Management of life-threatening asthma in adults

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Asthma is a disease of predominantly reversible airway obstruction characterized by a triad of bronchial smooth muscle contraction, airway inflammation, and increased secretions; it is a major health problem for all age groups. For the majority, control of asthma symptoms is readily achieved; however, in a small minority, asthma may cause death. Although the mortality rate for asthma in those aged less than 65 yrs is now falling, there remain around 1400 asthma deaths in the UK each year (http://www.laia.ac.uk/kf_asthma_03.htm). Most of these occur in the pre-hospital setting and, in retrospect, the majority is considered potentially preventable. Factors associated with asthma death include disease severity, inadequate treatment, inadequate monitoring, the under use of written asthma management plans and adverse psychosocial and behavioural factors (www.sign.ac.uk/guidelines/fulltext/63/index.html).

Levels of severity of acute asthma exacerbations have been defined. The features of acute severe, life–threatening, and near fatal asthma are listed in Table 1. Of note, patients with life-threatening asthma may not appear distressed and might only display one of the features listed. Life-threatening asthma tends to occur as two sub-types.[1] Most commonly, there is a history of progressive worsening of symptoms over several days; the majority of patients in this group report nocturnal dyspnoea in the previous three nights. As a result of greater bronchial inflammation and mucous secretion, this group (occurring more frequently in females) tends to respond more slowly to treatment. In contrast, a smaller sub-group, more frequently male, presents with a rapidly progressive condition with highly reactive airways. These patients have intense bronchospasm that often responds more rapidly to bronchodilator therapy.

In February 2003, The British Thoracic Society together with the Scottish Intercollegiate Guidelines Network published guidelines on the management of asthma (http://www.brit-thoracic.org.uk/asthma-guideline-download.html). They were updated in November 2007. In common with other recommendations, these give guidance only up to the commencement of intensive care. Evidence for therapies in intensive care from randomized controlled trials remains sparse. Ongoing management of life-threatening episodes (Fig. 1) is often difficult with rapid and dynamic changes in physiology. Complications of treatment are frequent.

Pathophysiology

The pathophysiological feature of life-threatening asthma is gas trapping with dynamic hyperinflation and the generation of intrinsic positive end-expiratory pressure (PEEPi). This arises due to disproportionate increases in resistance to expiratory gas flow, rapid respiratory rates, changes in pulmonary elastic recoil, and asynchronous respiratory muscle activity. The consequences include impaired gas exchange, increased work of breathing with respiratory muscle fatigue, and increased risk of barotrauma. Hyperinflation may be so severe that lung volumes approach total lung capacity. Diaphragmatic flattening at such volumes reduces the efficiency of ventilation as inspiration becomes primarily by intercostal muscles rather than the diaphragm. Together, these factors reduce CO_2 elimination while increasing production. At a point, production will match and then exceed rate of elimination progressing to respiratory failure when there is inadequate alveolar ventilation. In addition, airway closure causes mismatches in ventilation-perfusion leading to hypoxaemia.

Large negative intrathoracic pressures generated by the augmented inspiratory effort, as well as PEEPi through its effects on right atrial filling, can impede cardiac output. Dehydration

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Table 1 Features of acute severe asthma

Near fatal asthma	Raised Pa_{CO_2} and/or requiring mechanical ventilation with raised inflation pressures
Life-threatening asthma	Any one of the following in a patient with severe asthma:
	PEF <33% best or predicted
	$Sp_{O_2} < 92\%$
	$Pa_{O_2} < 8$ kPa
	Normal Pa_{CO_2} (4.6–6.0 kPa)
	Silent chest
	Cyanosis
	Feeble respiratory effort
	Bradycardia
	Dysrrhythmia
	Hypotension
	Exhaustion
	Confusion
	Coma
Acute severe asthma	Any one of:
	PEF 33–50% best or predicted
	Respiratory rate ≥ 25 min^{-1}
	Heart rate ≥ 110 min^{-1}
	Inability to complete sentences in one breath

from reduced intake and increased respiratory losses, along with the development of hypoxaemia, hypokalaemia, and acidosis may further exacerbate this.

Management of life-threatening asthma

Initial management

A rapid ABC assessment should be undertaken and actioned. Many patients will be hypoxaemic, hypovolaemic, acidotic, and hypokalaemic.

Oxygen

Patients with acute severe asthma are hypoxaemic. This should be corrected urgently with high concentrations of inspired oxygen aiming to achieve oxygen saturations >92%. A Fi_{O_2} of 0.4–0.6 is often sufficient but, in general, start high and then titrate the Fi_{O_2} down. It is important to note that asphyxia remains the most common mechanism of death in severe asthma and should never be underestimated.

Nebulized β₂ agonists

Short-acting β₂-agonists (e.g. salbutamol) should be given repeatedly in 5 mg doses or by continuous nebulization at 10 mg h^{-1} driven by oxygen. Importantly, duration of activity and effectiveness are inversely related to severity of asthma; continuous administration is more efficacious in severe asthma. However, even under ideal circumstances only 10% of the nebulized drug will reach the bronchioles.[2] Administration should continue until there is a significant clinical response or serious side effects occur, these include tachycardia, arrhythmias, tremor, hypokalaemia, and hyperglycaemia. Inhaled longer acting β₂-agonists have no role in

IMMEDIATE TREATMENT

• Oxygen 40–60% (CO_2 retention is not usually aggravated by oxygen therapy in asthma)
• Salbutamol 5 mg or terbutaline 10 mg via an oxygen-driven nebulizer
• Ipratropium bromide 0.5 mg via an oxygen–driven nebulizer
• 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 is 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 min (unless already given)
• Give nebulized β₂ agonist more frequently, e.g. salbutamol 5 mg up to every 15–30 min or 10 mg continuously hourly

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SUBSEQUENT MANAGEMENT

IF PATIENT NOT IMPROVING AFTER 15–30 MIN:

• Continue oxygen and steroids
• Give nebulized β₂ agonist more frequently, e.g. salbutamol 5 mg up to every 15–30 min 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 min (unless already given)
• Senior clinician may consider use of IV β₂ agonist or IV aminophylline or progression to IPPV

Transfer to ICU accompanied by a doctor prepared to intubate if:
• Deteriorating PEF, worsening or persisting hypoxaemia or hypercapnia
• Exhaustion, feeble respirations, confusion or drowsiness
• Coma or respiratory arrest

Fig. 1 Management of acute severe asthma in adults.

management of acute severe asthma and may increase mortality in this setting.

Nebulized ipratropium bromide

This should be added to nebulized β₂ agonists treatment for all patients with life-threatening asthma (500 μg 4 hourly) as it has been shown to produce significantly greater bronchodilation than β₂ agonists alone. Side effects are minimal.

Steroids

Systemic steroids in adequate doses should be given to all patients with life-threatening asthma, as early as possible in the episode as this may improve survival. Steroid tablets (prednisolone 40–50 mg daily) have been shown to be as efficacious as intravenous steroids in acute severe asthma, provided tablets can be swallowed and retained. If in any doubt, the intravenous route should be used (hydrocortisone 200 mg stat followed by 100 mg 6 hourly). Inhaled/nebulized steroids do not provide additional benefit.

Intravenous magnesium sulphate

A single intravenous dose of magnesium sulphate 1.2–2 g over 20 min has been shown to be safe and effective in acute severe asthma. Magnesium is a smooth muscle relaxant, producing bronchodilation. Rapid administration may be associated with hypotension. Anecdotal evidence suggests repeated doses or infusions may be of benefit (dose limited by twice normal serum

magnesium concentrations); however, hypermagnesaemia is associated with muscle weakness and may exacerbate respiratory failure in spontaneously breathing patients.

Intravenous bronchodilators

Parenteral β_2 agonists, in addition to nebulized β_2 agonists, should be considered in ventilated patients and those with life-threatening asthma; intravenous salbutamol ($5-20~\mu g~min^{-1}$) or terbutaline ($0.05~\mu g~kg^{-1}~min^{-1}$) should be titrated to response. Lactic acidosis will develop in 70% of patients after $2-4$ h therapy, requiring careful monitoring with subsequent reduction or cessation of therapy. In extremis, salbutamol $100-300~\mu g$ can be given as an intravenous bolus or via an endotracheal tube.

An additional or alternative intravenous bronchodilator is aminophylline. Some patients with life-threatening asthma gain benefit from its intravenous use ($5~mg~kg^{-1}$ loading dose over 20 min unless on maintenance oral therapy, then infusion of $0.5-0.75~mg~kg^{-1}~min^{-1}$). Concern and controversy about its use arises from its side effects (arrhythmias, restlessness, vomiting, and convulsions) related to a narrow therapeutic window. Trials showing little overall benefit in lesser degrees of asthma may not be relevant when faced with impending asphyxia. Plasma aminophylline concentrations should be monitored frequently (therapeutic range $10-20~\mu g~ml^{-1}$).

Epinephrine

The additional use of epinephrine (adrenaline) should be considered in patients not responding adequately to the measures outlined above via the subcutaneous ($0.3-0.4$ ml 1:1000 every 20 min for three doses), nebulized ($2-4$ ml of 1% solution hourly) or, in extremis, the intravenous route ($0.2-1$ mg as a bolus followed by $1-20~\mu g~min^{-1}$).

Mechanical ventilation

Who should be intubated, and when and how should mechanical ventilation be initiated?

The initiation of invasive ventilation in life-threatening asthma is a bedside clinical decision based on an assessment of the balance of risks and benefits. It can be life saving, but has a higher incidence of complications relative to other causes of respiratory failure. Absolute indications are coma, respiratory or cardiac arrest and severe refractory hypoxaemia. Relative indications include an adverse trajectory of response to initial management, fatigue and somnolence, cardiovascular compromise, and the development of a pneumothorax. Prior to initiation, vigilant observation is mandatory as fatal apnoea can occur suddenly and unexpectedly.[3] Hypercapnia *per se* is not an indication for mechanical ventilation.

In life-threatening asthma, the induction of anaesthesia, tracheal intubation, and initial ventilation are all extremely hazardous as dramatic changes in physiology occur with the induction of anaesthesia, and with the switch from high intrinsically produced negative intrathoracic pressures to high positive pressures from extrinsic ventilation. Half of the life-threatening complications occur at or around the time of intubation in patients mechanically ventilated for asthma; consequently, intubation should be performed by the most senior and experienced member of anaesthetic staff available with the help of appropriately trained assistance. Where possible, pre-oxygenation should be performed diligently followed by a rapid sequence induction. Hypotension at the initiation of ventilation should be anticipated and attenuated by fluid pre-loading. Vasopressors should be immediately available for use post-induction. Hypotension can be severe enough to result in complete loss of cardiac output or mimic that occurring with a tension pneumothorax. Causes of hypotension are multifactorial, including vasodilatation and reduction in sympathetic tone on induction, absolute hypovolaemia and reduction in venous return consequent to high intrathoracic pressures precipitated by ventilating against high airway resistance. Initial hand ventilation is often over-enthusiastic and contributory; it should follow the principles outlined for the mechanical ventilation below and be kept to a minimum; rate should be kept low and no PEEP should be applied. If profound hypotension does occur when assisted ventilation has been initiated, consideration should be given to disconnecting the patient from the circuit (possibly with the addition of pressure on the chest wall to assist expiratory flow) to allow full passive expiration A chest x-ray should be performed following intubation when it is safe to do so, to assess correct positioning of the endotracheal tube and exclude pneumothoraces.

What are the initial goals of mechanical ventilation and how are they achieved?

The initial goals of mechanical ventilation are to correct hypoxaemia, reduce dynamic hyperinflation and to buy time for medical management to work.

Adequate sedation is vital and typically would be morphine and midazolam with ketamine. Morphine has a potential for histamine release so is avoided by some. Propofol and fentanyl, and ketamine plus midazolam alone are alternatives. The attraction of ketamine ($0.5-2~mg~kg^{-1}~h^{-1}$) is its action as a direct bronchodilator. Evidence of benefit is equivocal; use maybe limited by its effects on respiratory tract secretions and its sympathomimetic properties in a patient already in a heightened sympathetic state.

Initial neuromuscular blockade is often required. Rocuronium or pancuronium is the agents of choice. Atracurium is associated with histamine release. Some concern has been raised over the relative likelihood of developing a neuromyopathy with vecuronium in this setting (high-dose steroids, mechanical ventilation, and severe asthma), though the evidence is limited. The use of neuromuscular blockade should be discontinued as soon as possible.

Initial ventilator settings should adopt relatively low rates ($12-14$ breaths min^{-1}), tidal volumes of $4-8$ ml kg^{-1}, Fi_{O_2} sufficient to maintain adequate oxygen saturations ($>92\%$), relatively long-expiratory times (I:E 1:4) and little or no PEEP (<5 cm H_2O). If using volume controlled ventilation, appropriate goals would be to achieve a $P_{plat} <35$ cm H_2O with pH > 7.2. If $P_{plat} > 35$ cm H_2O,

minute ventilation should be reduced (V_t and/or rate), if pH < 7.2 and P_{plat} < 30 cm H_2O, minute ventilation should be increased (rate), if pH < 7.2 and P_{plat} > 35 cm H_2O no change may be appropriate. This guidance principally derives from Tuxen and Lane's[7] observations of volume controlled ventilation in asthma, namely that minute ventilation is the most important determinant of hyperinflation (inspiratory flow and shape of pressure wave-form being of much lesser importance), and that while increased-expiratory times are beneficial, the effect of increases above 3–4 s are minimal. In addition, the role of PEEPe to counter PEEPi in controlled mechanical ventilation has no rationale, although recently potentially beneficial effects of PEEPe have been reported in 'obstructive lung disease' (as opposed to asthma) suggesting that a trial of variable PEEPe may be required in some cases.[5]

Achieving the goals of a pH > 7.2 with a P_{plat} < 35 cm H_2O will often not be possible and requires ongoing clinical assessment. High airway pressures should prompt the exclusion of endobronchial intubation and pneumothorax, along with the re-evaluation of the adequacy of sedation.

Plateau airway and end-expiratory pressures generally reflect the degree of gas trapping in severe asthma; in addition, total exhaled volume during an apnoea for 20–60s gives a measure of the degree of hyperinflation.[6] Not all airways remain patent throughout expiration, any measurement will tend to be an underestimate and clinical assessment remains vital. Of note, barotrauma in the mechanically ventilated asthmatic including the risk of pneumothorax is proportional to end inspiratory lung volume.

Additional complications of mechanical ventilation in life-threatening asthma include profound hypotension, cardiac stunning, arrhythmia, rhabdomyolysis, lactic acidosis, myopathy, and CNS injury. Cardiac stunning is thought to be consequent to massive sympathetic activation, arrhythmias generally tend to be benign, rhabdomyolysis is rare and is thought to stem from hypoxaemia in combination with extreme exertion; lactic acidosis in severe asthma is poorly understood.

Management of hypercarbia

Permissive hypercapnia is a well-proven protective lung strategy for limiting the deleterious effects of barotrauma in many causes of respiratory failure. During the mechanical ventilation for life-threatening asthma, our ability to correct hypercapnia is generally limited and fraught with hazards. Although calling it 'permissive' might be a misnomer, hypercapnia is generally well tolerated, and there are numerous case reports in the literature of asthmatic patients with profound respiratory acidosis of several hours duration with no significant adverse effects. The exception is in those with cerebral anoxia secondary to a respiratory arrest. Control of intracranial pressure requires management of hypercarbia; urgent consideration should be given to extra corporeal CO_2 removal in these circumstances (see later).

Where respiratory acidosis is extreme and its ventilatory management impossible, buffering can be considered acutely.

Tromethamine (THAM) has some theoretical advantages over bicarbonate. Use with either agent is usually complicated by metabolic alkalosis on resolution of the acute bronchospastic episode. Measures to limit CO_2 production, such as anti-pyretics and/or active cooling, should be considered as adjuncts or alternatives.

Ongoing ventilatory management

The use of neuromuscular blockade and deep sedation should be discontinued as soon as the clinical situation allows and the return to spontaneous ventilation should be achieved as soon as is practical. During this process, patient ventilator interactions become more important and the use of PEEPe and the selection of appropriate trigger sensitivities assume important roles in reducing the work of breathing.

The ventilator care bundle approach should be considered and, if not already involved, advice from a respiratory physician should be sought with a view to planning the patient's ongoing management in hospital and in the community.

Additional management methods

Inhalational anaesthetic agents

Volatile inhalational anaesthetic agents (e.g. isoflurane and sevoflurane) are effective bronchodilators and their use is associated with reductions in PEEPi and Pa_{co_2} within hours. Increased benefit may occur with earlier administration and their use should be considered in patients with life-threatening asthma not responding to standard treatments. Hypotension is their principal side effect. The delivery of volatile anaesthetic agents can be difficult in the intensive care unit setting and may force the use of a lower fidelity ventilator in a sub-optimal environment. In line devices for use with high fidelity ventilators are available, but scavenging and agent monitoring are absolute requirements.

Extra-corporeal support

Case reports of the use of extra-corporeal membrane oxygenation in life-threatening asthma suggest that this may be successful, but its limited availability and the risk profile limit its applicability. In contrast, the development of less complex systems of extra-pulmonary gas exchange that facilitate CO_2 clearance (e.g. Novalung) brings extra-corporeal CO_2 removal (ECCO$_2$R) within bounds. Their use should be considered particularly where the control of hypercarbia is imperative.

Bronchoscopy

Bronchoscopy has a limited role in managing patients with persistent shunt consequent to mucus plugging. Lavage of the obstructed lung segments and the removal of mucus plugs may reduce the duration of ventilation, but is often complicated by bronchospasm. In general, patience and persistence with standard therapies and meticulous attention to the hydration and humidification are as effective.

Antibiotics

The majority of episodes of acute severe asthma that has an infective precipitant follow a viral infection. The routine use of antibiotics in life-threatening asthma has no rationale and they should be considered only in selected cases.

Non-Invasive ventilation

Although there is a sound evidence for the use of non-invasive ventilation (NIV) in acute exacerbations of chronic obstructive lung disease, its use in asthma is controversial. Objective evidence of benefit is very limited; a recent Cochrane review[7] could only find one well-conducted prospective, randomized trial of just 30 patients that showed improvements in the respiratory rates in asthmatics with mild to moderate exacerbations when NIV was added to the standard medical care. Currently, the use of NIV in even mild to moderate exacerbations of asthma cannot be recommended outside the randomized controlled trials. NIV has no role in the management of life-threatening exacerbations of asthma.

Heliox

Heliox (oxygen in helium) reduces the density of the gas mix to improve turbulent gas flow. Use has been reported in less severe acute exacerbations of asthma where, in spontaneously breathing patients, it may reduce the work of breathing. This use is not, however, supported by an evidence base and its utility is further limited by a maximum oxygen fraction of 0.4 making it unsuitable for those with life-threatening asthma. Use of heliox with a mechanical ventilator is complex, requiring the recalibration of the pneumotachographs and the use of density independent spirometry of exhaled gas flows.

Leukotriene antagonists

Currently available leukotriene antagonists (Montelukast, Zafirlukast) have no role in management of life-threatening asthma.

Monoclonal anti-IgE antibodies

Omalizumab is thought to be effective at reducing the number and possibly the severity of acute exacerbations of asthma in adults with moderate to severe allergic asthma that is inadequately controlled by inhaled steroids. It is a preventative measure and has no role in the management of acute life-threatening episodes.

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Please see multiple choice questions 14–17