should have occurred. This provides the opportunity to discuss “what should have happened in this attack” and recommend what steps might be taken to ensure a better outcome in the next attack. This advice may also serve as the basis for implementing a self-assessment and management plan prior to discharge.

Consideration should also be given to other disorders which may mimic or coexist with asthma. Particular consideration should be given to paradoxical vocal cord dysfunction (PVCD),<sup>19, 20</sup> which is normally recognised by patients attending the emergency room frequently with poorly reproducible lung function measurements and predominant wheezing during both expiration and inspiration originating from the larynx rather than the chest. Other distinctive features include a predominance in women, a background of psychological or psychiatric problems, and a lack of response to standard asthma management. Careful elicitation of symptoms and signs of PVCD at presentation may be helpful in its subsequent investigation, which is based on laryngoscopy and flow-volume loops. This is important not only because PVCD is amenable to treatment, but also because it can reduce the risk of substantial morbidity with intensive treatment including long-term oral corticosteroids.

**CLINICAL EXAMINATION**

The priority of the clinical examination is to confirm the diagnosis of asthma quickly and to assess its severity. The general appearance of the patient, including difficulty in talking, respiratory rate and heart rate form the basis of the clinical assessment of severity.<sup>21, 22</sup> Increasing pulse rate has a close correlation with worsening asthma severity, and it is incorrect to assume that the tachycardia is due to  $\beta$ -agonist treatment. Studies of the response to high-dose  $\beta$ -agonist treatment in severe asthma have shown that the heart rate falls in association with the bronchodilator response.<sup>21, 23</sup>

While it is generally well recognised that some patients may have a poor perception of the severity of their asthma,<sup>24, 25</sup> it is less well appreciated that such patients may also appear deceptively well, despite the presence of severe airflow obstruction.<sup>26</sup> These factors contribute both to delay in seeking medical help by the patient and a tendency for the doctor not to appreciate the severity when the patient does present. This underlies the importance of lung function measurements in severe asthma, as well as eliciting other clinical signs such as the difficulty a patient may have in talking,<sup>21</sup> blood pressure paradox, accessory muscle use and tracheal tug. In acute severe asthma, the marked hyperinflation and associated greater inspiratory muscle effort is responsible for the patient’s perception that the difficulty in breathing is predominantly inspiratory rather than expiratory.<sup>27</sup> The inspiratory muscle work may increase up to tenfold in patients with severe asthma in whom the FEV<sub>1</sub> is <50% of baseline.<sup>28</sup>

In clinical practice, signs such as a “quiet chest” and blood pressure paradox (>15 mm Hg) should alert the doctor to the presence of a severe attack.<sup>21, 29</sup> Although difficulties in their interpretation and wide observer variability have led to a reduced emphasis on their use, these clinical examination features are informative when carefully elicited, and clinicians are encouraged to develop and maintain these clinical examination skills. Other clinical signs which indicate life-threatening asthma include patients assuming the upright position (or an inability to lie supine), cyanosis and sweating.<sup>21</sup> Confusion or a reduced level of consciousness may be a premonitory sign, although many patients remain fully conscious until immediately before a fatal cardiac arrest.

The clinical severity markers that should alert the assessing doctor to the presence of a life-threatening attack are outlined

**Table 4** Levels of severity of acute asthma exacerbations

Moderate asthma exacerbation	Increasing symptoms FEV <sub>1</sub> >50% best or predicted
Acute severe asthma	No features of acute severe asthma Any one of: FEV <sub>1</sub> 30–50% best or predicted Respiratory rate ≥25/min Heart rate ≥110/min
Life-threatening asthma	Inability to complete sentences in one breath Any one of the following in a patient with severe asthma: FEV <sub>1</sub> <30% best or predicted SpO <sub>2</sub> <92% PaO <sub>2</sub> <8 kPa (60 mm Hg) PaCO <sub>2</sub> ≥6 kPa (45 mm Hg) Silent chest Cyanosis Feeble respiratory effort, exhaustion Confusion or coma
Near fatal asthma	Hypotension or bradycardia Raised PaCO <sub>2</sub> and/or requiring mechanical ventilation with raised inflation pressures

FEV<sub>1</sub>, forced expiratory volume in 1 s; PaO<sub>2</sub>, PaCO<sub>2</sub>, arterial oxygen and carbon dioxide tension; SpO<sub>2</sub>, oxygen saturation.  
Modified from table 4 in the British Guideline on the Management of Asthma.<sup>3</sup>

in table 4. While these criteria appear practical and simple to apply, they have inherent limitations.<sup>26</sup> First, the clinical symptoms and signs of severe asthma often do not correlate with the severity of physiological impairment and, as a result, their absence is not necessarily reassuring. Another limitation is that the components do not develop simultaneously or at unique levels of impairment. It is recommended that it is wise to base management on the “worst” abnormality and not be reassured because another feature does not fall within the definition of severe.<sup>18</sup> In this way, some patients may be admitted unnecessarily or be overtreated, but some “preventable” deaths from asthma can be avoided.

## ASSESSMENT

### Lung function tests

Lung function tests are the basis for assessment of the severity of the asthmatic attack (table 4).<sup>3 18 22</sup> Preferably, this should be undertaken by spirometry with measurement of the forced expiratory volume in 1 s (FEV<sub>1</sub>) expressed as a percentage of predicted normal values. The National Health and Nutrition Examination Survey (NHANES) reference prediction equations should be used rather than the traditional European Coal and Steel normal values which are now acknowledged to be out of date and underestimate normal reference values by about 15%.<sup>30</sup>

Measurement of the peak expiratory flow (PEF), with values expressed as predicted normal values, represents an alternative if spirometry is not available. The normal reference values sourced from the Nunn and Gregg nomogram are recommended for the calculation of “percent predicted” PEF values.<sup>31</sup> Contrary to current dogma, the PEF and FEV<sub>1</sub> are not equivalent when expressed as a percentage of predicted values, with the FEV<sub>1</sub> being on average 5–10 percentage points lower than the PEF (ie, FEV<sub>1</sub> of 30% predicted is equivalent to PEF of 35–40%).<sup>32 33</sup> There is also marked intra-patient variability in the relationship, with 95% confidence intervals of around 50 percentage points. This means that major differences in the classification of asthma severity may occur (and the treatment recommended on the basis of this classification), depending on the lung function measurement used. This caution particularly applies to the assessment and management of life-threatening asthma in which FEV<sub>1</sub> values are 4–10% lower than the PEF across the FEV<sub>1</sub> range of 20–33% predicted.<sup>34 35</sup>

While recognising the poor correlation between clinical signs and physiological measures, an FEV<sub>1</sub> of <30% predicted is likely to be present in a patient who is unable to speak more than a few words with an arterial carbon dioxide tension (PaCO<sub>2</sub>) of >5.3 kPa (40 mm Hg), a quiet chest with the absence of audible wheezing, respiratory rate >30/min or pulsus paradoxus >20 mm Hg.<sup>21 36 37</sup>

Importantly, the magnitude of the improvement in lung function following initial bronchodilator treatment represents the most informative measure of severity of the acute episode and likely requirement for hospital admission.<sup>38</sup> As a result, severity may be best defined in terms of outcome rather than the patient’s initial presentation.<sup>26</sup>

If one accepts that the FEV<sub>1</sub> is the “gold standard” method of assessing airflow obstruction in asthma, and that lung function measurements are essential in the assessment of asthma, a strong case can be made for the provision of spirometers in all hospital emergency departments. This case is further strengthened when one considers the use of spirometry in the assessment of other respiratory disorders and the costs and relative benefits of other medical equipment used in emergency departments. Peak flow measurements are preferred for monitoring lung function following admission to the ward.

While the measurement of the magnitude of hyperinflation is not indicated in the acute setting, it is informative to be aware that, in severe asthma, the residual volume can approach 400% and functional residual volume can be double the expected values.<sup>37</sup>

### Oxygen assessment and other tests

Measurement of oxygen saturation by pulse oximetry should be undertaken in all patients with severe asthma presenting to hospital. In the absence of oxygen therapy, arterial desaturation and hypercarbia occur concurrently and normally only develop in life-threatening asthma.<sup>37</sup> As a result, pulse oximetry is a suitable means for the routine assessment of ventilatory status. Analysis of arterial blood gases can be selectively reserved for those patients with oxygen saturations on room air of <92%<sup>39</sup> or those who do not respond to initial treatment, with the FEV<sub>1</sub> remaining <30%.<sup>38</sup>

In the interpretation of arterial blood gases, attention focuses primarily on the PaCO<sub>2</sub> with a normal value in a breathless asthmatic being a warning sign of impending hypoventilation and values above 6 kPa (45 mm Hg) indicating a life-threatening attack and probable need for transfer to a high dependency unit (HDU) or intensive care unit (ICU, table 4). Fortunately, arterial oxygen tensions <6.7 kPa (50 mm Hg) or carbon dioxide tensions >6 kPa (45 mm Hg) occur infrequently, being present in less than 10% of patients attending the emergency department with severe asthma.<sup>26 36</sup>

A chest radiograph is not routinely needed in an adult asthmatic attending the emergency department, being reserved for those who do not respond to initial treatment or in whom an alternative diagnosis such as pneumothorax or pneumonia is suspected.<sup>40 41</sup> The serum potassium concentration should be measured, particularly in patients with prior corticosteroid or diuretic treatment. Hypokalaemia caused primarily by high-dose β-agonist therapy is not uncommon in severe asthma and may require potassium supplementation. Other investigations include a full blood count and electrocardiography in older patients. Microbiological investigations are seldom required, although purulent sputum should be cultured if present.

## MANAGEMENT

The mainstay of treatment during the acute attack is supplementary oxygen, repeated inhaled bronchodilator and systemic corticosteroids (table 5).

**Table 5** Treatment for severe asthma

Initial
Oxygen (to keep saturation levels >92%)
Salbutamol 2.5 mg (to be repeated $\times 2$ over 60 min if required)
Prednisone 40 mg orally
Poor response/life-threatening attack
Salbutamol nebulisation continuously
Ipratropium bromide 500 $\mu$ g hourly via a nebuliser
Intravenous magnesium 2 g over 30 min in 50 ml saline
Contact ICU/HDU
Consider:
Intravenous hydrocortisone 100 mg
BiPAP
High-dose inhaled corticosteroids
Could be tried as adjunct to recommended treatment:
Intravenous salbutamol
Intravenous theophylline
Heliox

Modified from the British Guideline on the Management of Asthma.<sup>3</sup>

### Oxygen therapy

Although it is recommended that high-flow oxygen is administered to all patients presenting with severe asthma, there is some evidence to suggest that this approach should be modified. First, best practice indicates that oxygen should be prescribed in the dose required to relieve hypoxaemia, guided by measurements of oxygen saturation obtained by oximetry and/or arterial blood gases and not prescribed at high flow to all patients with respiratory difficulties regardless of need. The administration of excessive oxygen is not without potential risks, including atelectasis and increased intrapulmonary shunting, and a reduction in cardiac output and coronary blood flow.<sup>42</sup> Although carbon dioxide retention associated with high-flow oxygen therapy is not considered to occur in asthma, one small study raised the possibility that the administration of 100% oxygen to acutely ill asthmatics can induce or worsen carbon dioxide retention, particularly in patients with severe airway obstruction.<sup>43</sup> Another concern which is not widely recognised is that the use of high-flow oxygen has the potential to lead to a delay in recognising deteriorating respiratory function.<sup>44-45</sup> This delay is caused by the patient maintaining 100% oxygen saturations despite progressive clinical deterioration so that, when the oxygen saturations begin to fall, the deterioration is recognised late and the opportunity to “buy time” by increasing the oxygen concentration is not available. As a result, supplementary oxygen should only be prescribed in severe asthma if the patient is hypoxic with the flow adjusted to achieve saturations greater than 92%.

Heliox is a mixture of helium and oxygen which has been used in the treatment of severe asthma. The rationale is that its lower density results in increased airflow and reduced work of breathing. Some studies,<sup>46-47</sup> but not all,<sup>48</sup> have reported benefits in patients with severe asthma. However, systematic reviews<sup>49-50</sup> suggest that there is not yet sufficient evidence to recommend heliox as a routine treatment for severe asthma in the emergency department, perhaps to be reserved for those with refractory attacks.

### Non-invasive positive pressure ventilation (NIPPV)

While non-invasive ventilation has a well established role in the management of exacerbations of chronic obstructive pulmonary disease, its role in the management of severe asthma is less clearly defined. Although early reports are encouraging,<sup>51-52</sup> NIPPV does not yet have a place in current management guidelines. It has been suggested, however, that it may be useful in those patients with hypercapnic respiratory failure as long as they are protecting their own airways and are able to tolerate the

face mask. For those patients who are able to tolerate the positive pressures, NIPPV can reduce the work of breathing and respiratory muscle fatigue, thereby buying time for transfer to an ICU/HDU and for pharmacological intervention to take effect. There is also some evidence to suggest that it might decrease airways resistance, re-expand atelectatic areas of the lung and decrease the adverse haemodynamic effects of the large negative inspiratory pleural pressures.<sup>52</sup> Although it may prevent invasive ventilation in some patients, there is concern that it may delay timely intubation in deteriorating patients. For those in whom it is indicated and tolerated, bilevel NIPPV should be started with 5 cm H<sub>2</sub>O continuous positive airway pressure (CPAP) and 10 cm H<sub>2</sub>O pressure support (equivalent to inspiratory positive airway pressure of 15 cm H<sub>2</sub>O) with the inspired oxygen titrated to achieve an oxygen saturation >92%. Adjustments should be made to optimise patient comfort.

### Inhaled bronchodilators

Inhaled  $\beta$ -agonists are the mainstay of bronchodilator therapy, with the dose and frequency determined by the severity of the asthma attack and the response to treatment. With respect to bronchodilator treatment, the key points are:

- (1) In addition to increasing the total dose of  $\beta$ -agonist administered, increasing the frequency of administration also leads to a greater bronchodilator efficacy. However, there is no advantage to the repeat administration of doses of nebulised salbutamol of >2.5 mg every 20 min.<sup>53</sup> This regime has equivalent bronchodilator efficacy to 7.5 mg salbutamol every 20 min in acute severe asthma. If there is an inadequate response to this regime, the best option is to proceed to continuous  $\beta$ -agonist nebulisation.<sup>23-54</sup>
- (2) Metered dose inhalers with a holding chamber (spacer) produce outcomes that are at least equivalent to nebuliser therapy in severe asthma.<sup>55-57</sup> This finding includes those with life-threatening asthma, with an FEV<sub>1</sub> <30% predicted on presentation. As a guide, 400  $\mu$ g salbutamol via a spacer can be considered equivalent to a 2.5 mg dose of salbutamol via nebuliser. It is suggested that the  $\beta$ -agonist should be actuated into a spacer in individual puffs, inhaled by tidal breathing or single breaths. The frequency of treatments is adjusted to the individual patient response, as occurs with nebuliser therapy. The previous British recommendation of 50 puffs of  $\beta$ -agonist via a metered dose inhaler and spacer in a life-threatening attack of asthma can be considered excessive.<sup>1</sup>
- (3) The addition of ipratropium bromide to inhaled  $\beta$ -agonist therapy provides an increase in the bronchodilator response in severe asthma.<sup>58-59</sup> This additional bronchodilation has now been shown with multiple dose regimes (as well as the administration of single doses), leading to both an improvement in lung function and a reduction in the requirement for hospital admission. In the absence of an established dose-response relationship in severe asthma, a 500  $\mu$ g dose can be administered by nebulisation if there is a poor initial response to inhaled  $\beta$ -agonist therapy, repeated after 60 min if there is minimal interval improvement. The standard dose of nebulised ipratropium bromide is 500  $\mu$ g 6-hourly. The absolute benefit of ipratropium bromide in combination with a  $\beta$ -agonist is achieved in patients with the most severe airflow obstruction. One important indication for the use of anticholinergic bronchodilators is as first-line treatment for  $\beta$ -blocker induced attacks.<sup>60</sup>
- (4) Bronchodilator nebuliser solutions should be administered from preservative-free sterile unit dose vials.<sup>61</sup> The use of multidose nebuliser solutions with the preservative benzalkonium chloride should be avoided as such preparations

have the potential to reduce the magnitude of bronchodilation or cause paradoxical bronchoconstriction.<sup>62–63</sup>

- (5) There is preliminary evidence to suggest that salbutamol nebuliser solution administered with isotonic magnesium sulphate results in a greater bronchodilator response than the standard isotonic salbutamol solution.<sup>64–65</sup> The greatest efficacy with the adjuvant magnesium solution occurs in those with life-threatening asthma, defined by a baseline FEV<sub>1</sub> of <30% predicted. Further research is now needed to determine whether salbutamol nebuliser solution with adjuvant magnesium should become the preferred agent for the treatment of severe asthma. Regrettably, there is no commercially available salbutamol solution which incorporates isotonic magnesium for use.
- (6) In life-threatening asthma the greatest bronchodilator response to nebulised  $\beta$ -agonist is achieved with continuous administration. For example, 2.5 mg at 30 min intervals for 2 h results in a lesser degree of bronchodilation than the same dose (10 mg in 70 ml) administered continuously over the 2 h period in those with life-threatening asthma.<sup>66</sup> There appears to be no benefit in nebulising higher concentrations continuously.<sup>54</sup>
- (7) In view of the theoretical risk of oxygen desaturation while using air-driven compressors to nebulise  $\beta$ -agonists, oxygen-driven nebulisers are the preferred method of delivery. The absence of supplemental oxygen should not prevent nebulised therapy from being administered.<sup>67</sup>

One regimen which incorporates these features is the administration of 2.5 mg salbutamol via nebulisation every 20 min for 1 h (or 400  $\mu$ g salbutamol by metered dose inhaler with spacer) as the initial bronchodilator treatment for severe asthma, with the frequency of further administration and the use of ipratropium bromide and/or intravenous magnesium determined by the response to treatment. In patients with life-threatening asthma, continuous nebulised salbutamol should be undertaken with the co-administration of nebulised ipratropium bromide every 60 min.

### Intravenous bronchodilators

It is with the intravenous administration of bronchodilators that the major changes in management have occurred over the last decade.

- (1) Current evidence does not support the use of intravenous  $\beta$ -agonists in patients with severe asthma as its use does not result in greater benefit than repeat nebulised  $\beta$ -agonist.<sup>68–70</sup> The role of intravenous  $\beta$ -agonist in addition to nebulised  $\beta$ -agonist has not been adequately studied, nor has its role in ventilated patients. As a result, its use should be restricted to patients with refractory life-threatening asthma as an adjunct to conventional intensive treatment. The recommended dose of salbutamol when administered by intravenous dose infusion is 200  $\mu$ g over 10 min, followed by an infusion of 0.1–0.2  $\mu$ g/kg/min with the rate of the infusion adjusted according to the therapeutic response.
- (2) Adding intravenous theophylline to repeated administration of  $\beta$ -agonist via a nebuliser does not increase the efficacy but does increase the risk of side effects.<sup>71</sup> No subgroups in which aminophylline might be more effective have been identified. As with the use of intravenous  $\beta$ -agonists, its use should be restricted to patients with refractory life-threatening asthma as an adjunct to conventional intensive treatment. Intravenous aminophylline is given in a dose of 6 mg/kg over 30 min, then infused in the dose range 0.5–0.9 mg/kg/h. A loading dose should not

be given to patients who are already receiving oral theophylline. The maintenance infusion rate is altered according to plasma theophylline levels, which should be measured within 24 h. For the continuous infusion, lower doses may be required in patients with liver disease or cardiac failure and those taking cimetidine, ciprofloxacin or erythromycin. Higher doses may be required in smokers.

- (3) The use of intravenous magnesium can now be recommended in patients with life-threatening attacks.<sup>72</sup> Its use leads to an improvement in lung function and a reduction in hospital admissions in those who respond poorly to initial treatment, but not those with less severe asthma responding to initial treatment. Currently, the evidence relates to a single dose (2 g MgSO<sub>4</sub> diluted in 50 ml 0.9% normal saline administered over 30 min) and the efficacy of a continuous infusion or repeated dose has yet to be determined. As a result of these studies, if an intravenous bronchodilator is to be administered, current evidence favours the use of intravenous magnesium rather than intravenous  $\beta$ -agonist or aminophylline.

### Systemic corticosteroids

Systemic corticosteroids administered on presentation to the emergency department markedly reduce the need for hospital admission in patients with severe asthma.<sup>73</sup> The benefits are greatest in patients with life-threatening asthma and those not currently receiving steroids. Significant benefit with systemic steroid therapy is observed within 4 h of administration.

The major issue that has been clarified over recent years is the optimal dose and route of administration. It has been shown that there is no benefit in using very high intravenous doses in severe asthmatics needing hospital admission.<sup>74</sup> In this meta-analysis, no additional benefit was observed with doses of >50 mg prednisolone or 200 mg hydrocortisone per day. In terms of lower doses, the most informative double-blind randomised study has shown that intravenous hydrocortisone 50 mg four times a day for two days, followed by prednisone 20 mg daily, is as effective in resolving acute severe asthma as either hydrocortisone 200 mg or 500 mg four times daily followed by prednisone 40 or 60 mg daily, respectively.<sup>75</sup> These findings apply to the situation of life-threatening asthma, as the presentation FEV<sub>1</sub> was 19% predicted and similar efficacy between the three treatment groups was observed in the subgroup whose FEV<sub>1</sub> after initial bronchodilator treatment remained <30% predicted.

Several studies have shown a similar efficacy with oral and intravenous steroids in severe asthma, suggesting that intravenous treatment is often unnecessary.<sup>76–77</sup> This is because of the rapid absorption of prednisolone and its high bioavailability. When the added costs and potential minor complications of intravenous treatment are considered, these results support the initial use of oral steroids, except in patients who are vomiting or too breathless to swallow or in those in whom an intravenous line is already in place or is required. Thus, initial treatment with intravenous hydrocortisone 100 mg stat and/or 30–60 mg prednisone is likely to be adequate with subsequent treatment determined by the response.

### Inhaled corticosteroids

One issue that has not been resolved is the role of high-dose inhaled corticosteroids as an adjunct to—or in place of—systemic corticosteroids in asthma.<sup>78</sup> It has been shown that a 2 week course of high-dose inhaled corticosteroid (eg, fluticasone 2000  $\mu$ g/day) may be as effective as a course of oral steroids (prednisolone starting at 40 mg and reducing by 5 mg every other day) in the treatment of mild to moderate

exacerbations not requiring hospital admission (presentation PEF >60%).<sup>79</sup>

However, it has recently been reported that, in adults with severe asthma, the use of repeated high doses of inhaled corticosteroids (fluticasone propionate 3000 µg/h administered by metered dose inhaler and spacer for 3 h) was more effective than intravenous hydrocortisone (500 mg).<sup>80</sup> This therapeutic benefit was evident within 90 min of presentation at the emergency department and was particularly marked in those patients with more severe airways obstruction in which there was a significant reduction in hospitalisation rate. It was proposed that the beneficial effect may be related to vasoconstriction and possibly mucosal decongestion rather than modulation of gene expression because of the time course of the benefit.

It has yet to be determined whether inhaled corticosteroid treatment provides additional benefit when used in combination with standard systemic steroids for severe asthma. However, it may be worthwhile following a pragmatic approach of administering high-dose inhaled corticosteroids in addition to systemic steroids in patients with life-threatening asthma who respond poorly to conventional treatment.

## RESPONSE TO TREATMENT

The response to treatment determines both the further treatment requirements and the need for hospital admission.<sup>38–81</sup> Assessment of the response is based on repeat clinical examination, lung function tests and oximetry. Of these, the magnitude of improvements in FEV<sub>1</sub> and absolute FEV<sub>1</sub> values following bronchodilator treatment are the best indicators of requirement for admission and likely relapse at discharge. The initial FEV<sub>1</sub>, clinical signs or laboratory parameters such as arterial blood gas measurements are less reliable as predictive indices than post-bronchodilator FEV<sub>1</sub>. In part this is because small improvements in the degree of airflow obstruction in severe asthma may produce substantial changes in clinical signs and symptoms, with dyspnoea normally resolving once the FEV<sub>1</sub> reaches only 50% of the predicted normal value.<sup>37</sup> As a result, severity may be best measured as the response in lung function to high-dose inhaled bronchodilator therapy rather than in terms of the patient's initial presentation.

## ICU TRANSFER

Patients with features of potentially life-threatening asthma who are not responding to treatment, or those with features suggesting that they are at imminent risk of death, should be admitted to an ICU or HDU if adequate facilities are available (table 4). Transfer to such units will ensure that these patients are intensively monitored and can be ventilated without delay should the need arise. Early referral, before the need for ventilation arises, usually makes the process easier. The intensive care management of life-threatening asthma including invasive ventilation is beyond the scope of this review, but it has been reviewed elsewhere.<sup>82–83</sup>

## WARD ADMISSION

If repeated bronchodilator treatment does not increase the FEV<sub>1</sub> to >50–60% predicted, or if clinical features of severe asthma persist, admission is recommended. Patients may also require admission if, despite achieving an FEV<sub>1</sub> >60%, there are other concerns, as outlined in table 6.<sup>3</sup> Depending on resources, admission to a respiratory ward is preferable as this is likely to lead to a higher standard of care and better outcome than admission to a general medical ward.<sup>84</sup>

A doctor and/or nurse should remain with the patient after initial treatment has started, or at least until clear improvement is seen. The patient should be assessed regularly, with

**Table 6** Criteria for admission

Patients with any feature of a life-threatening or near fatal attack
Patients with any feature of a severe attack persisting after initial treatment
Patients in whom other considerations suggest admission may be appropriate:
Still have significant symptoms
Concerns about compliance
Living alone/socially isolated
Psychological problems
Physical disability or learning difficulties
Previous near fatal or brittle asthma
Exacerbation despite adequate dose steroid tablets pre-presentation
Presentation at night
Pregnancy

Modified from the British Guideline on the Management of Asthma.<sup>3</sup>

measurement of lung function and heart rate. The frequency of these measurements will be dictated by the response—at least every 15 min initially. Once improvement has occurred, a suitable regimen would be to monitor these measurements before and after bronchodilator treatment. Patients who are stable can be transferred to a medical ward where oxygen can be continued if hypoxic and nebulised β-agonists given every 2–4 h. There is no major advantage in continuing inhaled ipratropium bromide treatment beyond the initial 12–24 h period.<sup>85</sup>

Oral steroids should be continued throughout the admission. A single morning dose of steroid may not adequately protect the circadian narrowing of the airways experienced at night. The peak effect of oral steroids occurs at around 9 h and then declines and, as a result, may not provide sufficient effect throughout the 24 h dosing interval.<sup>86</sup> The clinical significance of this time course of effect is suggested by a small study in which a small dose of prednisolone given at 15:00 hours was shown to be more effective in protecting against nocturnal bronchoconstriction than an 08:00 or 20:00 hours dosing regime.<sup>87</sup> To overcome this problem, the preferred dosing regime in hospital is twice daily, in contrast to the once morning regime routinely used as an outpatient. As discussed, the effective daily dose of oral prednisolone is between 30 and 50 mg.<sup>88</sup>

On average, it takes 7–10 days for symptoms and lung function to stabilise after an asthma exacerbation and, for this reason, a 10–14 day course is usually recommended. Unless the patient is on maintenance oral steroids, tapering the dose at the end of the course is unnecessary. Studies comparing abrupt cessation with a tapering regime found no difference in lung function or relapse rate between the two groups.<sup>89–90</sup> Suppression of the hypothalamic pituitary axis is not clinically significant after a short course in a patient who is not on maintenance steroids.

Treatment with inhaled corticosteroids should be continued throughout the admission as there is evidence that it may have efficacy in this situation<sup>79–80</sup> and to reinforce the importance of this long-term treatment to patients.

The prescription of sedatives has been associated with sudden death due to their effect in reducing respiratory drive and alertness, and they are therefore contraindicated outside the ICU.<sup>13–14</sup> Percussive physiotherapy is likely to distress a severely ill asthmatic patient and is contraindicated in the initial stages, although relaxation techniques to achieve control over the rate, depth and pattern of breathing may be helpful in the recovery phase.

### Asthma assessment sheet

To be placed in the accident and emergency department notes and a copy in the patient's hospital records.  
If discharged, copies to be given to patient and sent to GP

Name		Date	
Hospital number		Time of arrival	
Name of GP			

Asthma history:		Usual medications:	
Duration of current attack		Beta agonist	
Beta agonist use, last 24 h	.....times	Inhaled steroid	
Previous ICU admission	Yes    No	Other	
Number of hospital admissions in last 12 months			

Lung function:	Initial oximetry:	Blood gases: (if indicated)
Predicted FEV <sub>1</sub> :	Saturation (%):	pH:
Predicted VC:	O <sub>2</sub> therapy (l/min):	PaCO <sub>2</sub> :
		PaO <sub>2</sub> :

Progress report:

Data	Initial assessment	Post-nebuliser (1)	Post-nebuliser (2)	Final assessment
Time				
Difficulty talking				
Respiratory rate				
Pulse rate				
FEV <sub>1</sub> litres	L	L	L	L
% Pred	%	%	%	%
O <sub>2</sub> Sats	%	%	%	%
O <sub>2</sub> Therapy	L/min	L/min	L/min	L/min
Treatment given				

Outcome:		Discharge medications:	
Admitted	Ward	Bronchodilator	
Discharged		Inhaled steroid	
Date to see GP		Oral prednisone	
Predicted PEF		Inhaler technique	
Pre-discharge PEF			
Urgent medical help to be sought if PEF<		Name of doctor: _____	
Self-management plan		Signature: _____	

**Figure 1** Asthma Assessment Sheet currently in use in the Wellington Hospital Emergency Department, Wellington, New Zealand. FEV<sub>1</sub>, forced expiratory volume in 1 s; ICU, intensive care unit; VC, vital capacity; PaCO<sub>2</sub>, arterial carbon dioxide tension; PaO<sub>2</sub>, arterial oxygen tension; PEF, peak expiratory flow.

Antibiotics should not be routinely prescribed as bacterial infections seldom provoke exacerbations (in contrast to viral respiratory tract infections), and their routine prescription does not influence outcome in exacerbations of asthma.<sup>91</sup> Consideration may need to be given to use of a macrolide if chronic *Mycoplasma* or *Chlamydia pneumoniae* infection are suspected in chronic unstable disease; however, data to support this approach are not yet conclusive.<sup>92</sup>

It is difficult to determine the optimal duration of hospital stay for an admission for severe asthma. Because of the

widespread under-resourcing of medical inpatient beds, there is often considerable management pressure to discharge patients early. However, in the case of asthma, this approach is not without risk, not least because there is an increased risk of early relapse and readmission in the two to three months after admission.<sup>93</sup> Perhaps the best predictor of outcome is the PEF variability in the 24 h before discharge, for which it has been shown that a diurnal variation in PEF of >20% is associated with an increased risk of further severe attacks requiring repeat hospital admission.<sup>94</sup>

(A): The asthma management protocol currently in use in the Wellington Hospital Emergency Department

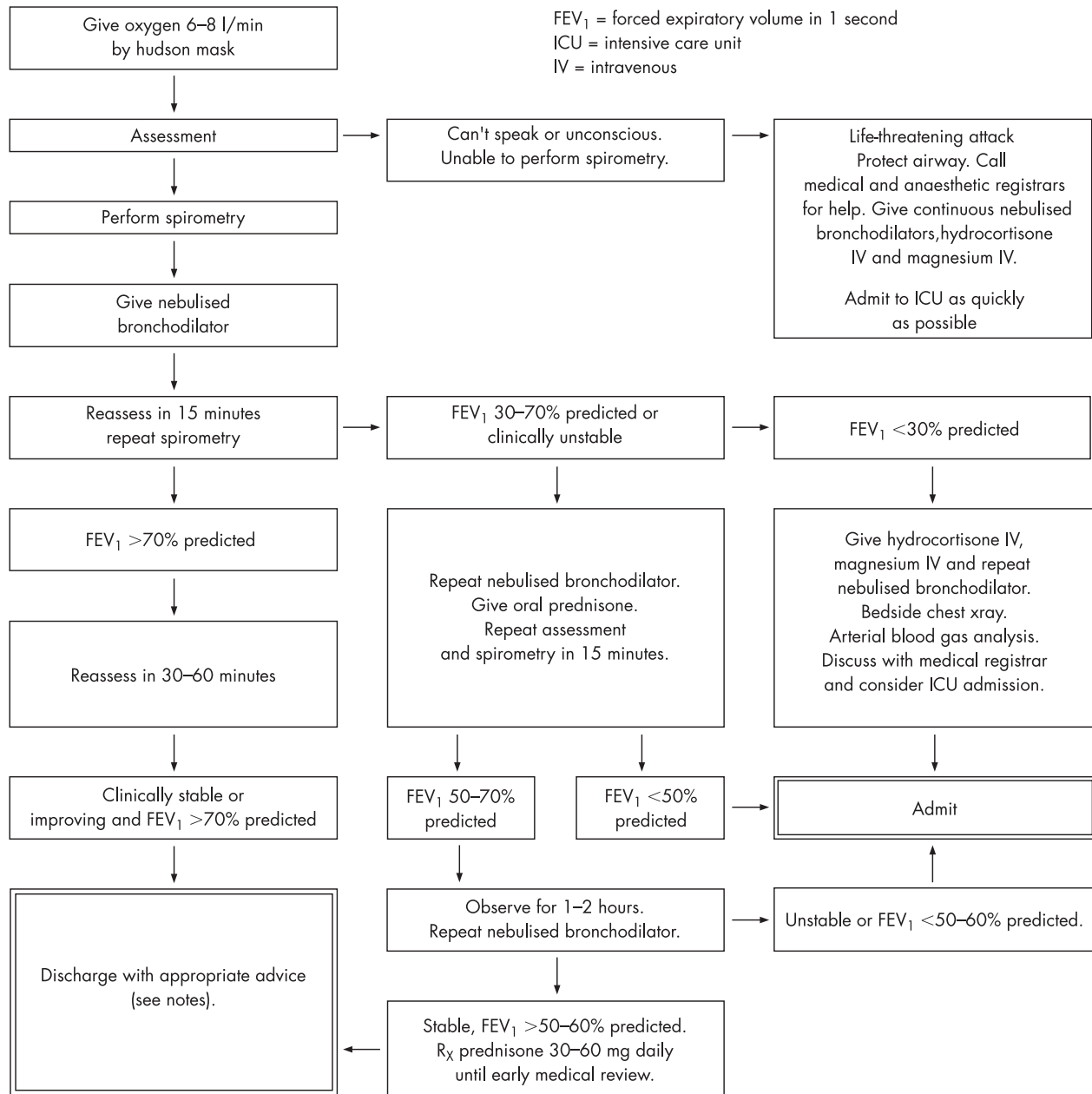


Figure 2 (A) Asthma management protocol and (B) Information Sheet currently in use in the Wellington Hospital Emergency Department, Wellington, New Zealand.

One approach which facilitates early discharge is the use of nebulised  $\beta$ -agonist treatment according to an “as required” regime rather than a regular 4-hourly regime from 24 h after hospital admission.<sup>95</sup> Implementation of this “as required” regime has similar efficacy but results in an average reduction in the length of hospital stay of about 1 day. This outcome is achieved with about half the total dose of  $\beta$ -agonist administered, a reduced incidence of side effects and a strong patient preference for this regime. At least 24 h before scheduled discharge, the patient should be changed from nebulised to their routine aerosol or dry powdered metered dose inhaler to

ensure that clinical stability is maintained on this lower dose of  $\beta$ -agonist.

As improvement is achieved, the emphasis shifts to investigation of the causes and circumstances of the severe attack, and arrangements are made for management following discharge, long term treatment, the institution of a self-management plan and appropriate follow-up arrangements.

**DISCHARGE ARRANGEMENTS**

Whether the discharge occurs from the emergency department or hospital ward, it is crucial that doctors address the problems



**(B): Guidelines for the initial management of asthma in adults**

(notes to accompany management protocol)

## Treatment

## 1. Nebulised bronchodilators

Salbutamol (ventolin) 2.5 mg nebulised, using oxygen at 6–8 l/min, until finished.

If there is a poor response to initial nebulised treatment, salbutamol can be administered either continuously, or 2.5 mg every 20 min with the addition of ipratropium bromide up to 0.5 mg hourly.

## 2. Corticosteroid therapy

- a. Hydrocortisone 100 mg intravenous stat, and/or
- b. Prednisone 30–60 mg orally stat.

## 3. Parenteral magnesium therapy

Magnesium sulphate (IV infusion 1.2–2 g MgSO<sub>4</sub> in 100 mls N/saline over 20 mins)

## Pre-discharge considerations

1. Before discharge, consider whether the patient needs
  - a course of oral prednisone, 30–60 mg daily, until early medical review
  - to start or increase the dose of inhaled corticosteroid
  - specialist referral, if high-risk asthmatic
2. Before discharge, ensure that the patient
  - can use their inhalers correctly patiently and has a supply of their medications
  - has been advised to make an early follow-up appointment with their GP
  - has a peak flow meter and knows at what level to contact emergency medical help
  - has a copy of the assessment sheet
  - has an asthma self-management plan in place

## Note:

These are guidelines only and may not suit all patients. If there is any doubt about a particular patient, discuss with the ED consultant or medical registrar. Admit any patient who is unstable regardless of the FEV<sub>1</sub>.

that may have led to the hospital admission. Patients admitted to hospital with asthma and those who make frequent attendances at the emergency department are recognised as a particularly high-risk group of patients who have poor self-management skills and often have inadequate medical follow-up in the community. For this reason, doctors should ensure that patients are prescribed regular inhaled corticosteroids and that their inhaler technique is checked before discharge. It is also worthwhile to provide simple advice on what to do if their asthma worsens again. This can be achieved by giving patients a peak flow meter with instructions concerning the level at which to seek medical care either from their GP or, if necessary, the emergency department. Doctors are also encouraged to prescribe a course of oral steroids, based on the evidence that in this situation it greatly improves outcome with a fourfold reduction in relapse rate in the following week.<sup>96</sup> This recent systematic review reported that about 15 patients need to be treated to prevent relapse requiring medical care after discharge from the emergency department with an exacerbation of asthma.<sup>96</sup>

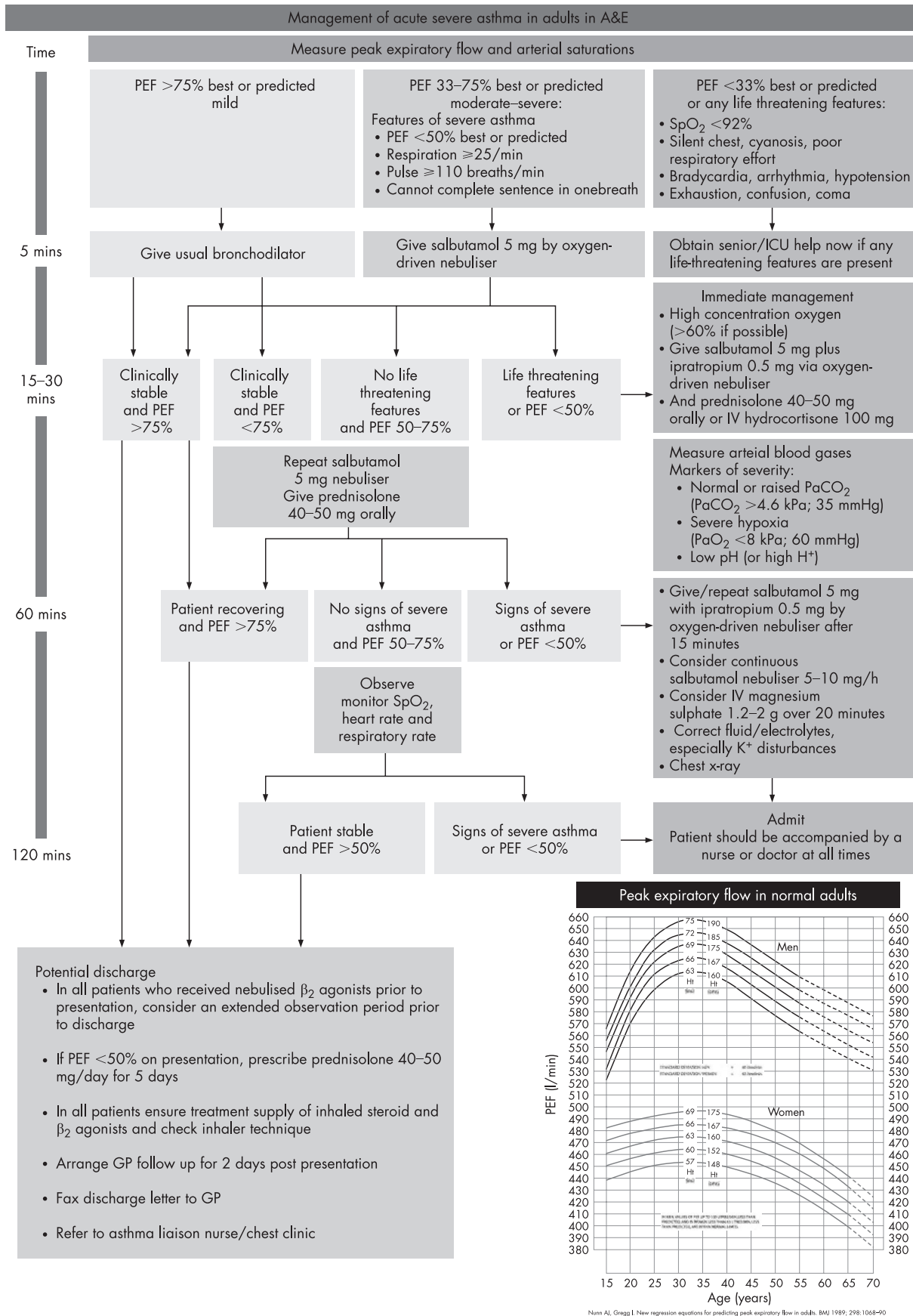
Written communication with the GP via letter or email concerning the details of the ED attendance and/or hospital admission is essential to help address the problem of discontinuity of care. Alternatively, it may be advisable to phone if there is a delay in letters being typed and sent out, due to the high rate of relapse in the first week following discharge. Arrangements need to be made for medical follow-up both with the GP and with the respiratory specialist in the case of life-threatening asthma. An open access self-admission service

should be considered in patients who have experienced a life-threatening or precipitate attack. The advantages of such a service, which may require prior arrangement with the ambulance service, have been shown.<sup>97</sup>

**ASSESSMENT SHEETS AND TREATMENT PROTOCOLS**

One approach which has been used to facilitate clinical practice in accordance with guidelines is the implementation of assessment sheets and treatment protocols.<sup>98–103</sup> When used in the emergency department, they have been shown to identify rapidly individuals at risk of an adverse outcome, ensure a high standard of management, facilitate the appropriate referral to respiratory wards and medical ICU and improve outcomes such as length of stay and number of subsequent return visits. Treatment protocols are traditionally limited to algorithm-based flow charts, but the addition of an assessment sheet facilitates their implementation. This is particularly the case with severe asthma in which management is determined by asthma severity and in which doctors seem to have major difficulties in following this approach.

A guideline-based asthma assessment and associated treatment algorithm is shown in figs 1 and 2. The assessment sheet is designed to encourage a quick focused history to identify baseline and acute risk, an objective assessment of asthma severity, and repeat clinical examination and measures of FEV<sub>1</sub>. The response to treatment can thus be assessed and a decision made on whether the patient requires admission or can be discharged. In this case, a structured approach is provided to address issues relating to long-term care and advice on when



**Figure 3** Management of acute severe asthma in adults in A&E (reproduced from the British Guideline on the Management of Asthma).<sup>3</sup>

## Key points

- The management of asthma in the emergency department can be improved through the use of simple assessment and treatment protocols.
- Assessment of asthma severity should be based primarily on the measurement of FEV<sub>1</sub>, expressed as the percentage of normal predicted values.
- For most patients, initial treatment with high-flow oxygen, nebulised  $\beta$ -agonist and oral corticosteroids is sufficient.
- Currently available evidence does not support the routine use of intravenous theophylline or intravenous  $\beta$ -agonist treatment in acute asthma; magnesium is the preferred intravenous bronchodilator in life-threatening asthma.
- Patients with any feature of a severe attack persisting after initial treatment should be admitted; patient circumstances should also be considered.
- For patients who are discharged, long-term management should be reviewed and medical follow-up arranged.

the patient should present again if their asthma deteriorates further.

The algorithm recommended in the British guidelines, based on peak flow, is shown in fig 3. Modification of the current protocols and assessment sheets for use in general practice is encouraged, where similar problems in the assessment and management of severe asthma may also be encountered.<sup>104</sup>

## CONCLUSIONS

It is difficult to understand why there is such a huge discrepancy between the management of severe asthma recommended by evidence-based guidelines and that observed in clinical practice. The recommendations are relatively straightforward and have been widely promoted both in guidelines<sup>1-3</sup> and reviews.<sup>18 22 26 105</sup> It is likely that the problems are related in part to the inexperience of the junior medical staff who are commonly delegated responsibility for the hospital care of patients with severe asthma, and to inadequate senior medical supervision. Specialist physicians need to be more proactive in their implementation of such guidelines through the use of locally derived protocols and assessment sheets, reinforced by audit.

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