Review article

Current approaches to the assessment and treatment of acute severe asthma

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Abstract

Despite the decline in overall asthma mortality, acute severe asthma continues to be a significant challenge to clinicians. Patients with acute severe asthma present unique clinical features that require early recognition and aggressive treatment. The aim of this review is to describe the most current evidence that supports diagnostic and therapeutic approaches in the management of patients with acute severe asthma in the clinical setting.

Keywords: Asthma, asthma disease management, asthma therapy, acute severe asthma, refractory asthma, status asthmaticus.

Background

Asthma remains one of the most common chronic diseases affecting almost 300 million people worldwide.[1-3] Acute severe asthma represents one of the more common medical emergency situations and the most serious clinical presentation of asthma.[4] Although the precise definition of acute severe asthma presents difficulties, it is typically characterised by the presence of severe respiratory distress due to an asthma episode that requires the use of bronchodilators, oxygen, and oral or intravenous corticosteroids.[4] Other terms such as asthma exacerbation, status asthmaticus, near-fatal asthma and life-threatening asthma have been used to describe the severity of acute asthma events. An asthma exacerbation can usually be presented in the clinical setting under one of two subcategories; *severe* [dyspnoea at rest; interferes with conversation, peak expiratory flow rate (PEFR) <40% predicted, usually requires emergency department (ED) visit and likely hospitalisation, partial relief from frequent inhaled short-acting beta-agonists (SABA), oral systemic corticosteroids; some symptoms last for >3 days after treatment is begun, and/or adjunctive therapies are helpful], and *respiratory arrest imminent* (too dyspnoeic to speak; sweating, PEFR <25% predicted, requires ED/hospitalisation; possible ICU, minimal or no relief from frequent inhaled SABA, intravenous corticosteroids, and/or adjunctive therapies are

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helpful).[5,6] Status asthmaticus has often carried the connotation of being a refractory condition characterised by progressive respiratory distress that is refractory to the continuous administration of short-acting bronchodilators in the emergency department.[7] *Near-fatal asthma* and *life-threatening asthma* are defined as asthma attacks that can progress rapidly to hypercapnia and hypoxaemia, leading to impending or full respiratory arrest, usually requiring intensive care unit admission.[4,8-10] While fewer than 10% of patients present with acute severe asthma, as many as 20% of these patients may end up being admitted to the ICU, and 4% intubated and mechanically ventilated.[7,11] Preventive therapies are often ignored and primary care follow-up inadequate among children and adolescents treated in the ED. The morbidity and mortality associated with acute severe asthma can be primarily attributed to inadequate recognition and identification of the underlying type of asthmatic exacerbation, the underestimation of severity resulting in delay of emergency treatment, and poor baseline control due to inhaler incompetence.[8,12,13]

The aim of this review is to describe the most current evidence that supports diagnostic and therapeutic approaches in the management of patients with acute severe asthma in the clinical setting.

Asthma Phenotypes

Several studies have demonstrated that not all asthmatics that have acute severe asthma have the same clinical presentation. Since onset of an exacerbation could be rather fast or gradual, and their recovery could be quick or require prolonged hospitalisation, classification of severe asthma into different phenotypes has been proposed by several authors *(Table 1)*.[9,14,15] However, the prescribed management for patients with acute severe asthma should depend more on the clinical condition than a particular phenotype since acute severe asthma can lead to acute respiratory failure and death if left untreated.[16,17] Most patients who present to the emergency department with acute severe asthma typically have a prior history of similar visits despite being managed at home with inhaled corticosteroids, long-acting β_2-agonists or theophylline, and at times even with oral corticosteroids.[8]

Patients with a gradual onset of acute asthma are generally slow to respond to frontline pharmacologic agents, such as corticosteroids, often necessitating adjunctive treatments such as mechanical ventilation,[20] magnesium sulfate,[22] and leukotriene modulators.[23] Most fatalities in this phenotype occur in middle-aged or elderly female patients with severe and poorly controlled chronic asthma.[8,16,25,26] The second and most common phenotype, produces an acute onset of symptoms. These *'brittle asthmatics'* have an acute asphyxic asthma attack typically due to a massive allergen exposure or emotional distress.[21] Respiratory failure may develop within two hours of the onset of symptoms and death can be sudden and unexpected.[10,19,21,27] While characterised by its rapid onset, patients with this phenotype are generally younger males who respond quickly to treatment. They typically have normal lung function hours or days prior to the acute severe asthma attack and often require admission to the hospital ward only for short term monitoring.[21] Virtually all patients

Table 1. Phenotypes of Acute Severe Asthma [8,10,12, 18-21]

	Phenotype	
	Gradual Onset	**Sudden Onset**
Course	Days	Hours – asphyxic asthma
Incidence	10-33%	45-88%
Airway pathology	Gelatinous mucus plugging	No mucus plugging
Predominant inflammatory cell*	Eosinophil	Neutrophil
Response to treatment	Slow	Faster
Hospitalisation course	Long	Short
Prevention	Possible	Undetermined**

* Blood and sputum cells when no infection is present.

**Avoidance of aspirin/Non-steroidal anti-inflammatory drugs and daily use of PEFR measurements will likely reduce incidence.

presenting with an acute severe asthma event require hospitalisation and are considered at risk for respiratory failure or death.[28]

Risk Factors

A history of prior hospital admission due to asthma within the past year, that requires mechanical ventilation, is considered the greatest predictor of acute severe asthma.[28-30] Lack of utilisation of inhaled corticosteroids (ICS) two weeks prior to the onset of symptoms has been strongly associated with the development of acute severe asthma.[8] When compared with mild-to-moderate asthma, patients with acute severe asthma had lower adherence to anti-asthma treatment and low serum level concentrations of prednisolone and cortisol.[8,31] Increased use of nebulisers, delays in medical care and initiation of corticosteroid therapy typically also result in a higher risk of acute severe asthma.[30] The incidence of poor perception of dyspnoea in patients with severe asthma could be as high as 36%.[31] Determining the presence and extent of reversible, allergen-induced bronchoconstriction by utilising a methacholine challenge, while useful in the outpatient setting, carries serious risks in the already established severe asthmatic. Physicians and asthma educators are encouraged to routinely measure dyspnoea scores at least once during the follow up of all their patients who have asthma to modify or develop therapeutic plans that prevent acute severe asthma episodes.[32] Poor perception of dyspnoea can cause treatment delay, near fatal events, and death in some asthmatic patients.[31,33] In addition, patients with asthma are also more likely to be treated for mental health problems such as anxiety, panic disorders, depression and demonstrate more negative social outcomes.[34,35]

Pathophysiology

Acute severe asthma is characterised by severe dynamic hyperinflation due to marked limitation of the expiratory flow.

Dynamic hyperinflation: The progressive narrowing of the airway, shorter expiratory times and breath-stacking by the patient, ultimately leads to gas trapping and lung hyperinflation.[23,36,37] The presence of intrinsic positive-end expiratory pressure (PEEP) or autoPEEP results from incomplete expiration and increases with increase in minute ventilation and degree of airflow obstruction. Dynamic hyperinflation also results in a significant decrease in systemic venous return.[38] Pulmonary hypertension caused by lung hyperinflation may result in increased right ventricular afterload. The presence of pulsus paradoxus in patients with acute severe asthma is an indication of ventilatory muscle fatigue and impending respiratory failure.

The gas exchange abnormalities observed in acute severe asthma largely depend on the extent of intrapulmonary shunting due to bronchospasm, airway oedema, inflammation and mucus plugs.[39,40]

Patient assessment

Acute severe asthma attacks are episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms. The general appearance of the patient can often precede the recognition of significant respiratory distress. Signs such as cyanosis, gasping, exhaustion, hypotension and decreased consciousness are suggestive of acute severe asthma and indicate the need for immediate therapeutic decisions including mechanical ventilation.[40] Good clinical judgment should always come first.

Diagnostic methods

Therapeutic interventions should not be delayed as a result of waiting for laboratory data. Nevertheless, patients with acute severe asthma must be closely monitored for deterioration in their condition and response to therapy. This should include blood gas analysis, chest radiography, blood counts and drug monitoring.

Lung function

Changes in peak flows of patients with asphyxic asthma typically reflect acute bronchospasm rather than airway oedema and inflammation.[19,21] While measurements of peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV_1) in patients with acute severe asthma may be challenging, they should be obtained on all patients capable of performing this manoeuvre.

However, caution is warranted since the deep inspiratory manoeuvre involved in PEFR and FEV_1 may precipitate worsening bronchospasm and even respiratory failure.[40]

The variability of peak flows is directly associated with severity of airway obstruction and has been identified as a prognostic marker in patients with acute severe asthma.[40,42] In the urgent care setting, to classify the severity of exacerbation and to determine the clinical course, an expert panel chose the cut off point for PEFR to be <40% predicted (or personal best). It has been shown that obtaining an FEV_1 or PEFR at baseline, with repeated measurements every hour following treatment, to be the single most influential predictor of hospitalisation in adults who present to the ED with acute severe asthma.[40] If the patient presents with an FEV_1 or PEFR <25% of predicted and has<10% reversibility after therapy, they should be considered for ICU admission.[40]A PEFR greater than 50L/min above baseline and a FEV_1 greater than 50% of predicted measured 30 minutes after initiation of treatment have been associated with excellent prognosis in patients with acute severe asthma.[43] Some patients with acute severe asthma have a marked diurnal variations in PEFR and may develop sudden severe acute attacks, typically early in the morning (*'morning dippers'*).[19]

Blood gas analysis

Arterial blood gases may be useful in guiding the management of patients with asthma exacerbations; however, they are not a predictor of outcome. The most common abnormality seen in the early stages of acute severe asthma is hypocapnia and mild hypoxaemia. The transition from hypocapnia to normocapnia during an acute severe asthma exacerbation is very concerning and should be considered an important sign of severe clinical deterioration and an indication of patient exhaustion.[19] Transient paradoxical deterioration of gas exchange, while PEFR improves is not uncommon after β_2 agonist administration.[40] The presence of hyperventilation during treatment of acute severe asthma may be a manifestation of metabolic acidosis with hyperventilation rather than worsening airway obstruction and denotes impending respiratory arrest. Use of β_2 agonists in the acute setting can cause lactic acidosis, which often leads to hyperventilation. This apparent increased work of breathing may be misinterpreted by the clinician as lack of response to the bronchodilator and often result in inappropriate intensification of bronchodilator therapy.[44]

Blood counts and drug monitoring

Blood counts are only indicated if patients are febrile and/or present with purulent sputum in order to rule out an infection. Leukocytosis, however, is not uncommon in acute severe asthma and corticosteroids may increase the neutrophil count as a consequence of demargination. Plasma theophylline levels are mandatory in patients being treated with theophylline due to its very narrow therapeutic window and high toxicity, which may lead to cardiac arrhythmias and seizures.[45]

Chest imaging studies

While it is a valuable tool to exclude acute severe complications, obtaining and interpreting a chest radiograph should never delay initiation of treatment. Despite the prevalence of dynamic hyperinflation in acute severe asthma, chest radiographs in these patients vary from normal, hyperinflated or hypoinflated. In cases of pulmonary hypoinflation it is important to consider upper airway obstruction as a possibility. Although rare, hypoinflation on chest radiographs has been shown revealing pneumomediastinum and percutaneous emphysema in asthmatics.[46-48] In fact, lung hypoinflation has been associated with a greater likelihood of hospital admission in children aged 6 years or older, and therefore, it should be considered a poor prognostic sign that may warrant more aggressive therapy.[49] High-resolution computed tomography (CT) scan may demonstrate prominent centrilobular structures in 70% of patients with moderate-to-severe asthma.[50,51] Although chest imaging may help in identifying the underlying problem and provide information regarding asthma severity, it is not routinely recommended. The costs and risks may outweigh the benefits especially if CT scans are routinely ordered for the same patient due to radiation exposure.[52]

Treatment

The management of acute severe asthma should start by determining the best clinical area to treat the patient. Since the most important prognostic factor in acute severe asthma appears to be the response to therapy,[53] the first four to six hours of treatment in the ED are critical to evaluate the disposition of patients.[53,54] In about 60–70% of patients, response to the initial three doses of β_2-agonists in the ED within the first two hours that will be sufficient to discharge them.[40] Most patients have a significant response after the first dose.[40] The remaining 30-40% of patients undergo a refractory period that usually requires an additional 24-hour observation or hospital admission.[40,55] Recognition of factors will aid the clinician making the decision to admit the patient to the medical ward or to the ICU. Patients with a pretreatment PEFR or FEV_1<25% or < 40% predicted after two hours of continuous nebulisation with β_2 agonists in the ED should be considered for admission to the general medical ward while those with an improvement in PEFR or FEV_1<10-20 % or with persistent hypercapnia, tachypnea, or altered mental status should be admitted to the ICU. In addition, the presence of respiratory failure and imminent exhaustion, a lack of clinical benefit after continuous nebulisation of short-acting β_2 agonists, the need for intravenous administration of salbutamol and/or the need for mechanical ventilation will require management in the ICU.[6,56-60] *Table 2* lists some of the criteria used to determine hospitalisation *vs* ICU admission.

Pharmacologic Therapy

The cornerstone of management of acute severe asthma is the administration of short-acting β_2 agonists (SABAs), systemic corticosteroids, and maintenance of effective oxygenation and ventilation. Magnesium sulfate, heliox, subcutaneous β_2-agonists, and theophylline may be useful in refractory cases. Other emerging therapies that warrant further investigation include inhaled corticosteroids, leukotriene antagonists, long-acting beta-agonists, and anti-IgE therapy.

Oxygen

Oxygen therapy should be titrated against pulse oximetry. Most asthma exacerbations are not associated with significant hypoxaemia.[40] However, the use of nasal cannula or mask is recommended to maintain SaO_2>90% (95% in children), and > 92% in patients with coronary artery disease and pregnant women.

Short-acting bronchodilators

The leading therapeutic intervention for acute severe asthma is the administration of aerosolised short-acting bronchodilators.[61] Administration of SABAs and anticholinergics are widely recognised as the first-line pharmacologic agents for an acute event due to their quick onset of action. Inhaled therapy with SABAs appears to be equal to or better than intravenous infusion for treating airway obstruction in patients with severe asthma.[62,63] The most frequently administered SABA is salbutamol. The use of its S-isomer, levosalbutamol, initially suggested for its role in preventing salbutamol-induced tachycardia and tachyarrhythmias is very controversial and appears not very well evidence-based.[63,64] Furthermore, despite preclinical studies suggesting a theoretical clinical benefit, any therapeutic advantage of levosalbutamol over

Table 2. Important considerations for hospitalisation *vs* ICU admission.

Hospitalisation	Intensive care unit admission
Duration and severity of symptoms	Drowsy or confused
Severity of airflow obstruction	Paradoxical thoracoabdominal movement
Course and severity of prior exacerbations	Absence of wheeze
Medication use at the time of exacerbation	Bradycardia
Access to medical care and medications	Absence of pulsus paradoxus
Adequacy of support and home conditions	PEFR <25%
Presence of psychiatric illness	SaO_2 <90%

salbutamol on pulmonary function and length of stay is still debated and requires further research.[65]

Administration *via* pressurised metered dose inhaler (pMDI) with spacer provides equivalent efficacy compared to nebulised treatments.[66,67] Seventy percent of the patients respond to 4-8 puffs every 10 minutes or between 5.0 and 7.5 mg of nebulised salbutamol. However, an acutely short of breath and anxious patient may not be capable of properly performing the specific actuation technique required to effectively administer medication *via* pMDI. For this reason and perhaps due to the nature of the existing clinical data, nebulisation either intermittently or continuously is the predominant method of administration in many emergency departments. Despite literature analysing the efficacy of continuous *versus* intermittent nebulised administration, data from these studies continues to be somewhat inconsistent.[68] Earlier studies have shown that continuous nebulisation reduces hospital admissions and improves lung function,[68-70] especially in the most severe cases of asthma exacerbations while some randomised controlled trials show no significant difference between the two methods. [71] The conflicting nature of these findings suggest that until further research demonstrates superiority of one type of administration over the other, a reasonable approach would be to use whichever method is deemed most patient-appropriate and achieves the best clinical response with the fewest adverse side-effects. In patients who are refractory to aggressive β_2-agonist therapy, the presence of salbutamol-induced hyperlactic acidosis needs to be considered. Tapering and supportive care are recommended.[72-75]

While there is controversy on the ability of anticholinergic agents to offer significant additional bronchodilation, recent guidelines recommend that repetitive doses of ipratropium bromide (0.5 mg nebuliser solution or 8 puffs by MDI in adults; 0.25–0.5 mg nebuliser solution or 4–8 puffs by MDI in children) be added to a selective β_2-agonist since this combination has been associated with fewer hospital admissions in patients with acute severe asthma or those with a poor initial response to SABA therapy.[40,76-78] In patients with FEV_1 less than 50% predicted, the addition of ipratropium bromide to SABAs has shown to be more beneficial with improvements in PEFR, FEV_1, and a decrease in the risk of hospital admission when compared to SABAs alone.[79] While this benefit may persist for up to 48 hours, it is suggested that short-acting anticholinergic therapy be continued only until the patient stabilises, and should not be added to the patient's chronic asthma management regimen or post-stabilisation.[40]

Systemic epinephrine and terbutaline

Subcutaneous epinephrine or terbutaline should be considered in patients unresponsive to continuous nebulised SABAs, and in patients unable to cooperate due to alteration of mental status or an inability to tolerate inhaled therapy.[80] In intubated patients refractory to inhaled therapy during mechanical ventilation, subcutaneous epinephrine, 0.3–0.5 ml (1:1000), can be administered every 20 minutes to a maximum of three doses. Subcutaneous terbutaline, 0.25 – 0.5 mg, may be considered as an alternative. Subcutaneous administration of epinephrine or terbutaline is well tolerated even in older patients as long as they have no history of coronary artery disease.[81-82] Intravenous infusion of terbutaline, 0.25 mg every 20 minutes for a maximum of three doses in adults and 0.01 mg/kg every 20 minutes for three doses in children then every 2-6 hours as needed, has been utilised predominantly in patients who are unresponsive to inhaled or subcutaneous treatment.[83] Intravenous terbutaline may be considered in patients with acute severe asthma in whom respiratory arrest is imminent, or in patients not adequately ventilated despite optimal ventilator management. However, a randomised control trial evaluating the benefit of intravenous terbutaline *versus* normal saline in nonventilated children, with acute severe asthma being treated with continuous nebulised salbutamol, did not show statistically significant differences in the amount of time spent on continuous nebulisers, length of hospital stay, or clinical asthma severity scores.[84] The most recent Cochrane meta-analysis did not identify significant benefits for adults with severe acute asthma.[85]

Corticosteroids

Corticosteroids have been shown to reduce airway inflammation, increase the number and sensitivity of β_2 receptors, and inhibit the migration and function of eosinophils.[86,87] Systemic corticosteroids should be administered to all asthmatics who do not respond to SABA therapy, indicated by a peak flow or FEV_1 greater than or equal to 80% predicted after one hour of treatment.[40,88] Their use as monotherapy, however, for the treatment of acute severe asthma has been considered unacceptable. Since benefits from corticosteroid treatment are not usually seen for 6 to 24 hours after administration, therapy should be instituted early. Administration within one hour of patient presentation has proven to reduce the rate of hospitalisation and improve pulmonary function.[89,90] For this reason, corticosteroids are recommended for all severity categories of asthmatic exacerbations in the ED, with variation only in the route of administration.

Several studies have documented the efficacy of inhaled corticosteroids (ICS) in comparison to systemic administration in the acute setting.[40,91,92] However, although promising, their use is not fully evidence-based and therefore not recommended over the more traditional and accepted systemic administration. Large doses of ICS (flunisolide 6 mg over 3 hours or fluticasone propionate 3 mg/hour for 3 hours) administered in the ED, in addition to SABAs, have shown to accelerate the rate of recovery of the acute bronchospasm.[93-94] Additional research is also required to consider the potential benefit of mixing nebulised ICS and bronchodilators. Furthermore, there is insufficient evidence that when used in addition to systemic corticosteroids, ICS lead to clinically important changes in pulmonary function or clinical scores. Therefore, until further evidence is available, ICS should not be used in place of systemic corticosteroid therapy when treating severe acute asthma.[93,95-98] Despite the reduction of unwanted systemic side-effects, local adverse effects such as oropharyngeal candidiasis are possible.

In an attempt to avoid systemic side-effects from long durations of oral corticosteroid use in asthmatics post-exacerbation, research has evaluated the efficacy of dexamethasone *versus* prednisone. Because dexamethasone has a longer half-life than prednisone, lower dosages (0.3-0.6 mg/kg daily for 1-5 days in children - 16 mg daily for 2 days for adults) have been shown to be as effective as higher doses of prednisone (1-2 mg/kg daily for 5 days in children - 50 mg daily for 5 days in adults).[99] Evidence has also shown that dexamethasone may have an increase in patient compliance and may require shorter durations of therapy without need for tapering.[99,100]

Methylxanthines

The use of other agents such as methylxanthines in acute severe asthma remains controversial. Plasma theophylline levels are mandatory in patients being treated with theophylline due to its very narrow therapeutic window and high toxicity, which may lead to cardiac arrhythmias and seizures. In addition, the benefit of methylxanthines as add-on treatment in adults with severe asthma exacerbations has not been demonstrated.[101,102] The British Thoracic Society/Scottish Intercollegiate Guideline Network British Guideline on the Management of Asthma suggests that, in acute asthma, intravenous aminophylline is not likely to result in any additional bronchodilation compared with inhaled bronchodilators and corticosteroids.[45] Children with severe acute asthma however may show a more rapid improvement in their clinical asthma scores when theophylline is used in combination with SABAs, systemic corticosteroids, and anticholinergics. In children with a severe asthma exacerbation, the addition of intravenous aminophylline to SABAs and systemic corticosteroids improves lung function within 6 hours of treatment. However there is no apparent reduction in symptoms, number of nebulised treatment and length of hospital stay.[103]

Leukotriene modulators

Leukotriene modulators may play an important role in the treatment of acute severe asthma since they complement the anti-inflammatory effects of systemic corticosteroids. Leukotriene agonists such as montelukast offer bronchodilation and anti-inflammatory effects and have shown to result in improvements in FEV_1 and reduced dyspnoea additive to the effect of bronchodilators.[104] While

oral montelukast is rapidly absorbed and has few side-effects, it typically takes between sixty to ninety minutes to provide benefit. A single intravenous dose of montelukast has shown to provide significant improvement in pulmonary function within ten minutes of administration and patients tended to require fewer SABAs and have a lower incidence of treatment failures.[105,106] In a study by Silverman *et al*, the addition of zafirlukast was associated with a reduction in the rate of hospitalisation of patients with acute severe asthma.[107] Although there is insufficient evidence to recommend routine use of leukotriene modulators in acute severe asthma, a 2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma suggests that intravenous administration of these agents could be considered as an adjunct therapy to avoid intubation.[40]

Magnesium sulfate

Intravenous administration of magnesium sulfate (IV $MgSO_4$) has been considered as an adjunct therapy for severe asthma exacerbations due to the significant improvements observed on PEFR and FEV_1 after its administration.[108-114] While it has an excellent safety profile, if appropriately administered, there are minor adverse effects such as flushing, headache, and burning sensation at the IV site.

Despite the many uncertainties surrounding the use of IV $MgSO_4$, the 2007 Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma recommends consideration of intravenous magnesium sulfate in patients who have acute severe asthma and do not respond after one hour of intensive conventional therapy.[40] Currently, the recommended dose for IV $MgSO_4$ is 2.0 g intravenously over twenty minutes in adults and 25-75 mg/Kg up to 2 grams in children.[40] The 2012 Global Initiative for Asthma report recommends IV $MgSO_4$ in adults with severe airway obstruction who do not respond promptly to bronchodilators, including those with FEV_1 values 25–30% of predicted at presentation.[115] Nebulised $MgSO_4$ in addition to SABAs appears to improve pulmonary function, especially in more severe asthma exacerbations.[116]

Heliox

Heliox, a gas of very low density, decreases turbulent flow generated by the passage of air through constricted airways, but does not possess inherent bronchodilatory or anti-inflammatory effect.[117] It is therefore another controversial method of treatment for acute severe asthma. Although a randomised control trial failed to demonstrate sustained improvement in pulmonary function testing or hospital admissions,[118] some studies and case reports have shown that heliox administration improves ventilation and aerosol particle deposition to distal airways, [119-122] decreased pulsus paradoxus, work of breathing, decreased peak airway pressures and PCO_2 in intubated patients have also been noted.[123,124] It is currently recommended to consider heliox for severe acute asthma when it does not resolve after 1 hour of intensive conventional therapy.[40] An 80:20 mixture delivered *via* nonrebreather mask has shown significant improvements in pulmonary functions over the first three hours of treatment.[118] Complications and adverse effects of heliox administration are minimal and to date the primary concern appears to be consideration of the potential for hypoxia for those patients requiring a higher FIO_2 than what is available in the standard 70/30 or 80/20 heliox mixtures.

Considering the limited evidence in regard to heliox administration, its primary role appears to be that of a temporary agent, which allows traditional interventions to reach their maximal effect and as such, is generally relegated to adjunctive status in current guidelines.[125]

Noninvasive Ventilation

The role of noninvasive ventilation (NIV) in acute severe asthma is not clearly defined. However, it appears to reduce the rate of intubation, shorten ICU and hospital stay,[126] decrease inhaled bronchodilator use, and improve CO_2 clearance.[127-129] A recent retrospective study evaluated possible benefits of bilevel positive airway pressure in conjunction with SABA therapy in the treatment of eighty-three paediatric patients with severe acute asthma who were refractory to conventional medical therapy.[130] The use of bilevel positive airway pressure

ventilation resulted in an 88% patient tolerance, a 22% reduction of admissions to the PICU, and a reduction of respiratory rate and improvement in oxygen saturations in 77% and 88% of the subjects, respectively. Despite the paucity of data supporting the use of NIV, the most recent Cochrane meta-analysis revealed that NIV was associated with a reduction of risk for endotracheal intubation (RR 4.48; 95% CI 0.23-89.13) and reduced need for hospitalisation (RR 0.28, 95% CI 0.09-0.84).[131]

Invasive ventilation

The main objective of the initial ventilator management is to ensure adequate gas exchange and to prevent further hyperinflation and ventilator-associated lung injury. Although intubation and mechanical ventilation should be considered for patients with progressive deterioration despite aggressive treatment, there are no randomised controlled trials identifying the best mode to use in status asthmaticus. Intubation should be considered when signs of acute deterioration such as exhaustion and fatigue despite maximal therapy, altered mental status, refractory hypoxaemia, increasing hypercapnia, haemodynamic instability, or apnoea are present.[132] Mechanical ventilation of patients with acute severe asthma is challenging and not without complications. Benzodiazepines can be safely used for sedation of the asthmatic patient, but time to awakening after discontinuation should be considered. For patients with acute severe asthma for whom extubation is anticipated within a few hours, one of the most commonly used agents is propofol. In addition to having bronchodilatory properties, propofol can be easily titrated to a deep sedation level and has rapid reversal after discontinuation. The addition of an opioid (fentanyl or remifentanil) administered by continuous infusion to benzodiazepines or propofol is recommended in order to provide sedation, amnesia, analgesia and respiratory drive suppression. Morphine can cause histamine release that can lead to hypotension and bronchoconstriction. Ketamine also is a good bronchodilator but can increase respiratory secretions.[133] Recently, Takasaki *et al* reported the successful use of dexmedetomidine to facilitate induction of NPPV for patients with acute severe asthma in respiratory failure.[134] Since the concomitant use of corticosteroids and neuromuscular blocking agents is associated with acute myopathy, sedation has been advocated to be much safer than paralysis for patients with acute severe asthma.[135] A recent retrospective analysis however showed a minimal reduction of muscle weakness using heavy sedation when compared to continuous paralysis in adults with status asthmaticus.[136] In the setting of severe patient-ventilator dyssynchrony, short-term use of neuromuscular blockers (20-60 min) may still be required.

The oral route of intubation is preferred since it minimises airway resistance and maximises airway clearance. The in-hospital mortality rate for all asthmatics is between 1-5%, but for critically ill asthmatics, that require intubation, the mortality rate is between 10-25%, primarily from anoxia and cardiopulmonary arrest.[137] A recent retrospective study evaluated patients with acute severe asthma admitted to the ICU over a span of 30 years in order to reveal whether or not mechanical ventilation in itself had any potential adverse effects. Without regard to permissive hypercapnia or mode of ventilation, overall complication rates remained low; hospital stay in comparison to nonventilated patients (5.8 vs 6.8 days; p=0.07), overall mortality 0.4%, pneumothorax 2.5%, and pneumonia 2.9%.[7]

The specific mode and settings of ventilation should be selected carefully to avoid barotrauma, minimise dynamic hyperinflation, maintain adequate oxygenation, and allow some degree of permissive hypercapnia until bronchodilators and steroids improve airflow.[138-40] Monitoring of plateau pressure (<30 cm H_2O) and intrinsic PEEP (<10-15 cm H_20) is critical since they are considered surrogate indices of dynamic hyperinflation and are agreed upon by most clinicians as reciprocals to better patient outcomes.[141] Volume-limited ventilation may be preferred for patients with frequent changes in airway resistance to avoid fluctuation in tidal volumes that increase the risk for hypoventilation.[142] Current recommendations suggest adjusting ventilator parameters to correlate a minute ventilation of 90-130 mL/kg ideal body weight and then by further adjusting respiratory

rate and tidal volume to achieve plateau pressures between 25-30 cm H_2O.[143]

Although prolonging the expiratory time may facilitate CO_2 clearance and prevent additional air trapping, reduction of minute ventilation is the most critical parameter to prevent and/or reduce air trapping. Rapid respiratory rates (>15 breaths/min), large tidal volumes (>10 mL/kg), low peak inspiratory flows (<60 L/min) and short expiratory times can generate intrinsic or auto-PEEP, which has been strongly associated with patient-ventilator dyssynchrony and worse clinical outcomes.[144] In general, after about 4 seconds of expiration there is nominal gain in reducing hyperinflation.[145] The patient with auto-PEEP is forced to work against the resistance of the ventilator circuit and against his own internal impedance to flow and chest expansion. With dynamic hyperinflation, only the most vigorous efforts can trigger the ventilator, and ineffective trigger can be observed.[146] Ventilator-related hypotension in these patients may indicate severe air trapping and require a brief disconnection of the patient from the ventilator.[147,148] Since the pressure and flow waveforms displayed on the ventilator monitor can alert the clinician if the patient's inspiratory effort is insufficient to trigger the ventilator, ventilator graphics may be an invaluable tool for monitoring extrinsic PEEP titration and its effects on the degree of hyperinflation, minute ventilation, CO_2 clearance, and the overall patient ventilator interaction.[37,149-151] Its use on sedated and paralysed patients who are on controlled ventilation has been noted to adversely increase lung volumes resulting in dynamic hyperinflation.[144]

The application of extrinsic PEEP in severe acute asthma is still a controversial issue and by several authors not recommended.[144,152,153] In patients with dynamic collapse of the airways such as emphysema, the addition of extrinsic PEEP can counterbalance the auto-PEEP without affecting expiratory flow.[154] However, the relative stiffness of the asthmatic airways caused by inflammation causes resistance to dynamic collapse. This may increase backpressure to expiratory flow when extrinsic PEEP is applied and result in more hyperinflation.[155] Previous reports have revealed that when applying extrinsic PEEP to asthmatics three different outcomes occurred; a paradoxical response with a decrease in lung volumes, a biphasic response in which no change occurred until applied PEEP reached 80% of the patient's auto-PEEP, and an overinflation response where an increase in air trapping was directly related to an increase in PEEP.[156,157] A study conducted by Caramez *et al* has suggested that physiology in the asthmatic may be more variable and some patients respond to PEEP with increased air trapping, some with no change in lung volume, and some with a paradoxical decrease in lung volume.[158] Whether the clinician ultimately decides to use PEEP or not, every attempt should be made to optimise tidal volume, respiratory rate, and the inspiratory to expiratory ratio before considering extrinsic PEEP as a magic bullet in acute severe asthma.

Permissive hypercapnia, or controlled hypoventilation, on the other hand should be considered in all patients with acute severe asthma to reduce the risk of severe dynamic hyperinflation and barotrauma.[159] Permissive hypercapnia is a lung protective strategy that involves maintaining peak airway pressures < 50 cm H_2O irrespective to $PaCO_2$ levels, delivering the lowest FIO_2 required to maintain adequate PaO_2 levels, and treating acidosis with sodium bicarbonate in order to limit over ventilation.[160] Permissive hypercapnia can be achieved by decreasing the respiratory rate, tidal volume, and/or simply by allowing the $PaCO_2$ levels to rise, which has been reported to be well tolerated even with $PaCO_2$ values as high as 90 mm Hg in critically ill patients.[38] Caution should be used when initiating permissive hypercapnia in patients with intracranial hypertension as cerebral blood flow reaches its maximum threshold at $PaCO_2$ levels of approximately 120 mm Hg, which may increase intracranial pressures and further complicate preexisting intracranial hypertension (head trauma, severe hypertension, and space-occupying lesions).[161]

Biologically variable ventilation (BVV) is a mode of mechanical ventilation that emulates healthy variation. Unlike conventional ventilation, which has a set tidal volume and respiratory rate, BVV is initiated by delivering a set minute volume while a microprocessor randomly generates varying

respiratory rates and corresponding tidal volumes in order to imitate natural breathing. When compared to conventional ventilation in an animal model of bronchospasm, BVV was associated with improved gas exchange, lower peak inspiratory pressures, a greater static and dynamic compliance and lower total respiratory system resistance.[162] Although the majority of studies have been performed on animals, a recent pilot study by Kowalski *et al* revealed when implementing BVV on patients with acute lung injury, that they demonstrated improved oxygen indices, lung compliance, and decreased dead space to tidal volume ratios.[163] Further human trials using BVV on asthmatic patients need to be completed before recommendation can be made.

Intrapulmonary Percussive Ventilation

Mechanical ventilation merely attempts to stabilise the patient until the bronchodilators and corticosteroids begin to take effect. Airway obstruction is also related to increased secretory production due in large proportion to goblet cell hyperplasia and submucosal gland hypertrophy. Mucus in the small airways cannot be typically cleared by cough and has a tendency to accumulate leading to worsening of airway obstruction. Postmortem examination of patients with fatal asthma often reveals extensive mucus plugging of the airways. Therefore, airway clearance techniques may have to be considered for some patients. Intrapulmonary percussive ventilation (IPV) is a modality of treatment designed to improve secretion clearance[164] and improve gas exchange in patients with obstructive lung pathology.[165] Cephalad displacement of airway secretions by bursts of gas can help in the mobilisation of mucus and enhance the effect of air-liquid interaction on mucus movement created by expiratory flow bias from the use of IPV.[166] A recent computed tomographic evaluation of the acute effects of IPV in patients with COPD revealed changes in the airway patency even after a single IPV treatment compared with before treatment.[167] Although this positive effect could be extrapolated to patients with airway obstruction such as those with severe asthma, the use of IPV merits further study in status asthmaticus in a randomised fashion.

Inhaled anaesthetics

Inhaled anaesthetics have only been used sporadically for the treatment of patients with acute severe asthma to avoid bronchoconstriction and to induce bronchodilation. Publications on the use of inhalational anaesthetics in acute severe asthma have been limited to case reports for a relatively small number of asthmatic patients who required mechanical ventilation.[168,169] Inhalational anaesthetics may cause a decrease in airway pressures and improvement in blood gases.[170-172] A recent update on the anaesthetic approach for the asthmatic patient recommends regional over general anaesthesia, if feasible, to reduce airway irritation and post-anaesthesia complications.[173] However, when general anaesthesia is chosen over regional, it is suggested that a laryngeal mask airway be chosen over endotracheal intubation. Lidocaine inhalation, via nebuliser, has been shown to reduce histamine-induced bronchoconstriction.[174] Ketamine may decrease the risk of bronchospasm. Certain nondepolarising neuromuscular blocking agents such as vecuronium, rocuronium, cisatracurium, and pancuronium do not induce bronchospasm; however, rapacuronium, an ultra-short acting non-depolarising agent, has been shown to cause bronchoconstriction and death.[175] Both atracurium and mivacurium have been shown to induce the release of histamine in a dose-dependent fashion.[176]

Extracorporeal Life Support

Extracorporeal life support could provide adjunctive pulmonary support for intubated asthmatic patients who remain severely acidotic and hypercapnic in spite of aggressive conventional therapy and unconventional therapies, including inhaled anaesthetics.[177]

Most of the previously described treatments are considered adjunctive to traditional interventions and are generally limited to physicians and emergency centres familiar and comfortable with their administration. Although they cannot be routinely recommended for treating acute severe asthma, they should be considered as a means of possibly avoiding intubation, which has a significant

impact on mortality rates and ICU and hospital length of stay for asthmatic patients.

Prognosis and Post-Acute Follow Up

Mortality rate of patients with acute severe asthma has decreased significantly in recent years. However, nearly 10 to 30% of patients with acute severe asthma may still require positive pressure ventilation and mortality could be as high as 22%.[178]

Design and implementation of an asthma action plan is a critical element of the post-acute care.[179] Asthma triggers should be adequately identified and controlled. Patients and their families must receive education on how to use aerosol devices and peak flow meters. Asthma educators and physicians should put in place a mechanism to monitor adherence to therapy and use of short-acting bronchodilators to reduce frequency of exacerbations and emergency department, hospital, or ICU admissions.[180-182]

Asthmatics should also be aware of environmental triggers that may worsen their asthma symptoms, which include allergens, infections, occupational sensitisers, tobacco smoke (passive and active smoking), outdoor/indoor air pollution, and/or diet.[183] One of the best approaches for an asthmatic to alleviate their symptoms and help prevent exacerbations is to follow an asthma action plan.[40,184] This plan enables the patient to monitor and help control their asthma outside of the clinical setting once they have been discharged from the hospital. An asthma action plan is a tool that is designed for each individual patient that contains PEFR monitoring (green zone; doing well if >80% of best, yellow zone; asthma is getting worse if >50-79% of best, and red zone; medical alert if <50% of best), list of prescribed maintenance and emergency medications, dosages of medications, and when to take these medications.[40] Bad asthma control has been linked to inhaler incompetence due to improper inhaler technique in an average of 50% of the patients (14-90%).[185] Recent studies have linked lack of and/or neglected inhaler education by physicians to patient incompetence in the use of inhalers. In one study, only 5% of medical interns knew how to properly use a pMDI.[186]

Omalizumab, a recombinant DNA-derived humanised IgG1 monoclonal antibody that selectively binds to free and membrane-bound immunoglobulin E (IgE) antibodies, has been recently evaluated in patients with severe uncontrolled allergic asthma. Several studies have shown a significant decrease in the risk of severe asthma exacerbations requiring emergency department visits or hospitalisations, and oral intake of corticosteroids.[187-188]

Bronchial thermoplasty is a new bronchoscopic procedure approved by the FDA in 2010 that reduces excess airway smooth muscle by applying controlled thermal energy to the airway walls. In patients with severe refractory asthma this therapy has been associated with a significant reduction in hospitalisations and emergency department visits for respiratory symptoms and improvement in the quality of life.[189-191]

Conclusion

While current pharmacotherapy is typically effective, acute severe asthma continues to be challenging to clinicians. Early detection of high-risk patients, adequate outpatient therapy, and extremely close observation of these patients in the ED may decrease the incidence of fatalities. A clear understanding of the acute asthmatic event may shed some light to the best therapy and the prevention of life-threatening events. Clinical outcomes in this group of patients with severe asthma in the post-acute phase can be dramatically improved if preventive measures are in place. Adequate identification and management of triggers, implementation of a rigorous asthma action plan, monitoring for good adherence to inhaled anti-inflammatory therapy, regular peak flow monitoring, and close medical follow-up decrease the number of exacerbations and reduces the risk for life-threatening events.

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