Management of Life-Threatening Asthma in Adults

Praveen Mannam, MD, MS, and Mark D. Siegel, MD

Abstract
Asthma remains a troubling health problem despite the availability of effective treatment. A small but significant number of asthmatics experience life-threatening attacks culminating in intensive care unit admission. Standard treatment includes high dose systemic corticosteroids and inhaled bronchodilators. Patients with especially severe attacks may develop respiratory failure and need endotracheal intubation and mechanical ventilation. Severe airway obstruction may lead to dynamic hyperinflation and the possibility of hemodynamic collapse and barotrauma. Fortunately, most intubated asthmatics survive if physicians adhere to key management principles intended to avoid or minimize hyperinflation. The purpose of this review is to discuss the pathogenesis of life-threatening asthma and to provide practical guidance to promote rationale, safe, and effective management.

Keywords
dynamic hyperinflation, fatal asthma, near fatal asthma, status asthmaticus, permissive hypercapnia, respiratory failure, mechanical ventilation, corticosteroids, bronchodilators

Received January 23, 2009, and in revised form April 2, 2009. Accepted for publication April 16, 2009.

The best treatment of status asthmaticus is to treat it three days before it occurs.

Thomas L. Petty, MD, Master FCCP

Introduction
Asthma is a disease characterized by airway inflammation and airflow obstruction. Treatment with inhaled steroids and bronchodilators has greatly improved asthma control and decreased morbidity. Nevertheless, death from asthma remains an important and preventable problem. In the last two decades, improved treatment for those requiring mechanical ventilation has radically improved short-term prognosis. This review will describe the epidemiology of life-threatening asthma, characterize its pathology and pathogenesis, and summarize current management principles, emphasizing a safe and effective approach to mechanical ventilation.

Epidemiology
More than 22 million Americans suffer from asthma. Most are treated as outpatients, but a minority experience uncontrolled disease requiring hospital visits. In the United States, acute asthma results in 1-2 million emergency-department (ED) visits annually, 450,000 hospital admissions, and approximately 5000 deaths. In a year-long study of 3372 patients with acute asthma conducted in 37 centers in France, 26% presented with life-threatening asthma and 7% were admitted to the intensive care unit (ICU). In another study done over 10 years at a tertiary hospital, 4% of hospitalized asthma patients were admitted to the ICU.

Patients with prior intubation or ICU admission are at greatest risk for life-threatening asthma. Other risk factors include use of more than 2 canisters of short-acting β agonist per month, difficulty perceiving airway obstruction or worsening asthma, low socioeconomic status, illicit drug use, major psychosocial problems or psychiatric disease, and comorbidities, such as cardiovascular or other chronic lung disease. Inhaled long-acting β agonists prescribed as monotherapy may increase mortality, particularly if used without inhaled corticosteroids. In the United States, Puerto Rican and African American males have a 360% and 200% higher risk respectively of asthma-related death compared to whites and asthma mortality is 45% higher in females than in males.
Precipitants

Common triggers of asthma flares include viral upper respiratory tract infection, nonsteroidal anti-inflammatory drugs in susceptible individuals, exercise, stress, sulfites, and inhalation of crack cocaine or heroin. Respiratory tract infections are among the most common precipitants. In 12% to 56% of ED patients, respiratory tract infections are identified as a trigger. Of hospitalized asthmatics, 37% have evidence of a recent infection, most commonly influenza A or rhinovirus and as many as 59% of hospitalized patients with near fatal asthma had evidence of viral infection, commonly picornavirus and adenovirus.

Two distinct presentations characterize life-threatening asthma exacerbations. The first and most common type presents with several days of worsening symptoms and distress. Pathologically, mucus plugs obstruct the airways and eosinophilic inflammation predominates. Response to therapy is often delayed. The less common subset present with “acute asphyxic asthma,” characterized by worsening dyspnea developing within hours of presentation, often in response to an acute irritant. Disease may be relatively mild at baseline. Pathology may reveal neutrophils and evidence of bronchoconstriction with smooth muscle shortening. Response to therapy is often rapid (Table 1). Because many asthmatics underestimate the duration of their symptoms, it may be difficult to distinguish between these subtypes by history alone.

Pathophysiology

Hyperinflation

Airway obstruction with hyperinflation is the sine qua non of asthma flares. When severe, airway narrowing due to bronchoconstriction, wall edema, and mucus plugging causes expiratory flow limitation; in the setting of insufficient expiratory time, this precludes return to functional residual capacity (FRC) at end-exhalation, resulting in dynamic hyperinflation (DHI). Other contributing factors include postinspiratory respiratory muscle activity, glottic narrowing, and reduced pulmonary elastic recoil. Dynamic hyperinflation has important consequences from both a respiratory and hemodynamic perspective. Distended alveoli can compress the pulmonary capillaries, increasing dead space and making gas exchange less efficient, while airway occlusion leads to severe ventilation/perfusion mismatch. In addition, DHI increases the work of breathing because ventilation occurs along a less compliant portion of the pressure volume curve. At the same time, the diaphragm may flatten, placing it at a mechanically disadvantageous position, reducing force of contraction. The combination of increased work of breathing and inefficient ventilation may precipitate respiratory muscle fatigue and failure if these conditions persist.

Dynamic hyperinflation may cause profound hemodynamic changes. Prominent among these include increased intrathoracic pressure caused by retained air, which leads to decreased venous return, ventricular preload, and stroke volume. As a consequence, this may lead to decreased left ventricular (LV) preload and stroke volume. As a consequence, this may lead to decreased right ventricular (RV) preload and stroke volume. Also during inhalation, large drops in intrathoracic pressure may augment venous return and RV preload. This will tend to shift the interventricular septum toward the LV, further impairing LV diastolic filling and preload. If severe, these factors may contribute to wide systolic blood pressure drops during inhalation, beyond the 10 mm Hg that is normally seen, resulting in pulsus paradoxus.
Clinical Presentation and Assessment of Severity

Initial Assessment

Patients typically present with classic symptoms such as dyspnea, cough, or wheezing of variable duration. For unclear reasons, many patients, particularly those with a history of severe and near fatal asthma, have impaired perception of dyspnea and may underestimate the severity of their attacks. A brief history should be taken concurrent with initial management. It is crucial to identify patients at risk for fatal asthma (Table 2). Directed questions should focus on timing and onset of symptoms, exacerbating factors, medication use, allergies, and a history of prior severe attacks.

Important signs may help identify patients at greatest risk for life-threatening asthma (Table 3). Key signs include tachycardia, tachypnea, anxiety, diaphoresis, and inability to speak in complete sentences or phrases. Accessory muscle use may be prominent. Wheezing may be severe, although the chest may become silent as airflow decreases with the onset of respiratory failure. Depressed mental status is ominous. A search should focus on potential complications such as pneumothorax, pneumomediastinum, and subcutaneous emphysema. It must be stressed that life-threatening asthma may present with highly variable signs and symptoms and may present in the absence of many of these signs.

Differential Diagnosis

In evaluating asthma, it is useful to remember the clinical aphorism “All that wheezes is not asthma.” It is important to consider alternative diagnoses, especially if the presentation is atypical, the patient is older, or if a prior diagnosis of asthma has not been established (Table 4). Potential life-threatening mimics include congestive heart failure, anaphylaxis, upper airway obstruction, and pulmonary embolism. Other considerations include chronic obstructive pulmonary disease (COPD), pneumonia, vocal cord dysfunction, and, as a diagnosis of exclusion, hyperventilation disorder. Upper airway obstruction, particularly vocal cord dysfunction, may become self-evident when there is no evidence of lower airway obstruction after intubation.

Patient Monitoring

To objectively quantify the degree of obstruction and monitor the response to therapy, patients should be monitored by measuring the peak expiratory flow rate (PEFR) or forced expiratory volume in 1 second (FEV1). A PEFR or FEV1 less than 40% of predicted or personal best characterizes severe exacerbation; a value <30% of predicted or personal best is life-threatening. Measurement of pulsus paradoxus may also help identify patients with severe disease. However, pulsus paradoxus may be absent in severe asthma if the patient develops respiratory muscle fatigue and cannot generate sufficiently large intrathoracic pressure swings. Regardless of the severity of initial presentation, patients who do not respond promptly to treatment tend to have a more severe course, requiring admission to the hospital or ICU.

Pulse oximetry should be used to monitor arterial oxygen saturation. In addition, pulse oximetry can be used to measure the severity of airflow obstruction as there is a correlation with the respiratory variation in pulse oximetry baseline.

Table 2. Risk Factors for Asthma-related Death

- Previous severe exacerbation (e.g., intubation or intensive care unit admission for asthma)
- Two or more hospitalizations or >3 emergency visits in the past year
- Heavy use of short acting beta agonist
- Difficulty perceiving airway obstruction or the severity of worsening asthma
- Low socioeconomic status
- Illicit drug use
- Major psychosocial problems or psychiatric disease
- Comorbidities, such as cardiovascular disease or chronic lung disease

Table 3. Levels of Severity of Acute Asthma Exacerbations

<table>
<thead>
<tr>
<th>Life-threatening asthma</th>
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<tbody>
<tr>
<td>Any one of the following in a patient with severe asthma:</td>
</tr>
<tr>
<td>FEV1 &lt;30% best or predicted</td>
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<tr>
<td>SPO2 &lt;92% PaO2 &lt;8 kPa (60 mm Hg)</td>
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<tr>
<td>PaCO2 &gt; 6 kPa (45 mm Hg)</td>
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<tr>
<td>Silent chest</td>
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<tr>
<td>Cyanosis</td>
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<tr>
<td>Feeble respiratory effort, exhaustion</td>
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<tr>
<td>Confusion or coma</td>
</tr>
<tr>
<td>Hypotension or bradycardia</td>
</tr>
<tr>
<td>Near fatal asthma</td>
</tr>
<tr>
<td>Raised PaCO2 and/or requiring mechanical ventilation with raised inflation pressures</td>
</tr>
</tbody>
</table>

Table 4. Differential Diagnosis of Severe Asthma

- Congestive heart failure
- Myocardial infarction
- Pulmonary embolism
- Upper airway obstruction
- Foreign body aspiration
- Tracheobronchomalacia
- Endobronchial lesion
- Chronic obstructive pulmonary disease (COPD)
- Bronchiolitis
- Vocal cord dysfunction
- Hyperventilation syndrome
- Acute bronchitis/pneumonia

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tracing and presence of pulsus paradoxus in patients with severe asthma. The value of arterial blood gases to monitor ventilation is uncertain. Decades old evidence has shown that initial blood gases do not reliably predict a patient’s subsequent course. In nonintubated asthmatics, a respiratory alkalosis with mild hypoxemia is common. Hypercapnia and a concomitant respiratory acidosis indicate more severe disease, associated with worse airway obstruction. A quiet chest on auscultation, inability to talk, and cyanosis correlate with hypercapnia. A respiratory acidosis that develops or worsens during treatment and normalization of arterial partial pressure of carbon dioxide (PaCO₂) are potentially ominous signs if the patient is deteriorating or failing to improve clinically. Importantly, severe obstruction and impending respiratory failure may occur without hypercapnia. The absence of hypercapnia should not preclude ventilatory support in a patient who is clinically deteriorating. Conversely, hypercapnia in isolation is not an indication for intubation if a patient is clinically improving or has not had sufficient opportunity to respond to therapy.

Some patients may develop a nonanion gap hyperchloremic acidosis as a result of compensatory renal bicarbonate excretion. Lactic acidosis is commonly seen in sicker patients, and may result from a combination of factors, including hypoxemia, respiratory muscle exertion, and catecholamine therapy. The chest x-ray (CXR) is normal in most patients; some show evidence of hyperinflation (Figure 2) and only 2% show abnormalities such as atelectasis, pneumonia, pneumomediastinum, or pneumothorax. Although not routinely indicated in mild, straightforward exacerbations, the CXR may be useful in severe exacerbations or atypical presentations with fever or leukocytosis. Chest x-rays are needed for all patients admitted to the ICU and should be done promptly after intubation to ensure proper positioning of the endotracheal tube.

Criteria for ICU admission

Patients with severe exacerbations (FEV1 or PEFR <40%), particularly those not responding despite 1 to 2 hours of therapy should be considered for ICU admission. Those with risk factors for fatal asthma and/or signs of severe illness, such as altered mental status, hypercarbia (Paco₂ > 45 mm Hg), or hypoxemia (Pao₂ < 60 mm Hg on room air) requiring supplemental oxygen, should be considered ICU candidates as well. In many hospitals, the need for frequent albuterol treatments or continuous therapy may mandate ICU admission, given the caregiver workload required, regardless of severity.

Pharmacotherapy

The primary aims of treatment are to relieve airflow obstruction quickly and to promptly institute therapy to decrease airway inflammation. Key therapies include repetitive administration of rapid-acting inhaled bronchodilators, early use of systemic glucocorticosteroids, and oxygen. Commonly used drugs and dosing schedules are shown in Table 5.

Bronchodilators

Inhaled short-acting ß agonists such as albuterol, levalbuterol, and pirbuterol are the drugs of choice to relieve acute symptoms. ß-agonists relax smooth muscle, decrease bronchoconstriction and airway obstruction, and may begin to provide symptomatic relief within 3 to 5 minutes. Other actions include mast cell stabilization and inhibition of release of inflammatory mediators. Delivery of ß agonists with a metered dose inhaler (MDI) combined with a spacer device appears to be as effective as nebulization. However, nebulizers may be more effective for acutely dyspneic patients who may have trouble using the MDI. The standard doses for asthma treatment are 2.5 to 5 mg by nebulization every 20 minutes for 3 doses, then 2.5 to 10 mg every 1 to 4 hours as needed. If using an MDI with a spacer, an appropriate dose is 4 to 8 puffs every 20 minutes for up to 4 hours, then every 1 to 4 hours as needed, although modifications may be necessary for individual patients. For critically ill patients not responding to intermittent therapy, continuous nebulization with administration of 10 to 15 mg over 1 hour is used. Many patients with acute severe asthma respond to this treatment but there are some who do not respond to high doses of albuterol. In 1 study, 70% of patients responded to 2.4 to 3.6 mg albuterol by MDI in 1 hour while 30% of patients did not. The nonresponder group was characterized by higher severity of airway obstruction and may have relative resistance to typical doses of ß agonists.
Methylxanthines such as theophylline and aminophylline were once widely used to treat acute asthma. Concerns about their narrow therapeutic range and the development of effective inhaled bronchodilator therapy have marginalized their use. Theophylline is uncertain at best. A meta-analysis of 15 randomized controlled trials found that IV aminophylline failed to provide additional bronchodilation compared to standard care with β-agonists alone.49

Anticholinergic Agents

Inhaled anticholinergics such as ipratropium may provide a useful adjunct to β agonists, further promoting bronchodilation and alleviating symptoms.46,47 The doses used are 0.5 mg every 20 minutes for 3 doses then as needed by nebulization or 8 puffs every 20 minutes as needed up to 3 hours by MDI.2 Anticholinergics appear to be most helpful in patients with severe obstruction. The lack of significant side effects argue for their use in patients with insufficient response to β-agonists alone.46,48

Leukotriene modifiers: Consider montelukast 10 mg per oral (PO) daily.

Methylxanthines

Methylxanthines such as theophylline and aminophylline were once widely used to treat acute asthma. Concerns about their narrow therapeutic range and the development of effective inhaled bronchodilator therapy have marginalized their use. The benefit of methylxanthines when added to inhaled β agonists is uncertain at best. A meta-analysis of 15 randomized controlled trials found that IV aminophylline failed to provide additional bronchodilation compared to standard care with β agonists and adverse effects were more common with aminophylline.49 Methylxanthines may be considered in patients already taking them.50 In these patients, if serum levels are low, aminophylline can be given as 5 mg/kg IV loading dose followed by 0.4 mg/kg per hour IV. Side effects of theophylline increase at plasma levels above 20 mg/mL and may include headache, nausea and vomiting, abdominal discomfort, and restlessness. At high concentrations, convulsions, cardiac arrhythmias, and death may occur.50 Theophylline should be initiated by a physician familiar with the side effects; close monitoring of the serum levels is warranted.

Corticosteroids

Inflammation contributes significantly to airway obstruction in severe asthma. To address inflammation, systemic corticosteroids must be administered immediately, although they generally require several hours to take effect.2 Steroids act through multiple mechanisms, including inhibition of the inflammatory effects of the NFκB transcriptional system, the mitogen-activated protein kinase (MAPK) pathway, and phospholipase A2.51 The oral and IV routes are equally effective,52 so that the oral route may be used if patients can swallow. Prednisone at dose of 40-80 mg per day in divided doses or equivalent doses of IV methylprednisolone are recommended by the latest U.S guidelines.2 This is substantially lower than the prior guidelines that recommend 120–180 mg of methylprednisolone given IV, divided into 3 or 4 doses per day28 and reflects analysis showing low dose corticosteroids (≤80 mg/day of methylprednisolone or ≤ 400 mg/day of hydrocortisone) appear to be adequate in the initial management of hospitalized patients with severe asthma.53

Inhaled steroids may cause nonspecific vasoconstriction and reduction of airway wall edema vascular congestion and plasma exudation in addition to anti-inflammatory effects.54 Some studies have shown the benefit of inhaled steroids in acute asthma when added to inhaled bronchodilators in patients not receiving systemic steroids55,56 but in 1 study, inhaled corticosteroids conferred no added benefit to patients already receiving systemic steroids.57 Inhaled corticosteroid therapy can be considered in patients not responding to conventional therapy.

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists (LRAs) are frequently used in chronic asthma and have both bronchodilator and anti-inflammatory properties. In 1 study, 7 mg or 14 mg of montelukast given IV in the emergency room resulted in rapid improvement in the FEV1 within 12 minutes. Further 59 A single dose of 160 mg improved the FEV1 and reduced the need for hospitalization. LRAs may be useful adjuncts in the treatment of severe asthma but further studies are needed to evaluate their role in patients with life-threatening disease.
**Magnesium**

A single dose of IV magnesium (2 gm infused over 20 minutes) is safe and effective in some patients with acute severe asthma and can improve spirometric values up to 10% to 16%. Intravenous magnesium is recommended for patients who are unresponsive to initial treatment with FEV1 less than 40% of predicted. Magnesium should be given with caution to patients with renal insufficiency. Magnesium given by inhalation may be useful as well, although the benefit appears to be less than IV therapy. A meta-analysis concluded that there appears to be improvement in FEV1 by a mean value of 0.30 L with this therapy and a trend toward less hospitalization. However, considerable heterogeneity in the included trials precluded definitive conclusions.

**Oxygen Therapy**

Patients with acute severe asthma are frequently hypoxemic and require supplemental oxygen to maintain a saturation greater than 90%. The average PaO2 in asthmatic patients is about 69 mm Hg on room air and oxygen tensions less than 50 mm Hg are infrequent and were seen in just 8% of patients. In most acute asthma exacerbations, hypoxemia can be easily corrected with minimal supplementation. Care must be taken against excessive use of oxygen as this may result in reduction of carbon dioxide elimination and precipitate hypercapnic respiratory failure.

**Ventilation**

**Noninvasive Positive Pressure Ventilation**

The literature on the use of noninvasive positive pressure ventilation (NPPV) for asthma is sparse. In a small prospective study comparing NPPV to usual care in 30 patients presenting with an acute attack, NPPV decreased the need for hospitalization and improved the FEV1, FVC, PEFR, and respiratory rate. Larger studies demonstrating the value of NPPV are needed before it can be recommended. At present, a trial of NPPV may be warranted in selected patients who are alert, hemodynamically stable, and able to protect their airway. Contraindications to NPPV include cardiac or respiratory arrest, nonrespiratory organ failure, severe encephalopathy, hemodynamic instability, or unstable cardiac arrhythmia, facial surgery, trauma, or deformity, upper airway obstruction, inability to cooperate/protect the airway, inability to clear respiratory secretions and high risk for aspiration.

**Invasive Mechanical Ventilation**

A subset of asthmatics who deteriorate or fail to improve despite maximal therapy will require intubation and mechanical ventilation. The decision to intubate an asthmatic patient requires careful clinical judgment. However, important signs include persistent or progressive hypoxemia and hypercarbia, hemodynamic instability, worsening of mental status, apnea, or signs of muscle fatigue or failure. Once it becomes apparent that intubation is warranted, the process must not be delayed as patients can deteriorate rapidly.

**Intubation**

Asthmatics requiring intubation pose special challenges (Table 6). Intubation should be performed by an experienced operator using a large bore endotracheal tube to allow adequate secretion management. Airway manipulation can produce laryngospasm or exacerbate bronchospasm. Immediately after intubation, there is an elevated incidence of arrhythmias secondary to electrolyte, acid base disturbances, or secondary to β agonist or methylxanthine therapy. Arrhythmias are usually transient and rarely life-threatening. Short-term sedation for intubation can be achieved with either etomidate or thiopentone, which are a short-acting imidazole and barbiturate, respectively. Rapid sequence intubation using an IV sedative/anesthetic with succinylcholine is preferred to secure the airway rapidly while preventing aspiration of stomach contents.

Hypotension has been reported in 25% to 35% of patients after intubation. Contributing factors include underlying intravascular volume depletion, loss of endogenous catecholamine release, anesthetic and sedative-induced vasodilation, and high intrathoracic pressures that can impede venous return. Vigorous bagging peri-intubation can cause or exacerbate DHI by reducing expiratory time, contributing to hypotension. Adequate venous access is essential and should be implemented preintubation if possible. Central venous access can also assist in determining the volume status and empiric IV fluids given preintubation may be prudent if volume depletion is suspected.

Hypotension after intubation can be managed by fluid bolus and temporary disconnection of the patient from the ventilator if DHI is present. It is important to distinguish decreased venous return from barotrauma and tension pneumothorax as a cause of hypotension. Tension pneumothorax must always be considered and equipment for needle or tube thoracostomy should be immediately available. Signs suggestive of tension pneumothorax include reduced breath sounds on one side of the chest, tracheal shift, and failure to respond hemodynamically to disconnection from the ventilator. If time permits, a chest radiograph may be obtained to confirm pneumothorax, but in

**Table 6. Recommendations for Process of Intubation**

- Performed by experienced anesthetist or intensivist.
- Ensure adequate sedation and paralysis for intubation.
- Intubate by direct laryngoscopy.
- Correct electrolyte disturbances.
- Ensure adequate fluid hydration.
- Monitor with continuous pulse oximetry and telemetry.
- Preoxygenate before intubation.
- Prepare for rapid correction of hypotension, arrhythmias or barotrauma.
- Ensure adequate venous access before intubation. Arterial line blood pressure monitoring is useful but not mandatory.
emergent conditions, it may be necessary to intervene before a chest x-ray can be obtained.

**Drugs for Mechanical Ventilation**

**Sedation.** Adequate sedation is important during mechanical ventilation to ensure patient comfort, to reduce dysynchrony with the ventilator, and to decrease the risk of barotrauma. Respiratory distress exacerbated by hypercapnia and profound airway obstruction can make mechanical ventilation exceedingly challenging. Adequate sedation is therefore a critical adjunct. Although light sedation is optimal (i.e., allowing the patient to be easily arousable), heavier sedation may be needed in many patients to achieve synchrony with the ventilator. Sedation and paralysis may decrease endogenous CO₂ production thus ameliorating hypercarbia seen in life-threatening asthma attacks.

Benzodiazepines, particularly midazolam and lorazepam, are commonly used for sedation. Doses should be titrated to achieve the intended depth of sedation. If repeated boluses are necessary, continuous infusions of midazolam (0.04-0.2 mg/kg per hour) or lorazepam (0.01-0.1 mg/kg per hour) may be needed. Propofol may be particularly useful given its rapid onset of action and ability to titrate. Propofol may also have bronchodilator effects. Opioids may be useful as well. In addition to their analgesic properties, opioids exert powerful respiratory depressant effects that may aid patient-ventilator synchrony. Morphine should be avoided as large boluses can cause histamine release and worsen bronchoconstriction. Fentanyl is a safe alternative.

**Paralytic agents.** Neuromuscular blocking agents (NMBAs), particularly vecuronium, cixatracurium, and pancuronium, may be required if sedation alone proves ineffective. Potential benefits include improved patient-ventilator synchrony, reduced oxygen consumption and carbon dioxide production, and decreased risk of barotraumas. Neuromuscular blocking agents are associated with important potential complications, particularly myopathy and muscle weakness, as well as increased risk of ventilator-associated pneumonia, loss of the ability to evaluate mental status and neurological function, and prolonged length of ICU stay. Neuromuscular blocking agents should be given by intermittent dosing if possible and stopped immediately when no longer needed. Infusions, if used, should be stopped every 4 to 6 hours to prevent accumulation and to allow patient evaluation. Finally, if NMBAs are used, heavy sedation to the point of anesthesia is mandatory.

**Asthmatics Management**

Asthmatics requiring intubation are among the most challenging to care for in the ICU. The goals of mechanical ventilation are to ensure adequate gas exchange while avoiding the complications associated with DHI, particularly barotrauma and hemodynamic compromise, while awaiting response to pharmacologic therapies. Timely recognition of DHI and the use of protective ventilation strategies are key to avoiding complications.

**Monitoring for DHI**

Proper attention must be paid to ensure sufficient lung emptying during expiration. The complications of DHI can be sudden and catastrophic and it is therefore essential to recognize it so that ventilator settings can be adjusted accordingly. Although some DHI may be unavoidable, the degree of hyperinflation can be mitigated by carefully monitoring lung mechanics and making necessary ventilator adjustments.

Several parameters of varying utility have been used to monitor for DHI. Examples include (a) increased peak airway pressures (Ppk) and plateau pressures (Ppl) during volume-regulated ventilation; (b) reductions in tidal volume/minute volume during pressure-regulated ventilation; (c) increased chest wall girth; (d) increased patient effort; (e) persistent expiratory flow at end-expiration or intrinsic positive end-expiratory pressure (PEEP); and (f) hemodynamic compromise. Airway pressure measurements—Ppk, Ppl, and PEEPi—are readily available and may help identify DHI. Unfortunately, none of these measurements are perfect and each has drawbacks.

The use of airway pressures to measure DHI requires patient-ventilator synchrony and absence of spontaneous respiratory activity. Leaks around the endotracheal cuff or in the ventilator circuit can result in faulty measurements. Substantial variation in measurements between breaths is an important clue suggesting that airway pressures should not be relied upon until synchrony and cessation of respiratory muscle activity is achieved.

For many reasons, Ppk is an unreliable measure of DHI. Ppk represents the sum of pressures required to overcome the elastic recoil pressure of the inflated respiratory system (ie, the Ppl) and to overcome resistance in the airway (Pr):

\[ P_{ppk} = P_{ppl} + P_{r} \]

Pr is a function of the airway resistance (Raw) and inspiratory flow rates (Fi):

\[ P_{r} = Raw \times Fi \]

Changes in Raw and modifications in the set Fi can alter Pr and, consequently, Ppk without necessarily affecting DHI. In particular, an increase in Fi, used to shorten inspiratory time in an effort to promote sufficient expiratory time, as discussed below, may increase Ppk even though DHI decreases. Conversely, a decrease in Fi may lower Ppk while exacerbating DHI. In addition, the clinical consequences of elevated airway pressures resulting from proximal airway obstruction are unknown, recognizing that these pressures may dissipate distally and be less likely to contribute to barotraumas. Because Ppk may be elevated, it may be necessary to adjust the ventilator appropriately to ensure that set tidal volumes are delivered.

The presence of DHI can be deduced by observing persistent end-expiratory air flow. However, simply observing flow does
not allow DHI to be quantified. PEEPi can be measured using an end-expiratory hold maneuver, which allows equilibration of pressures in the distal airways and alveoli with the airway opening (Figure 3). Unfortunately, measured PEEPi may underestimate DHI in severe asthma, because measurement assumes airway patency, a necessary condition to ensure that pressures at the airway opening reflect those in the distal airways and alveoli. In severe asthma, airway closure and plugging may occlude many airways at end-expiration, leading to underestimation of DHI (Figure 4). Thus, marked pulmonary hyperinflation may be present despite relatively low measured PEEPi. Similarly, PEEPi may remain constant or rise despite improvement in DHI as plugging and airway closure resolve.

In general, end-inspiratory Ppl provides a better estimate of DHI than Ppk or PEEPi. It is important to remember that Ppl is affected by chest wall compliance (Ccw). When Ccw is low, for example if patients are obese or if they have chest wall deformities, an elevated Ppl may lead to an overestimate of DHI if these influences are not accounted for. Nevertheless, the American College of Chest Physicians (ACCP) consensus statement on mechanical ventilation has concluded that Ppl provides the best measure of lung hyperinflation. In general, the Ppl should be kept <30 cm H2O to minimize the risk of DHI-associated complications.

**Mode of Ventilation and Settings**

Mechanically ventilated asthmatics are at great risk for developing DHI. Spontaneously breathing patients cannot inspire beyond total lung capacity (TLC). In contrast, during mechanical ventilation, machine-delivered breaths can push inhalation beyond TLC, leading to dangerous levels of DHI, resulting in hemodynamic collapse or barotrauma, particularly tension pneumothorax. In the early years of mechanical ventilation, attempts to ventilate asthmatics aggressively to prevent hypercapnia had the unintentional effect of increasing complications, particularly barotrauma, hemodynamic compromise, and death. Subsequently, a classic study by Darioli et al showed that a protective approach to mechanical ventilation, which allowed hypercapnia to develop as necessary to avoid hyperinflation, led to substantially improved outcomes as long as oxygenation was maintained. Subsequent studies have confirmed that careful ventilator management that avoids hyperinflation dramatically decreases the complications associated with mechanical ventilation.
Table 7. General Principles of Mechanical Ventilation

<table>
<thead>
<tr>
<th>Controlled hypoventilation with low tidal volume, respiratory rate, and longer expiratory time to reduce hyperinflation</th>
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<tbody>
<tr>
<td><strong>Recommended Initial Ventilator Settings</strong></td>
</tr>
<tr>
<td>• Tidal volume 8 cc/kg</td>
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<tr>
<td>• Rate 10-12 breaths/min</td>
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<tr>
<td>• Inspiratory flow rate 80-100 cc/h</td>
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<tr>
<td>• Plateau pressure &lt;30 cm H2O</td>
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<tr>
<td>• Inspiration:Expiration ratio &gt;1:3</td>
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<tr>
<td>• FiO2 to maintain saturation &gt;90%</td>
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Determinants of DHI include (1) tidal volume (2) expiratory time, and (3) the degree of airflow obstruction. Reversal of airflow obstruction depends on pharmacologic therapy while the other 2 parameters require manipulation of the ventilator. Dynamic hyperinflation can be limited by ensuring sufficient expiratory time to maximize lung deflation after each breath. Expiratory time can be maximized by decreasing minute ventilation (VE) by lowering respiratory rates, tidal volumes, or both and by increasing inspiratory flow rates. Although arterial CO2 almost always rises, decreasing VE is the most reliably effective way to prevent or ameliorate DHI. Increases in Fi may play an adjunctive role, but are generally not as effective and may produce intolerable elevations in Ppk. In addition, increases in Fi may stimulate the respiratory drive, producing unwanted increases in VE.

Ventilator settings must be crafted to meet the individual patient’s needs, particularly as dictated by measures of DHI. Frequent changes may be necessary as the patient’s condition evolves. Examples of reasonable initial settings are shown in Table 7. These settings have been shown to be appropriate for 80% of ventilated patients with severe asthma while resulting in only mild DHI in the remaining 20%.

Use of Extrinsic PEEP

Dynamic airway collapse toward the end of expiration in some lung units can contribute to air trapping and DHI. As in patients with COPD, extrinsic PEEP (PEEPe) could split open these airways and promote more effective emptying of the lung. Traditional teaching has recommended against using PEEP in severe asthma, however, because of concerns that it would impede exhalation and exacerbate hyperinflation. In a study of 6 ventilated patients with severe airflow obstruction, a stepwise increase of PEEPs from 5 to 15 cm H2O increased hyperinflation and reduced cardiac output and blood pressure. However, this observation has not been universal. In a more recent study, 5 of 8 patients with airway obstruction demonstrated increased expiratory flow and decreased evidence of hyperinflation when PEEPe was applied. Thus, at least some asthmatics may benefit from the cautious addition of PEEP. Extrinsic PEEP should never be set above measured PEEPi; a goal of 80% of the PEEPi is a reasonable target. Among spontaneously breathing patients, PEEPe may help overcome PEEPi and make it easier for them to trigger a breath.

Unconventional Therapies

General Anesthesia

Several case reports have described the use of general anesthesia for the management of life-threatening asthma, although there has been no systematic study of its efficacy.
Inhalational anesthesia, using either halothane or isoflurane, may exert useful bronchodilating effects in refractory patients. Hypotension is an important potential side effect. The use of inhalational anesthesia is limited by the need for special equipment and an anesthesiologist. The bronchodilating effect of IV ketamine has been used to treat asthma. However, ketamine has sympathomimetic effects and great caution must be exercised in patients with hypertension and elevated intracranial pressure.

**Heliox**

Heliox is a blend of helium and oxygen usually in a 80:20 or 70:30 ratio. It has been used to reduce the work of breathing, improve ventilation by reducing turbulent airflow, and improve delivery of bronchodilators to the distal airways. The utility of heliox is controversial. A recent meta-analysis concluded that available evidence failed to support routine use in nonintubated asthmatics. However, several reports have described improvement in pulsus paradoxus in nonintubated patients. In a report in intubated patients, heliox appeared to improve airway pressures, CO₂ retention, and acidosis. Unfortunately, most ventilators are designed for a mixture of oxygen and air and the low density of helium alters flow through the valves, regulators, and tubing. As a result, pressure changes and response to therapy may be hard to assess reliably in intubated patients. Heliox is used in premixed concentrations, hence the fraction of administered oxygen that may be used is limited. In select patients, heliox may be considered as a temporizing measure until bronchospasm responds to traditional therapy. However, the inconvenience, increased cost, and lack of discernible benefit in most patients preclude widespread use.

**Extracorporeal membrane oxygenation**

Extracorporeal membrane oxygenation (ECMO) has been used rarely to treat life-threatening asthma. The technique has been described in several case reports. Bronchoscopy with lavage has been proposed to remove mucus plugs in intubated patients with life-threatening asthma; however, its use cannot be routinely recommended as there is a risk of worsening bronchospasm and gas exchange.

**Weaning and Extubation**

Weaning from the ventilator should commence as soon as the patient’s condition allows. Signs that weaning is appropriate include improved air movement on examination and the ability to tolerate ventilation sufficient to normalize the Paco₂. When patients are ready, sedation should be minimized or stopped and spontaneous breathing trials begun. Barring contraindications, patients should be extubated once they successfully complete a spontaneous breathing trial. In a minority, a myopathy caused by prior treatment with high-dose corticosteroids and neuromuscular blockade may impose a barrier to extubation.

**Follow-Up Care**

Patients admitted to the ICU and particularly those requiring intubation are at high risk for recurrence of life-threatening asthma. In a study following intubated patients with near fatal asthma after discharge from hospital, mortality was 10.1% after 1 year, 14.4% after 3 years, and 22.6% after 6 years, all occurring from asthma attacks. Noncompliance and poor access to medical care contribute to the development of subsequent exacerbations. Patients require extensive education on the use of peak flow meters for monitoring and must learn to recognize signs of worsening control such as increasing need for β agonist rescue therapy. They should also be counseled to avoid triggers and to develop an emergency plan. Patients must be treated with inhaled steroids and close follow up with an asthma specialist should be considered prudent.

**Summary**

Managing patients with life-threatening asthma is one of the most difficult challenges facing critical care physicians. Although any asthmatic is theoretically at risk for life-threatening attacks, it is becoming clear that those with life-threatening asthma are a unique group characterized by poor baseline asthma control and severely inflamed airways. Fortunately, advances in management, emphasizing high doses of corticosteroids and safe mechanical ventilation techniques, ensure survival in the vast majority who come to the ICU. Still, the severe morbidity associated with life-threatening asthma makes it critical that outpatient management be enhanced to prevent this disorder.

**References**


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