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Acute Severe Asthma

New Approaches to Assessment and Treatment

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Abstract

The precise definition of a severe asthmatic exacerbation is an issue that presents difficulties. The term 'status asthmaticus' relates severity to outcome and has been used to define a severe asthmatic exacerbation that does not respond to and/or perilously delays the repetitive or continuous administration of short-acting inhaled β_2-adrenergic receptor agonists (SABA) in the emergency setting. However, a number of limitations exist concerning the quantification of unresponsiveness. Therefore, the term 'acute severe asthma' is widely used, relating severity mostly to a combination of the presenting signs and

symptoms and the severity of the cardiorespiratory abnormalities observed, although it is well known that presentation does not foretell outcome.

In an acute severe asthma episode, close observation plus aggressive administration of bronchodilators (SABAs plus ipratropium bromide via a nebulizer driven by oxygen) and oral or intravenous corticosteroids are necessary to arrest the progression to severe hypercapnic respiratory failure leading to a decrease in consciousness that requires intensive care unit (ICU) admission and, eventually, ventilatory support. Adjunctive therapies (intravenous magnesium sulfate and/or others) should be considered in order to avoid intubation. Management after admission to the hospital ward because of an incomplete response is similar.

The decision to intubate is essentially based on clinical judgement. Although cardiac or respiratory arrest represents an absolute indication for intubation, the usual picture is that of a conscious patient struggling to breathe. Factors associated with the increased likelihood of intubation include exhaustion and fatigue despite maximal therapy, deteriorating mental status, refractory hypoxaemia, increasing hypercapnia, haemodynamic instability and impending coma or apnoea. To intubate, sedation is indicated in order to improve comfort, safety and patient-ventilator synchrony, while at the same time decrease oxygen consumption and carbon dioxide production. Benzodiazepines can be safely used for sedation of the asthmatic patient, but time to awakening after discontinuation is prolonged and difficult to predict. The most common alternative is propofol, which is attractive in patients with sudden-onset (near-fatal) asthma who may be eligible for extubation within a few hours, because it can be titrated rapidly to a deep sedation level and has rapid reversal after discontinuation; in addition, it possesses bronchodilatory properties. The addition of an opioid (fentanyl or remifentanil) administered by continuous infusion to benzodiazepines or propofol is often desirable in order to provide amnesia, sedation, analgesia and respiratory drive suppression.

Acute severe asthma is characterized by severe pulmonary hyperinflation due to marked limitation of the expiratory flow. Therefore, the main objective of the initial ventilator management is 2-fold: to ensure adequate gas exchange and to prevent further hyperinflation and ventilator-associated lung injury. This may require hypoventilation of the patient and higher arterial carbon dioxide ($PaCO_2$) levels and a more acidic pH. This does not apply to asthmatic patients intubated for cardiac or respiratory arrest. In this setting the post-anoxic brain oedema might demand more careful management of $PaCO_2$ levels to prevent further elevation of intracranial pressure and subsequent complications. Monitoring lung mechanics is of paramount importance for the safe ventilation of patients with status asthmaticus.

The first line of specific pharmacological therapy in ventilated asthmatic patients remains bronchodilation with a SABA, typically salbutamol (albuterol). Administration techniques include nebulizers or metered-dose inhalers with spacers. Systemic corticosteroids are critical components of therapy and should be administered to all ventilated patients, although the dose of systemic corticosteroids in mechanically ventilated asthmatic patients remains controversial. Anticholinergics, inhaled corticosteroids, leukotriene receptor antagonists and methylxanthines offer little benefit, and clinical data favouring their use are lacking.

In conclusion, expertise, perseverance, judicious decisions and practice of evidence-based medicine are of paramount importance for successful outcomes for patients with acute severe asthma.

1. Definitions

According to current guidelines,[1-3] asthmatic exacerbations are defined as episodes of increased breathlessness, cough, wheezing, chest tightness or some combination of these symptoms. Exacerbations may have a progressive or abrupt insurgence and are always related to decreases in expiratory (and in severe cases also in inspiratory) airflows that should be quantified objectively by lung function measurements. Decreases in airway flows are mainly related to both airway inflammation and airway smooth muscle constriction, which occasionally may be severe enough to lead to life-threatening airway obstruction even in the absence of mucous plugging.[4,5] Inflammation in asthma consists of airway oedema, cellular infiltration by eosinophils (and in some cases neutrophils), activated CD4+ T lymphocytes and mast cells, and intraluminal mucous plugs composed of mucin glycoproteins, plasma proteins, epithelial and inflammatory cells, and cellular debris.[1-7] In addition, dynamic hyperinflation in severe asthmatic exacerbations may consistently affect airflows.[8,9] Asthmatic exacerbations may be mild or severe, may resolve spontaneously, may be responsive or unresponsive to treatment, and may lead to death.[10-15] Poor perception of airway obstruction or hypoxaemia in some patients may herald an unfavourable outcome of their asthma.[16]

The precise definition of a severe asthmatic exacerbation is an issue that presents difficulties.[10] The term 'status asthmaticus' relates severity to outcome and has been used to define a severe asthmatic exacerbation that does not respond to and/or perilously delays the repetitive or continuous administration of short-acting inhaled β_2-adrenergic receptor agonists (SABAs) in the emergency setting.[17-21] However, a number of limitations exist concerning the quantification of unresponsiveness in terms of time and intensity of β_2-adrenergic receptor agonist treatment. Therefore, the term 'acute severe asthma' is widely used, relating severity mostly to a combination of the presenting signs and symptoms, and the severity of the cardiorespiratory abnormalities observed, although it is well known that presentation does not foretell outcome. In an acute severe asthma episode, close observation plus aggressive administration of bronchodilators (SABAs plus ipratropium bromide) and oral or intravenous corticosteroids, which are the mainstay of treatment, are necessary to arrest the progression to severe hypercapnic respiratory failure leading to a decrease in consciousness that requires ventilatory support and intensive care unit (ICU) admission. Near-fatal asthma mainly defines the resolution of a severe asthmatic exacerbation in a patient previously admitted into the ICU and/or mechanically supported.[22-25] Acute severe asthma is a life-threatening condition (one of the 'gates' of entry of asthma death) where the deterioration of the asthmatic exacerbation usually progresses over days or weeks, although in a few patients over hours or even minutes. Any patient with asthma may experience during his or her lifetime a severe asthmatic exacerbation. Occasionally, acute severe asthma may present as a new problem in a patient who is unaware of his or her asthma, and diagnosis needs to be established in the emergency department. Morbidity and mortality are mainly related to the underestimation of the severity of the exacerbation, delay in referring to hospital and/or inadequate emergency treatment. Occasionally, asthma fatalities are first diagnosed at autopsy.[26]

Asthma deaths appear to affect all age groups and bronchial asthma represents a significant cause of sudden unexpected deaths in the community. Most asthma fatalities occur outside the hospital and may present in one of two ways: 'slow-onset, late-arrival' events[27] and 'sudden-onset fatal asthma'.[28,29] The majority of asthma fatalities (80–85%) occur in middle-aged or elderly

patients with severe and poorly controlled disease who deteriorate over days or weeks prior to the respiratory arrest, which is the so-called slow-onset, late-arrival asthma death. A variation of this pattern is a history of unstable disease that is partially responsive to treatment, upon which a major attack is superimposed. In both situations, hypercapnic respiratory failure and mixed acidosis ensues, and the patient succumbs to respiratory arrest and to supervening arrhythmias and cardiac arrest,[22] or if mechanical ventilation is applied in a timely manner, the patient succumbs to complications such as barotrauma and ventilator-associated pneumonia. Pathological examination in such patients shows extensive airway plugging by dense and tenacious mucous mixed with inflammatory and epithelial cells, epithelial denudation, mucosal oedema and an intense eosinophilic infiltration of the submucosa.[30] Widespread lung hyperinflation and occasional areas of atelectasis usually coexist. The remaining asthma fatalities can be sudden and unexpected without obvious antecedent long-term deterioration of asthma control, the so-called sudden-onset fatal asthma. Affected individuals are younger with normal or quite normal lung function even a few days or hours before, without symptoms outside of the exacerbations that develop rapidly severe hypercapnic respiratory failure with combined metabolic and respiratory acidosis, and succumb to respiratory arrest. However, if treated in a timely manner (medically and/or mechanically ventilated), they present a faster rate of improvement than patients with slow-onset asthmatic exacerbation. Pathological examination in such patients shows 'empty' airways (no mucous plugs) in some and, in almost all patients, a greater proportion of neutrophils than eosinophils infiltrating the submucosa.

2. Epidemiology

Bronchial asthma remains one of the most common chronic diseases in the world. According to estimations, over 300 million people currently have asthma worldwide, with a constant trend of increase in rates as societies adopt Western lifestyles and become urbanized, and as greater awareness of this condition appears and standardized methods of diagnosis are established.[1-3] The recent publication of phase three from the ISAAC (International Study of Asthma and Allergies in Childhood) Study Group[31] brings to light once more the striking variations in the prevalence of asthma symptoms between different geographical areas and populations, with rates ranging from 3% to 38%. Although the English language countries and Latin America have the highest prevalence rates, bronchial asthma is more often under diagnosed and more severe in Africa, the Indian subcontinent and the Eastern Mediterranean. More precisely, the prevalence of severe asthma is found to range between countries from 1.1% to 20.3% in the 6- to 7-year-old age group.

The social and economic burden of such a common disease is another crucial parameter of its epidemiology, and is related to the costs of outpatient and in-hospital treatment, time lost from work and premature death. The financial burden is estimated to be >$US11.5 billion per year (year of cost 2005), the disability-adjusted life-years lost annually as a result of asthma are estimated to be 15 million and the case fatality rate ranges from <1 to >35/100 000 asthmatic patients (figure 1).[1,2,15,32] Although exacerbations in children and adults follow a seasonal pattern, the proportion of patients hospitalized for asthma requiring admission to an ICU or intubation is constant month by month in relation to the total admissions in that month.[33]

Fewer than 10% of patients have exacerbations severe enough to be judged life threatening, whereas around 2–20% of patients are admitted to the ICU and 4% of patients are finally intubated and mechanically ventilated, although numbers vary greatly between studies.[10,32] Interestingly, mild asthma is the cause of severe exacerbations requiring emergency consultation in 30–40% of cases.[34] The epidemiology of status asthmaticus in the emergency setting is described less meticulously. A recent study from the US reports a trend towards increasing severity of status asthmaticus in the recent 5-year period, as indicated by the degree of respiratory acidosis, need for neuromuscular blockade and longer duration of mechanical ventilation encountered in this group of patients.[35]

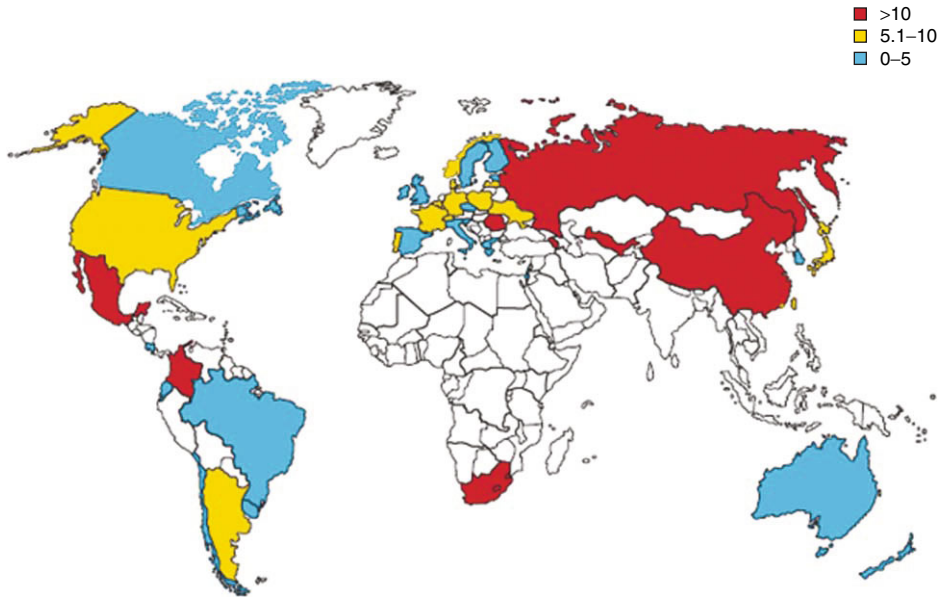

Fig. 1. World map of asthma case fatality rates (asthma deaths per 100 000 asthmatic patients in the 5- to 34-year-old age group). Countries are shaded according to the case fatality rate of that country; no standardized data were available for the unshaded areas (reproduced from Masoli et al.,[15] with permission from Wiley-Blackwell).

Annual worldwide deaths from asthma have been estimated at 250 000 people.[1] Fatalities appear to have been decreasing worldwide over the past 15 years, even in the face of an increasing prevalence of the disease.[1-3,36,37] As described in section 1, the majority of all asthma deaths occur before hospitalization and mostly in the older age groups. However, asthma mortality in studies is often defined in the 5- to 34-year-old age group due to the absence of other co-morbidities. In hospitals, mortality ranges from 0.4% to 12%.[38] Asthma patients usually die of respiratory failure outside the hospital, and of barotrauma and/or sepsis after ICU admission. No serious arrhythmias are encountered in patients with near-fatal asthma who are treated in the emergency department. Intubation/mechanical ventilation are associated with a significantly higher risk of death. After the epidemics of asthma mortality in the 1960s, 1970s and 1980s, studies in the last decade have shown that mortality rates have stabilized or gradually decreased in different countries, partly as a result of the increased rate of use of inhaled corticosteroids.[39,40] Reduction rates in mortality of up to 63% indicate that asthma mortality is preventable, and proper patient education, access to appropriate medical treatment and identification of risk factors of near-fatal asthma (table I) are actions that are desperately required to reduce the burden of asthma.[41,42]

3. Pathophysiology

The histopathological changes previously described in asthmatic fatalities support the hypothesis that peripheral airway occlusion forms the pathological basis of the gas exchange abnormalities observed in patients with acute severe asthma. In such patients, widespread occlusion of the airways leads to the development of extensive areas of alveolar units in which ventilation is severely reduced but perfusion is maintained (i.e. areas with ventilation/perfusion mismatch, frequently lower than 0.1).[43] Intrapulmonary shunt is uncommon in the majority of patients because of the collateral ventilation, the effectiveness of the hypoxic pulmonary vasoconstriction and the fact that the airway obstruction is rarely functionally complete. Therefore, hypoxaemia is common in

Table I. Risk factors for near-fatal asthma[9,40]

Risk factors
A history of prior mechanical ventilation and intensive care unit admission
Prescription of oral corticosteroids and theophylline
Evidence of worsening asthma over a period of 2–7 days and increasing use of short-acting β_2-adrenergic receptor agonists
Poor compliance with inhaled corticosteroid therapy
Atopy and sensitivity to *Alternaria* spp.
Home exposure to air-conditioning and dusty conditions
Male sex
Smoking history
Difference in perception of dyspnoea
Age >40 years
Hyperinflation on chest radiograph
Suboptimal medical advice

every severe asthmatic exacerbation, and although mild hypoxia is easily corrected with the administration of relatively low concentrations of supplemental oxygen,[44] more severe hypoxaemic values, such as arterial oxygen (PaO_2) <50 mmHg, require higher concentrations of supplemental oxygen and may relate to some contribution of shunt physiology. However, one should keep in mind that refractory hypoxaemia is not a common feature of acute severe asthma, and should rather prompt differential diagnoses, including pulmonary embolism, acute respiratory distress syndrome, exacerbation of chronic obstructive pulmonary disease (COPD) or pneumothorax.

Analysis of arterial blood gases is important in the management of patients with acute severe asthma, but it is not predictive of outcome. In the early stages of an asthmatic exacerbation, analysis of arterial blood gases usually reveals mild hypoxaemia, hypocapnia and respiratory alkalosis. If the exacerbation persists and deteriorates, and the patient's clinical status continues for a few days, there may be some compensatory renal bicarbonate secretion, which manifests as a non-anion-gap metabolic acidosis. As the severity of airflow obstruction increases, arterial carbon dioxide ($PaCO_2$) first normalizes and subsequently increases because of patient exhaustion, inadequate alveolar ventilation and/or an increase in physiological dead space. Hypercapnia is not usually observed for forced expiratory volume in 1 second (FEV_1) values >25% of predicted normal, but in general there is no correlation between airflow rates and gas exchange markers. In addition, a paradoxical deterioration of gas exchange (worsening hypoxaemia) while flow rates improve after the administration of β_2-adrenergic receptor agonists is not uncommon, and relates to the removal of hypoxaemic vasoconstriction operated by the vasodilating action of β_2-adrenergic receptor agonists. Respiratory acidosis is always present in hypercapnic patients who rapidly deteriorate, and in severe, advanced-stage disease metabolic (lactic) acidosis may coexist. Several mechanisms are probably involved in lactic acidosis:[45-47] (i) changes in glycolysis in the direction of an increase in glycogenolysis, gluconeogenesis and lipolysis related to the use of high-dose β-adrenergic receptor agonists; (ii) the highly increased work of breathing, resulting in anaerobic metabolism of the ventilatory muscles and overproduction of lactic acid; (iii) the eventually coexisting profound tissue hypoxia (occult shock); (iv) overproduction of lactic acid by the lungs; and (v) the decreased lactate clearance by the liver related to hypoperfusion.

During a severe asthmatic exacerbation, all indices of expiratory flow, including FEV_1, FEV_1/forced vital capacity (FVC), peak expiratory flow (PEF), maximal expiratory flows at 75%, 50% and 25% of FVC (MEF_{75}, MEF_{50} and MEF_{25}, respectively), and maximal expiratory flow between 25% and 75% of the FVC ($MEF_{25–75}$) are significantly reduced. The abnormally high airway resistance observed (5–15 times normal) is directly related to the shortening of airway smooth muscle, airway oedema and inflammation, and excessive luminal secretions, and leads to a dramatic increase in flow-related resistive work of breathing. Although the increased resistive work significantly contributes to patient functional status, the elastic work also increases significantly, and may lead to respiratory muscle fatigue and further deterioration of ventilatory failure.[48,49]

In acute severe asthma that is unresponsive to treatment, remarkably high volumes of functional residual capacity (FRC), total lung capacity (TLC) and residual volume can be observed, and tidal breathing occurs near predicted TLC

(figure 2a–c). Lung hyperinflation that develops as a result of acute airflow obstruction may have some beneficial effects because it improves gas exchange. The increase in lung volume tends to increase airway calibre and, consequently, may reduce the resistive work of breathing. However, this is accomplished at the expense of increased mechanical load and elastic work of breathing. Lung hyperinflation in acute severe asthma is related primarily to the fact that the highly increased airway expiratory resistance, high ventilatory demands, short expiratory time and increased post-inspiratory activity of the inspiratory muscles (all present at variable degrees) do not permit the respiratory system to reach static equilibrium volume at the end of expiration. Inspiration therefore begins at a volume at which the respiratory system exhibits a positive recoil pressure. This pressure is called intrinsic positive end-expiratory pressure (PEEPi) or auto-PEEP (figure 2a–c).[8,9] This phenomenon is called 'dynamic hyperinflation' and is directly proportional to minute ventilation and the degree of airflow obstruction. Dynamic hyperinflation has significant unfavourable effects on lung mechanics. First, it shifts tidal breathing to a less compliant part of the respiratory system pressure–volume curve, leading to an increased pressure–volume work of breathing. Second, it flattens the diaphragm and reduces the generation of force because muscle contraction results from a mechanically disadvantageous fibre length. Third, it increases dead space, thus, increasing the minute volume required to maintain adequate ventilation. The direct clinical consequence of dynamic hyperinflation is the lowering of inspiratory flows clinically observed as a 'silent chest'. Conceivably, asthma increases all three components of respiratory system load, namely resistance, elastance and minute volume. Finally, the diaphragmatic blood flow may also be reduced. Under these overwhelming conditions, as with the persistence of status asthmaticus, ventilatory muscles cannot sustain adequate tidal volumes and hypercapnic respiratory failure rapidly worsens.

Acute severe asthma also profoundly affects the function of the cardiovascular system of the patient.[50,51] In expiration, because of the effects of dynamic hyperinflation, the systemic venous return decreases significantly and again rapidly increases in the next inspiratory phase. Rapid right ventricular filling in inspiration, by shifting the interventricular septum towards the left ventricle, may lead to left ventricular diastolic dysfunction and incomplete filling. The large negative intrathoracic pressure generated during inspiration increases the left ventricular afterload by impairing systolic emptying. Pulmonary

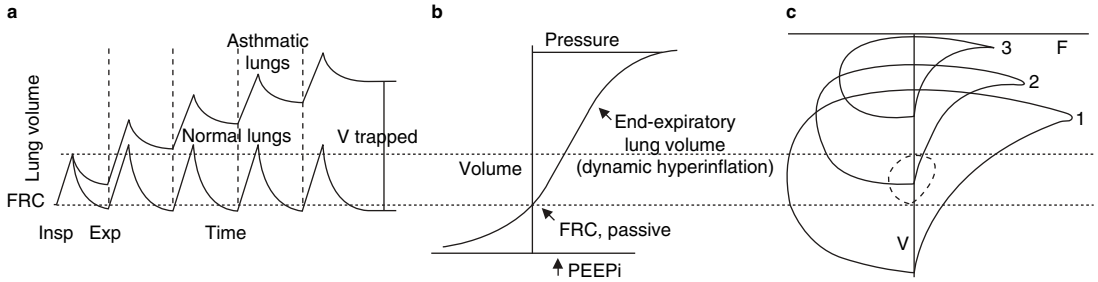

Fig. 2. (**a**) Mechanism of dynamic pulmonary hyperinflation in severe airflow obstruction. Inspiration begins before complete exhalation of the tidal breath, leading to gas trapping and an increased end-expiratory lung volume. The pressure within the airways and alveoli at the end of exhalation (which is higher than atmospheric pressure) is referred to as intrinsic positive end-expiratory pressure (PEEPi) or auto-PEEP. (**b**) Relationship between volume and pressure in the respiratory system. Dynamic hyperinflation adds an elastic load to inspiratory muscles. To initiate inspiratory flow the inspiratory muscles must first overcome PEEPi. Dynamic hyperinflation shifts tidal breathing to a less compliant part of the respiratory system pressure–volume curve, leading to increased pressure–volume breathing. (**c**) Flow–volume curves as asthma exacerbation aggravates (deteriorating airway obstruction from curve no. 1 to curve no. 3). All flows (inspiratory and expiratory) are reduced in relation to the effects of dynamic hyperinflation (reproduced from Levy et al.,[50] with permission from Springer Science+Business Media). **Exp** = expiratory time; **F** = flow; **FRC** = functional residual capacity; **Insp** = inspiratory time; **V** = volume.

artery pressure may also be increased due to lung hyperinflation, thereby resulting in increased right ventricular afterload. These events may accentuate the normal inspiratory reduction in left ventricular stroke volume and systolic pressure, leading to the appearance of pulsus paradoxus (significant reduction of the arterial systolic pressure in inspiration). A variation in systolic blood pressure of more than 12 mmHg between inspiration and expiration represents a sign of severity in asthmatic exacerbation. However, no delay in treatment decisions is justified by the attending physician in order to objectively quantify the appearance of pulsus paradoxus. In advanced stages, when ventilatory muscle fatigue ensues, pulsus paradoxus will decrease or disappear as force generation declines. Such a status harbingers impeding respiratory arrest.

4. Clinical Assessment

Clinical evaluation of a patient with acute severe asthma must be rapid but thorough (table II). It should include as complete a history as possible, insisting on special features such as previous hospitalizations and emergency department visits, ICU admissions resulting in intubation, co-morbid conditions, and current medications and time of last dose.[1-3] The patient should indicate whether they are experiencing breathlessness, cough, wheezing, chest tightness, chest pain or any combination of those symptoms.[52]

A focused physical examination should allow the physician to diagnose asthma and recognize the severity of the situation. It should also allow them to diagnose other medical entities that can be confused with asthma, including COPD, vocal

Table II. Formal evaluation of asthma exacerbation severity in the urgent or emergency care setting (for adults) [reproduced from the US Department of Health and Human Services,[3] with permission]

Symptom and assessment	Mild	Moderate	Severe	Respiratory arrest imminent
Symptoms				
Breathlessness	While walking, can lie down	While at rest, prefers sitting	While at rest, sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Use of accessory muscles, suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate, often only end-expiratory	Loud, throughout exhalation	Usually loud, throughout inhalation and exhalation	Absence of wheeze
Pulse per minute	<100	100–120	>120[a]	Bradycardia
Pulsus paradoxus (mmHg)	Absent <10	May be present 10–25	Often present >25	Absence suggests respiratory muscle fatigue
Functional assessment				
PEF predicted or personal best (%)	≥70	40–69 or response lasts <2 h	<40	<25[b]
SaO_2 (on air) [%]	>95 (arterial blood gases not necessary)	90–95 (arterial blood gases not necessary)	<90	
PaO_2 (on air) [mmHg]	Normal	≥60	<60 (cyanosis)	
$PaCO_2$ (mmHg)	<42	<42	≥42: possible respiratory failure	

a <10% of patients with acute severe asthma showed a respiratory rate >25 per minute. Similarly, <15% had a pulse rate >120 per minute. In fact, suprasternal retraction and functional assessment are the only specific findings for acute severe asthma.[10]

b PEF testing may not be needed in very severe attacks.

$PaCO_2$ = arterial carbon dioxide; **PaO_2** = arterial oxygen; **PEF** = peak expiratory flow; **SaO_2** = oxygen saturation.

cord dysfunction, cardiogenic and non-cardiogenic pulmonary oedema, bronchiectasis, endobronchial lesions and foreign bodies, extra- or intrathoracic narrowing of the trachea, and pulmonary emboli, as well as possible complicating conditions such as pneumonia, pneumothorax, pneumomediastinum and atelectasis.[53] The general appearance of the patient can often lead to the recognition of significant respiratory distress. Patients with the most severe conditions will be sitting upright, be seriously dyspnoeic and communicate using short phrases and/or words. Rapid, shallow breathing and the use of accessory muscles are indicators of severe obstruction. Signs such us cyanosis, gasping, exhaustion, hypotension and decreased consciousness are suggestive of a life-threatening attack and indicate the need for immediate therapeutic decisions, including mechanical ventilation.[1-3] The physical examination usually reveals inspiratory and expiratory wheezing or even the complete absence of audible sounds (silent chest), which is an indication of the most severe obstruction and the inability to generate inspiratory airflows due to dynamic hyperinflation. Nevertheless, the intensity of wheezing is not a predictor of respiratory failure or response to treatment. Respiratory rate >30 breaths/minute, heart rate >120 beats/minute and the presence of pulsus paradoxus are signs of a severe asthma exacerbation, whereas abdominal paradox, the absence of wheezing and bradycardia are indicators of an imminent respiratory arrest.[1-3]

Most asthma exacerbations are not associated with significant hypoxaemia, so an assessment of gas exchange should be obtained in cases of severe asthma when oxygen saturation (SaO_2) is <90%. In addition, measurement of arterial blood gas should be considered in patients with suspected hypoventilation, severe distress, or FEV_1 or PEF <25% of predicted after initial treatment. SaO_2 should be monitored closely, preferably by pulse oximetry. As previously described, blood gas abnormalities seen in acute asthma consist of a combination of hypoxaemia, hypocapnia and respiratory alkalosis, whereas normocapnia and hypercapnia indicate a more severe situation, especially in patients who have transitioned from initial hypocapnia to hypercapnia. Respiratory or metabolic acidosis indicates the need for close monitoring, aggressive treatment and decisions, including mechanical ventilation if other conditions to support clinical judgement for intubation exist.[54]

Blood counts are indicated in patients with fever and/or purulent sputum, taking into account that leukocytosis is not uncommon in asthma exacerbations (mainly eosinophilia), and that treatment with corticosteroids may cause a prompt reduction of eosinophils but may increase neutrophils within 1–2 hours of administration. Glucose levels in order to detect hyperglycaemia, electrolytes and serum theophylline levels should also be measured when indicated by co-morbidities and drug therapy of the individual patient. Hypokalaemia associated with the use of β_2-adrenoceptor agonists and systemic corticosteroids, especially in patients taking diuretics, is a common finding, along with decreased serum levels of magnesium and phosphate, although clinically significant reductions are considered unusual.[50] An ECG could reveal P-pulmonale, right axis shift, right bundle branch block and arrhythmias. Atrial arrhythmias are not common, but the most common finding is sinus tachycardia.[55] Myocardial ischaemia or infarction have been encountered as possible complications of a severe asthma exacerbation in patients with a history of coronary artery disease. A chest radiograph is not required routinely, but should be carried out in all hospitalized patients and in patients not responding to treatment, especially when a complication is suspected, such us pneumothorax, atelectasis or pulmonary oedema.[56] In most patients, a chest radiograph is expected to be normal or to show hyperinflated lung fields.[57]

Functional assessments such as measurement of PEF or FEV_1, and especially serial monitoring of these parameters, provide a useful and objective guide to estimate severity and clinical response to therapy. Nevertheless, it is of great importance to obtain a baseline, pre-treatment value of PEF or FEV_1 if possible, without seriously delaying treatment. According to a multicentre clinical trial, spirometry for the purpose of obtaining an FEV_1 can be performed from most acutely ill asthmatic patients in the emergency department.[58] It is recommended that FEV_1 or PEF be measured on admission and 15–20 minutes after bronchodilator therapy during the acute phase. Current guidelines

suggest that asthmatic patients with a PEF value between 33% and 50% of predicted or personal best are considered to be experiencing an acute severe asthmatic exacerbation, whereas patients with even lower values are considered to be experiencing a life-threatening asthma exacerbation.[2] Patients with a pre-treatment FEV_1 or PEF <25% of predicted or personal best, or those with a post-treatment FEV_1 or PEF <40% of predicted or personal best, usually require hospitalization. There have been reports in the literature of cardiopulmonary arrest in asthmatic patients after deep inspiration manoeuvres involved in PEF measurement, especially in patients who previously had acute bronchoconstriction or cough after these functional tests.[59] This is not to say that monitoring with PEF during a severe asthma attack is hazardous, but when PEF measurements are performed the patient should be observed carefully.

5. Principles of Treatment

The management of severe asthmatic exacerbations in the emergency department and after admission into the hospital ward or ICU is shown in figure 3. Close observation plus aggressive administration of bronchodilators (SABAs plus ipratropium bromide via a nebulizer driven by oxygen) and oral or intravenous corticosteroids is the mainstay of treatment in the emergency department (table III). Adjunctive therapies should be considered in order to avoid intubation. Management after admission to the hospital ward is similar (although ipratropium bromide is probably not necessary at this stage). Deterioration and/or persistence of severe clinical status warrant admission to the ICU. The decision to intubate is essentially based on clinical judgement. Although cardiac or respiratory arrest represents an absolute indication for intubation, the usual picture is that of a conscious patient struggling to breathe. Conditions supporting the clinician's assessment that maintenance of spontaneous ventilation is unlikely include exhaustion and fatigue despite maximal therapy, deteriorating mental status, refractory hypoxaemia, increasing hypercapnia, haemodynamic instability, and impending coma or apnoea.

6. Therapeutic Modalities

6.1 Oxygen

Oxygen supplementation is an integral part of the treatment of bronchial asthma exacerbations, along with β_2-adrenergic receptor agonists and corticosteroids. Supplemental oxygen should be started in order to achieve SaO_2 >90% for most patients, whereas in pregnant women and patients with heart disease, SaO_2 should be maintained at around 95%. Severe hypoxaemia is uncommon in most asthma exacerbations, and moderate hypoxaemia can usually be restored by nasal cannulae at flow rates of 2–4 L/minute or mask by giving modest concentrations of supplemented oxygen.[60] Nevertheless, in acute severe asthma, hypoxaemia is encountered reasonably frequently. In this situation, the fractional concentration of oxygen administered should be guided closely by pulse oximetry for the timely diagnosis of impending respiratory failure. In addition, bronchodilators are usually administered through nebulizers driven by oxygen, and each nebulizer device requires at least 10–12 L/minute flows in order to deliver drugs effectively in the lower airways. Administration of 100% oxygen to critically ill asthmatic patients should be given with caution because it may result in respiratory depression followed by carbon dioxide retention, especially in patients with severe airway obstruction.[61]

6.2 β_2-Adrenergic Receptor Agonists

Repetitive or continuous administration of SABAs is the cornerstone of therapy for acute severe asthma. These agents mediate bronchodilation via stimulation of β_2-receptors on airway smooth muscle, which in turn mediate smooth muscle relaxation. SABAs potentially induce additional responses that may be of benefit in asthma, such as decreased vascular permeability, increased mucociliary clearance and inhibition of release of mast cell mediators. The most commonly used agent is salbutamol (albuterol); terbutaline is an almost equally effective and selective SABA. Other selective SABAs are levosalbutamol (levalbuterol), fenoterol, reproterol and pirbuterol. Isoprenaline (isoproterenol) and

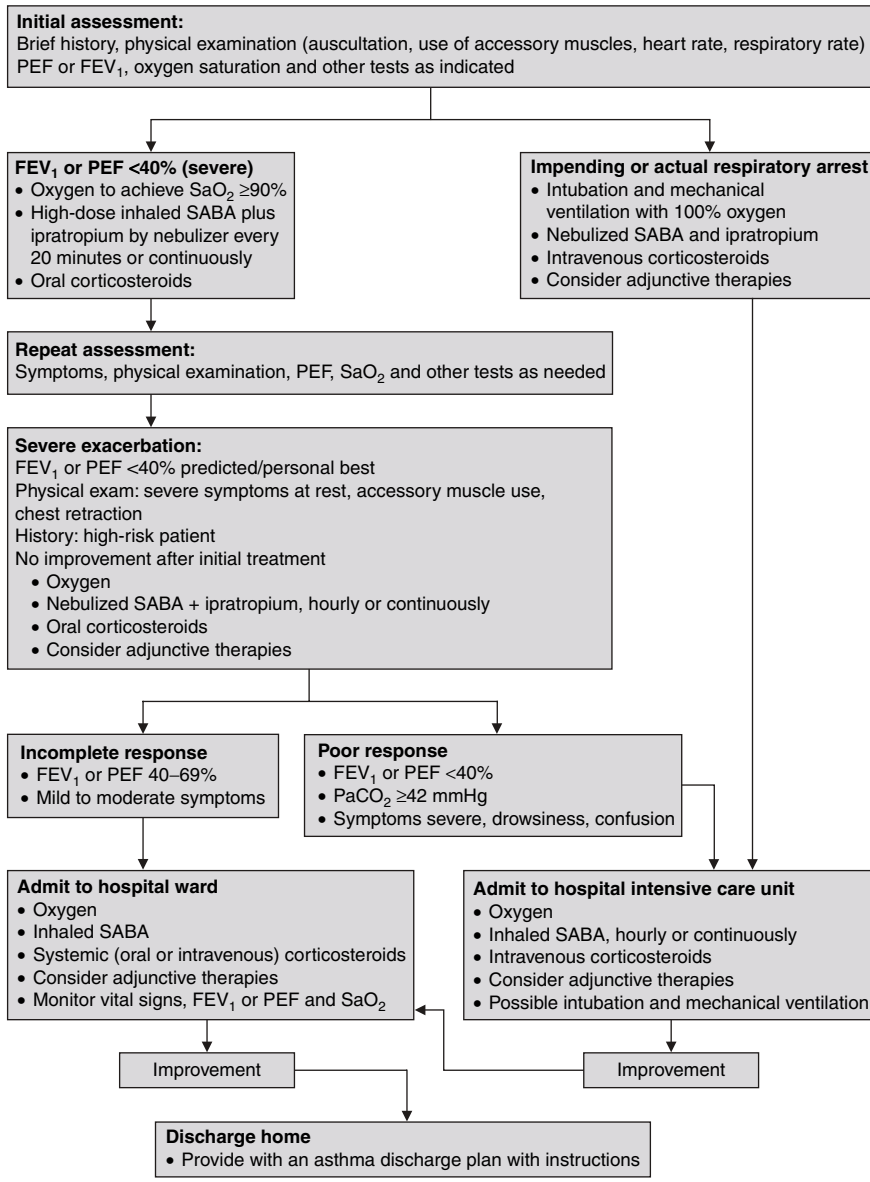

Fig. 3. Management of patients with severe asthma exacerbations and emergency department and hospital-based care (adapted from the National Asthma Education and Prevention Program Guidelines[3]). **FEV_1** = forced expiratory volume in 1 second; **$PaCO_2$** = partial pressure of carbon dioxide; **PEF** = peak expiratory flow; **SABA** = short-acting β_2-adrenergic receptor agonist; **SaO_2** = oxygen saturation.

epinephrine (adrenaline) are potent bronchodilators but less selective than SABAs. There is no evidence that epinephrine has a role in treatment when salbutamol is given adequately. Recommended dosage and administration of these agents are shown in table III.[1-3] The onset of action for SABAs is very rapid, being almost immediate, and repetitive or continuous administration produces incremental bronchodilation. The duration of action of bronchodilation from

Table III. Pharmacological management of patients with acute severe asthma in the emergency department

Drug or class	Regimen
Salbutamol (albuterol) solution for inhalation: single dose 2.5 mg (2.5 mL)	2.5 mg (2.5 mL) by nebulization continuously for 1 h, then reassess Thereafter, clinical response or occurrence of serious adverse effects influences the frequency of administration
Ipratropiun bromide	Nebulized ipratropium bromide (0.5 mg/2.5 mL, 4–6 h) combined with salbutamol May mix in the same nebulizer with salbutamol
Corticosteroids	Intravenous methylprednisolone 40 mg or hydrocortisone 200 mg or oral prednisone 40 mg; consider high-dose inhaled corticosteroids
Magnesium sulfate	A single 2 g infusion over 20 min in adults
Methylxanthines	Avoid; poor evidence and serious adverse effects
Leukotriene receptor antagonists	A single 7–14 mg infusion of montelukast over 5 min
Epinephrine (adrenaline) 1 : 1000 (1 mg/mL)	0.3–0.4 mL of a 1 : 1000 (1 mg/mL) solution subcutaneously every 20 min for three doses in case of no response (last chance to avoid intubation)
Terbutaline (1 mg/mL)	0.25 mg subcutaneously every 20 min for 3 doses. Preferable to epinephrine in pregnancy
Heliox	Helium/oxygen mixture in a ratio of 80 : 20 or 70 : 30

SABAs in severe asthma exacerbations is not precisely known, but this can be significantly shorter than that observed in stable asthma.

In acute severe asthma, the nebulized route is often utilized and the nebulization device should be driven by oxygen. Care must be taken to utilize adequate flow rates because aerosol particle size depends, among other factors, on nebulizer flow rate. The higher the flow rate, the smaller the particle size will be. Only aerosol particles with a median diameter of 0.8–3 μm are deposited in the small airways and alveoli, whereas larger particles are mostly deposited in the pharynx and upper airway, and smaller particles tend to be exhaled. Each nebulizer device has a different flow-particle size relationship, but most devices require 10–12 L/minute in order to deliver particles in the 1–3 μm range. Metered-dose inhalers (MDIs) with a spacer device or aerochamber have similar effects to nebulization and are given very rapidly. Indeed, aerosol is equal to or better than nebulization, without problems with particle size or flow rates if used in the appropriate setting. However, in acute severe asthma with life-threatening features the nebulized route (oxygen driven) is recommended, as well as in acute severe asthma that is poorly responsive to an initial bolus dose of a SABA.[2]

Studies of intermittent versus continuous nebulized SABAs in severe asthmatic exacerbations provide conflicting results. It has been proposed, but not conclusively proven, that continuous SABA nebulization could provide a more consistent delivery of medication and allow deeper tissue penetration, resulting in enhanced bronchodilation, as duration of activity and effectiveness of SABAs are inversely related to the severity of airway obstruction. Continuous nebulization of SABAs may be more effective in children and severely obstructed adults, and constitutes our current hospital practice.[62-64] Continuous nebulization is shown to reduce admissions in patients with severe asthmatic exacerbations.[65] A reasonable approach to inhaled therapy in severe exacerbations, therefore, should be the initial use of continuous nebulized salbutamol, continued until a significant clinical response is achieved or serious adverse effects appear (severe tachycardia or arrhythmias), followed by intermittent on-demand therapy for hospitalized patients. Prior poor response to or ineffectiveness of nebulized SABAs does not preclude their use and does not limit their efficacy. According to a recent systematic review, there is no evidence to support the use of intravenous SABAs, even in severe, life-threatening asthma.[66]

The most commonly used SABA is salbutamol. Salbutamol is a racemic mixture containing equal quantities of (R)- and (S)-isomers. Levosalbutamol ([R]-salbutamol) is a bronchodilator,[67] but the (S)-form has a longer half-life with

preferential pulmonary retention and potential pro-inflammatory properties.[68] It is theoretically possible that after repeated dosing the (S)-isomer can accumulate, leading to undesirable effects. The pure (R)-isomer (levosalbutamol) evokes bronchodilation comparable with the racemic mixture on a 4 : 1 dose-for-dose basis in chronic asthma and systemic adverse effects in a 2 : 1 ratio.[69] Preliminary trials in acute asthma suggest that levosalbutamol produces greater bronchodilation at lower cost than the racemic mixture.[70] Dose-response effects are found with the amounts commonly administered clinically.[71] Overall, levosalbutamol seems as safe and effective as the racemic salbutamol, albeit at a greater cost. Further studies are needed to elucidate the possible superiority of this drug, especially in acute and severe asthma patients and other subpopulations.[72]

The response to SABAs depends on a variety of factors. In addition to bronchospasm, airway oedema and increased mucous production and plugging are known to be pathophysiological contributors to acute asthma severity. It is possible that some patients with severe asthma exacerbations may have a relative predominance of airway oedema contributing to their respiratory distress, as well as mucoid impaction. Nevertheless, decreased tidal volume and/or near complete airway obstruction in severe status asthmaticus, also reflecting the establishment of dynamic hyperinflation, may act in synergy to prevent aerosolized bronchodilator delivery to the lower airways. In addition, there is evolving evidence that genetic variation in the β_2-adrenergic receptor influences bronchodilator response to both SABAs and long-acting β_2-adrenergic receptor agonists (LABAs). Occasional patients with specific β_2-adrenoreceptors appear to respond less favourably to traditional SABAs and may benefit from alternative bronchodilators.[73] These particular patients may respond more favourably to nebulized epinephrine, despite failure of aggressive SABA therapy.

The adverse effects of SABAs in asthma mainly affect the cardiovascular system, may develop for both unselective and selective (much fewer) SABAs, and may present both with intravenous (earlier and more consistent) and inhalational administration. Myocardial ischaemia is a documented complication with the administration of intravenous isoprenaline to asthmatic children. Other adverse effects of SABAs include hypokalaemia, tremor and worsening of ventilation/perfusion mismatch. Cardiovascular adverse effects and tremor show tachyphylaxis, whereas bronchodilator response usually does not.

Epinephrine possesses bronchodilator properties similar to those of more selective SABAs in addition to other favourable effects. First, through its α_1-adrenergic receptor agonistic effects, epinephrine induces potent microvascular vasoconstriction, thereby reducing bronchial mucosal oedema. Second, epinephrine decreases parasympathetic tone, leading to further bronchodilation.[74] Finally, epinephrine has been shown to improve PaO_2, which may paradoxically be worsened by SABAs.[75] Subcutaneous epinephrine or terbutaline are mainly administered in those patients who are unable to receive inhaled medications, such as patients experiencing delirium, coma or cardiopulmonary arrest, and occasionally when there is an inadequate response to inhaled therapy (table III). Caution is necessary in patients aged >40 years and those with existing heart disease. Epinephrine is the drug of choice for subcutaneous administration. Despite equivalent bronchodilation, terbutaline via the subcutaneous route appears to lose β_2-adrenergic receptor selectivity and may induce tachycardia more frequently than epinephrine, especially in older individuals. In pregnancy, epinephrine should be substituted with subcutaneous terbutaline, because the former has been associated with diminished uterine blood flow and congenital malformations.

6.3 Corticosteroids

Asthma is an inflammatory disease, and corticosteroids are widely recognized to be the most potent and effective drugs for the treatment of inflammation. Systemic corticosteroids decrease inflammation, increase the number and sensitivity of β-adrenergic receptors, and inhibit the migration and function of inflammatory cells, especially eosinophils.[76,77] In contrast to their anti-inflammatory properties, corticosteroids do

not have any inherent bronchodilator activity, and their use as monotherapy for the treatment of acute asthma is unacceptable. Corticosteroids are recommended for most patients in the emergency department, especially those who do not respond completely to initial SABA therapy, those whose exacerbation develops even though they were already taking oral corticosteroids and those with previous exacerbations requiring oral corticosteroids. However, despite extensive clinical experience with these agents, there remains considerable uncertainty as to the onset of action, dose-response characteristics, duration of treatment, optimal route of administration and the patient population likely to require or respond to corticosteroids in emergency situations when used for the treatment of acute severe asthma.[78]

The treatment of acute severe asthma with corticosteroids within 1 hour of presentation to the emergency department lowers hospitalization rates and improves pulmonary function.[79] Their onset of action may be seen in as little as 2 hours in studies measuring peak flow, but may be delayed as much as 6 hours in studies using FEV_1 as the pulmonary function outcome measure. Because of this, it is recommended that corticosteroids should be given as quickly as possible in order to facilitate recovery and it is imperative to continue aggressive bronchodilator treatment until they take effect. A clear dose response is seen at dosages <40 mg/day of methylprednisolone or equivalent; however, there is limited evidence of any added efficacy when dosages >60–80 mg/day are administered (table III). There is no clear benefit of the intravenous route of administration over the oral route for the treatment of acute severe asthma. Indeed, oral corticosteroids are usually as effective as those administered intravenously, require at least 4 hours to produce clinical improvement and are preferred because this route of administration is less invasive and less expensive. If vomiting has occurred shortly after the administration of oral corticosteroids, then an equivalent dose should be re-administered intravenously. High doses of corticosteroids are associated with several adverse effects, including hyperglycaemia, hypokalaemia, mood alterations, hypertension, metabolic alkalosis and peripheral oedema. If given in conjunction with a steroidal neuromuscular blocker during mechanical ventilation for respiratory failure, an ICU myopathy can develop and result in prolonged ventilator dependence.

It is estimated that as many as 25% of patients with difficult-to-control asthma may be 'steroid resistant'. This condition is defined as a failure to improve morning prebronchodilator FEV_1 >15% after 7–14 days of oral prednisone 30 mg in association with the presence of a significant bronchodilator response. Affected individuals have increased levels of T-cell activation, along with higher expression of genes for interleukin (IL)-2 and IL-4 in their airway. There is no information on whether corticosteroid resistance has an impact either on the severity or treatment of acute episodes.[80]

The inhaled route of administration of corticosteroids also appears to be effective as part of the management plan for asthma exacerbations. The combination of high-dose inhaled corticosteroids and salbutamol in acute asthma was shown to provide greater bronchodilation than salbutamol alone, and conferred additional benefit than the addition of intravenous corticosteroids across all parameters, including hospitalizations, especially for patients with more severe attacks, although further studies are required to document their potential role in acute asthma.[81-84] Currently, there is some evidence that repetitive administration in the emergency department of high doses of inhaled corticosteroids, flunisolide 6 mg over 3 hours or fluticasone propionate 3 mg/hour for 3 hours, is beneficial when initiated early in adults. Their efficacy might be related to their early and potent local vasoconstriction, leading to a decrease in oedema formation and plasma exudation.[85] These data suggest that patients with an acute severe asthma exacerbation may benefit from both systemic and inhaled corticosteroids in the emergency department, without a high dose of inhaled corticosteroids replacing systemic corticosteroids. Although these data are suggestive, because of the lack of large-scale trials investigating the place of inhaled corticosteroids in acute asthma settings, further studies are needed to confirm their efficacy, with

greater attention given to drug dosing and the level of acute asthma severity.

6.4 Magnesium Sulfate

Magnesium has been shown to have beneficial effects on smooth muscle relaxation and inflammation.[86] The use of magnesium sulfate in status asthmaticus has gained support recently. According to several systematic reviews and one large prospective cohort study, this agent appears to be of some benefit in the subpopulation of patients with severe exacerbations (defined as severe flow limitation, a relative failure to respond to inhaled bronchodilators and a high risk of admission). The addition of intravenous magnesium sulfate to the repetitive administration of inhaled SABAs and systemic corticosteroid treatment among individuals with severe exacerbations is shown to reduce hospitalizations and improve pulmonary function.[87,88] The role of nebulized magnesium sulfate is less clear, with a pooled analysis failing to provide clear evidence of benefit, although therapy with nebulized magnesium sulfate as an addition to that with inhaled SABAs may be considered, particularly in patients with the lowest levels of FEV_1, as there is weak evidence that such treatment improves lung function and reduces the number of hospitalizations.[89,90]

Although uncertainties still remain, the 2007 *Expert Panel Report 3*: Guidelines for the Diagnosis and Management of Asthma[3] recommends consideration of intravenous magnesium sulfate in patients who have life-threatening exacerbations and in those whose exacerbations remain in the severe category after 1 hour of intensive conventional therapy. Currently, the recommended dose is 2 g intravenously over 20 minutes in adults (table III). The 2008 Global Initiative for Asthma (GINA) report[1] recommends the parenteral administration of magnesium sulfate 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. In addition, it is stated that nebulized salbutamol administered in isotonic magnesium sulfate provides greater benefit than if it is delivered in normal saline. Adverse effects are usually minor and self-limited, and include flushing, fatigue and pain at the site of the infusion. Occasionally, hypermagnesaemia has been described in patients with abnormal renal function and elderly patients with small bowel hypomobility.

6.5 Anticholinergics

Ipratropium bromide is the anticholinergic agent of choice to administer in asthmatic patients in the emergency setting because of its selectivity for muscarinic airway smooth muscle receptors through which bronchodilation is mediated and its absent systemic anticholinergic adverse effects. Ipratropium bromide has a slow onset of action (60–90 minutes to peak) and produces less bronchodilation at peak effect compared with SABAs.[91] However, the rationale for implementation of a combination of SABAs and anticholinergic agents in patients with severe asthmatic exacerbations is based on targeting different sites of action (i.e. proximal vs distal airways) and different pathophysiological mechanisms of airway smooth muscle relaxation, and on differences in time to onset of effect and adverse effect profiles.[92] It was recently shown that the addition of repetitive doses of inhaled ipratropium bromide to the early administration of SABAs may significantly reduce airway obstruction and hospital admissions, especially for more severe asthmatic exacerbations. Patients with severe airway obstruction induced by β-adrenergic antagonists (β-blockers) and patients receiving therapy with monoamine oxidase inhibitors may particularly benefit from this class of bronchodilators.

Recent guidelines recommend the addition of repetitive doses of ipratropium bromide to a selective SABA because it produces additional bronchodilation, resulting in fewer hospital admissions, particularly in patients who have acute severe or life-threatening asthma or those with a poor initial response to SABA therapy (table III).[1-3] This recommendation is also supported by a recent meta-analysis.[93] There is also some evidence that further effects may be obtained when high doses of inhaled corticosteroids are added to this combination. More

precisely, it is suggested that there is an additional therapeutic benefit and improvement in lung function from the concomitant triple administration of ipratropium bromide, flunisolide and salbutamol in high doses, particularly in those patients with FEV_1 <30% of the predicted value.[94]

6.6 Methylxanthines

Methylxanthines (theophylline and its water-soluble derivative aminophylline) have been widely used in the treatment of asthma. The mechanism of action of theophylline in asthma remains unclear. In addition to its action as phosphodiesterase inhibitor, the drug has been postulated to stimulate endogenous catecholamine release, to act as a β-adrenergic receptor agonist and as a diuretic, to augment diaphragmatic contractility, to increase binding of cyclic adenosine monophosphate and to act as a prostaglandin antagonist.[95-100] However, a systematic review of various randomized controlled trials provided no support for the use of intravenous aminophylline in adults with acute severe asthma, as it did not result in any additional bronchodilation compared with standard care with SABAs, and the frequency of adverse effects was higher.[101]

The 2008 GINA report[1] recommends that in view of the much higher effectiveness and relative safety of SABAs, theophylline has a minimal role in the management of acute asthma, as its use is associated with severe and potentially fatal adverse effects, particularly in those receiving long-term therapy with sustained-release theophylline. In addition, the benefit of methylxanthines as add-on treatment in adults with severe asthma exacerbations has not been demonstrated. The British Thoracic Society (BTS)/Scottish Intercollegiate Guideline Network (SIGN) *British Guideline on the Management of Asthma*[2] suggests that, in acute asthma, intravenous aminophylline is not likely to result in any additional bronchodilation compared with standard care with inhaled bronchodilators and corticosteroids. Adverse effects such as arrhythmias and vomiting are increased if aminophylline is used. Some physicians advocate that patients with near-fatal asthma or life-threatening asthma with a poor response to initial therapy may gain some additional benefit from intravenous aminophylline (table III). Such patients are probably rare and could not be identified in a meta-analysis of trials. If intravenous aminophylline is given to patients on oral aminophylline or theophylline, blood levels should be checked on admission. Levels should be checked daily for all patients receiving aminophylline infusions.

6.7 Leukotriene Modulators

Leukotrienes are potent lipid mediators derived from arachidonic acid through the 5-lipoxygenase pathway and are divided into two main groups: LTB4 and the cysteinyl leukotrienes (CysLTs) LTC4, LTD4 and LTE4. Leukotrienes represent pivotal biomolecules in the complex network of inflammatory mediators that characterizes allergic airway disease.[102-104] They exert their effects following activation of specific receptors located on cell membranes of pulmonary smooth muscle and macrophages. CysLTs produce an array of effects implicated in the pathogenesis of the asthmatic inflammatory process (bronchoconstriction, mucous hypersecretion, inflammatory cell recruitment, increased vascular permeability and proliferation of airway smooth muscle cells).[105] Antagonizing the actions of CysLTs could thus play an important role in attenuating integral features of asthma pathophysiology, including patients with status asthmaticus. Pharmacologically, this can be achieved by drugs preventing their synthesis using a 5-lipoxygenase inhibitor e.g. zileuton) or blocking specific CysLT receptors using an leukotriene receptor antagonist (LTRA).[106,107] Leukotriene modulators are unique in that they demonstrate bronchodilator and anti-inflammatory properties (albeit far less than LABAs and corticosteroids, respectively), suggesting that they may have an important dual action in the treatment of allergic airways disease. A further therapeutic benefit is that LTRAs are clinically active following single doses. In addition, unlike LABAs, tolerance to their bronchoprotective effects has not been demonstrated.[107]

It seems logical that given the increased production of leukotrienes during an acute asthma

exacerbation, the LTRAs might be particularly effective.[108] A small number of studies have now been performed to determine whether two LTRAs, montelukast and zafirlukast, are effective in the treatment of acute asthma. A single dose of intravenous montelukast in moderate and severe exacerbations demonstrated a rapid and significant improvement in pulmonary function within 10 minutes of administration.[109] Patients treated with montelukast tended to receive less SABA therapy and had fewer treatment failures than patients receiving placebo. The oral formulations of LTRAs would not be expected to provide benefit for at least 90 minutes.[110,111] Leukotriene modulators may have a theoretical role in the therapy of life-threatening asthma because they complement the anti-inflammatory effects of systemic corticosteroids (table III).[112]

The 2007 US guidelines[3] state that intravenous LTRAs could be considered as an adjunct therapy to avoid intubation, although providing insufficient data to document this recommendation. Additional studies are necessary to determine whether these agents offer a significant benefit over and above that derived from routine therapy.[18]

6.8 Helium and Oxygen Mixtures (Heliox)

Heliox is a blend of helium and oxygen in concentrations ranging from 60% to 80% helium and from 20% to 40% oxygen. Helium is an inert gas with no known adverse effects or any direct therapeutic effect.[72] Because this mixture is less dense than air, turbulent flow is rendered more laminar, resulting in decreased airway resistance to gas flow. In some patients this low-density formulation given by a non-rebreather mask increases ventilation, decreases the work of breathing, pulsus paradoxus and alveolar-to-arterial gradient, and delays the onset of respiratory muscle fatigue. Meanwhile, heliox-driven aerosolized nebulization has a better deposition pattern, forestalling the development of respiratory failure. In other patients in whom the predominant mechanism of airflow limitation involves laminar flow in small airways, heliox is of no benefit and may interfere with usual care.[113-117] These properties suggest heliox is ideally suited to patients in status asthmaticus, but limited clinical data are available on its use in the adult ICU. The role of heliox in acute asthma remains controversial and it is generally limited to centres experienced in its administration.[50]

Further data on the therapeutic value of heliox are offered in a 2006 update of a Cochrane review,[118] which includes ten randomized controlled trials of 544 patients comparing heliox with placebo. Overall, this meta-analysis shows no clear benefit from heliox when administered to patients with asthma in the emergency department. Nonetheless, treatment with heliox may improve pulmonary function in patients with the most severe asthma. The discrepancy in findings may result from small sample sizes. More importantly, some studies neglected to account for the different effect of heliox versus oxygen (or room air) on respirable mass. For example, failure to increase the gas flow rate for those on heliox greatly complicates interpretation.[118,119] The 2008 GINA report suggests that there is no routine role for this intervention.[1] It might be considered for patients who do not respond to standard therapy. BTS/SIGN guidelines do not recommend the use of heliox (helium/oxygen mixture in a ratio of 80 : 20 or 70 : 30) in acute adult asthma on the basis of present evidence.[2] Moreover, there is no evidence to support the use of heliox for the treatment of acute asthma in childhood. The 2007 US guidelines[3] recommend that for severe exacerbations that are unresponsive to the initial treatments, whether given before arrival at the acute care setting or in the emergency department, adjunct treatments such as magnesium sulfate or heliox may be considered to avoid intubation, but intubation should not be delayed once it is deemed necessary. Because intubation of a severely ill asthmatic patient is difficult and associated with complications, additional treatments are sometimes attempted. In such cases heliox can be considered.

Finally, it should be mentioned that heliox can affect nebulizer function, peak flow meter and pulmonary function measurements unless they are adjusted for the mixture. For instance, nebulizer flow rates should be increased by about

50% to ensure adequate output. Pulse oximetry is essential during heliox therapy to ensure that adequate oxygen is being provided.[120]

6.9 Mechanical Ventilatory Support

6.9.1 Intubation

Intubation and mechanical ventilation of patients with status asthmaticus is a challenging task. The decision to intubate is essentially based on clinical judgement and should be considered for patients with progressive deterioration and/or poor response to aggressive treatment. Although cardiac or respiratory arrest represents an absolute indication for intubation, the usual picture is that of a conscious patient struggling to breathe. Factors associated with increased likelihood of intubation include exhaustion and fatigue despite maximal therapy, deteriorating mental status, refractory hypoxaemia, increasing hypercapnia, haemodynamic instability, and impending coma or apnoea. Experience plays an important role in making the right decision, and increased exposure and expertise have been associated with decreased intubation rates in paediatric populations.[121] Intubation should be performed by a physician who has extensive experience in intubation and airway management, and should not be delayed once it is deemed necessary.[1-3]

Oral intubation is the preferred route. Larger endotracheal tube sizes minimize airway resistance, allow faster delivery of the tidal volume and a favourable inspiration to expiration ratio. In addition, they limit peak inspiratory pressure and facilitate secretion clearance. If possible, endotracheal tubes with an inside diameter >8 mm for adult women and >8–9 mm for adult men should be used. Nasal intubation might be an option for patients expected to have a difficult oral intubation (e.g. extremely obese patients). In this setting, fibre optic intubation may offer valuable help. Increased incidence of nasal polyps and sinusitis, but mainly the use of smaller endotracheal tubes, is the major disadvantage of nasal intubation.

Intubation might cause severe derangement of the cardiopulmonary status of patient with status asthmaticus. Hypotension as a result of the direct effect of sedation, pre-existing dehydration and decreased venous return due to high intrathoracic pressures and overzealous ventilation are extremely common. Aggressive fluid resuscitation is often required, and if hypotension does not respond to fluid challenge then an emergent tension pneumothorax should be excluded.[122] Arrhythmias, barotrauma, aspiration, laryngeal oedema and seizures are often encountered during the peri-intubation period in ventilated asthmatic patients,[123] making the need for close monitoring the cornerstone of successful management.

6.9.2 Sedation and Paralysis

Sedation is indicated in order to improve comfort, safety and patient–ventilator synchrony, while at the same time decreasing oxygen consumption and carbon dioxide production (table IV). Benzodiazepines can be used safely for sedation of the asthmatic patient[124] and are cheap, but time to awakening after discontinuation is prolonged and difficult to predict. The most common alternative, propofol, is attractive in patients with sudden-onset (near-fatal) asthma who may be eligible for extubation within a few hours, because it can be titrated rapidly to a deep sedation level and has quick reversal after discontinuation. In addition, propofol possesses bronchodilatory properties.[125,126] Propofol should be administered cautiously in hypotensive asthmatic patients, and may require the use of fluids and vasopressors. The addition of an opioid administered by continuous infusion to benzodiazepines or propofol is often desirable in order to provide amnesia, sedation, analgesia and respiratory drive suppression. Because morphine can cause allergic reactions and exacerbate bronchospasm, the synthetic opioids fentanyl or remifentanil represent the preferred choices. Ketamine, an intravenous anaesthetic with bronchodilatory properties, is reserved for use in intubated patients with severe bronchospasm. Clinical benefit with ketamine was not shown in paediatric non-intubated patients with severe exacerbations,[127] and clinical trials in patients requiring ventilation are lacking. Both propofol and ketamine may decrease the risk of bronchospasm during anaesthesia induction. Finally, dexmedetomidine may be a useful sedative to

Table IV. Sedation, analgesia and paralysis in patients with status asthmaticus[a]

Drug	Regimen
Midazolam	Bolus of 0.03–0.1 mg/kg IV followed by an infusion of 3–10 mg/h
Propofol	Initial IV infusion of 60–80 mg/min, up to 2 mg/kg, followed by an infusion of 5–10 mg/kg/h as needed, and for sedation for protracted mechanical ventilation 1–4 mg/kg/h
Fentanyl	Bolus of 50–100 μg/kg IV, followed by an infusion of 50–1000 μg/h
Remifentanil	Initial dose of 1 μg/kg IV, followed by an infusion of 0.25–0.5 μg/kg/min (range 0.05–2 μg/kg/min)
Ketamine	Bolus of 1 mg/mL IV, followed by a maintenance infusion of 0.1–0.5 mg/min
Dexmetomidine	Initial loading dose of 1 μg/kg over 10–30 min IV, followed by a maintenance infusion of 0.2–0.7 μg/kg/h (continuous infusion should not exceed 24 h)
Cisatracurium	Bolus of 0.1–0.2 mg/kg IV, followed by an infusion of 3 μg/kg/min (range of continuous infusion 0.5–10 μg/kg/min)

a The individual responses to all anaesthetic agents may vary and depend on many factors, including dose and route of administration and age. Thus, any dosage recommendation cannot be absolutely fixed and all anaesthetic agents should be titrated against the patient's requirements.

IV = intravenously.

facilitate the induction of non-invasive ventilation.[128]

Extreme patient–ventilator asynchrony and severe hypercapnia may necessitate the paralysis of respiratory muscles. Non-depolarizing agents such as vecuronium bromide, rocuronium bromide, cisatracurium besilate and pancuronium bromide do not induce bronchospasm, whereas atracurium besilate and mivacurium chloride result in dose-dependent histamine release and their use is discouraged. Paralytic agents may be given either intermittently by bolus or by continuous infusion. The concomitant use of corticosteroids and paralytic neuromuscular agents increases the incidence of acute myopathy in ventilated asthmatic patients,[129,130] and the traditional approach has encouraged the use of heavy sedation, which is considered to be much safer than paralysis. This practice has been assessed in a recent retrospective study in patients with status asthmaticus,[131] which demonstrated that clinically significant muscle weakness was not eliminated by changing the method of achieving tolerance of ventilator support from continuous paralysis to prolonged deep sedation. The authors identified the duration of mechanical ventilation as the main risk factor for weakness.

6.9.3 Initial Ventilatory Management: Setting the Ventilator

Acute severe asthma is characterized by severe pulmonary hyperinflation due to marked limitation of the expiratory flow. Therefore, the main objective of the initial ventilator management is 2-fold: to ensure adequate gas exchange, and to prevent further hyperinflation and ventilator-associated lung injury. This may require hypoventilation of the patient and allowance of higher $PaCO_2$ levels and a more acidic pH (even down to 7.2),[132] which is generally well tolerated in asthmatic patients. Of note is that this does not apply to asthmatic patients who are intubated for cardiac or respiratory arrest. In this setting the post-anoxic brain oedema may demand more careful management of blood $PaCO_2$ levels in order to prevent further elevation of intracranial pressure and subsequent complications.[133] Indirect and non-invasive monitoring of cerebral blood flow in this case, such as provided by transcranial Doppler, may offer the opportunity of a tailored approach.

Following intubation, controlled modes of ventilation are usually employed for many reasons, and a fraction of inhaled oxygen (FiO_2) of 100% is recommended for the initial phase. Deep sedation is necessary to avoid patient-ventilator asynchrony and to manage controlled hypoventilation; in many cases, muscle paralysis may be required. The exhaustion of respiratory muscles after a varying period of spontaneous breathing against a heavy resistive load makes the control mode a reasonable choice in the first 24 hours in order to unload respiratory muscles and relieve fatigue. No firm guidelines exist on the mode of ventilation that should be used later. Traditionally, volume-controlled ventilation is preferred over pressure control, mainly because fluctuating and rapidly changing airway resistance and PEEPi may lead to variable tidal volumes and very low alveolar ventilation with

the latter. On the other hand, volume control ventilation obviates these disadvantages but mandates careful monitoring of inflation pressures. However, no strong clinical data prove the superiority of any type or mode of positive pressure in status asthmaticus, and barotrauma seems to occur regardless of the mode of delivery of positive pressure.[134]

If a volume-controlled mode of ventilation is employed, the initial ventilator settings should include a respiratory rate of 8–10 breaths/minute and a tidal volume of 7–8 mL/kg of ideal bodyweight in order to keep the minute ventilation below 10 L/minute (table V). The inspiratory flow rate must be set to 60–80 L/minute to allow adequate expiration time. A higher inspiratory flow rate will result in higher peak pressures. However, it is not the peak but the plateau pressure that has been associated with barotrauma. Plateau or end-expiratory pressure (Pplateau) should ideally be kept <30cm water.[135] With regard to the inspiratory flow waveform, none of the common morphologies (square, decelerating or accelerating) has demonstrated clinical superiority. Theoretically, a decelerating waveform leads to decreased peak pressure, with all other variables steady, but the clinical significance of the above remains unclear. The FiO_2 should target to SaO_2 >90%. Usually, an FiO_2 <50% suffices to achieve this goal and the need for a high O_2 mixture should trigger a search for other causes of hypoxaemia (e.g. pneumothorax and atelectasis). During the initial phase, the application of PEEP offers no benefit and may even have a detrimental effect with regard to hyperinflation.[8]

Table V. Initial ventilator settings in status asthmaticus

Mode	Volume-controlled ventilation
Tidal volume	7–8 mL/kg ideal bodyweight
Respiratory rate	8–10/min
Minute ventilation	<10 L/min
Inspiratory flow rate	60–80 L/min
Inspiratory to expiratory ratio	>1 : 3
Inspiratory flow waveform	Decelerating
Plateau pressure	<30 cm H_2O
PEEP	0 cm H_2O
FiO_2	FiO_2 100% initially and then titrate to achieve SaO_2 >90%

FiO_2 = fraction of inhaled oxygen; **PEEP** = positive end-expiratory pressure; **SaO_2** = oxygen saturation.

6.9.4 Monitoring Lung Mechanics

Monitoring lung mechanics is of paramount importance for the safe ventilation of asthmatic patients, and any physician caring for these patients should be familiar with the basic principles, and be capable of interpreting the waveforms and curves available in modern ventilators (figure 4a).[136] Most modern ventilators provide means of indirectly assessing and sequentially monitoring dynamic hyperinflation (figure 4b). In addition, modern technology has developed equipment capable of measuring FRC at the bedside integrated into commercially available ventilators. These ventilators employ an oxygen[137] or nitrogen[138] washout/washin technique, requiring a small change of the FiO_2 and allowing rapid measurement of FRC. Although very promising, a ventilatory strategy based on bedside evaluation of FRC, and indirectly hyperinflation, has not been validated in ventilated asthma patients so far.

Traditional surrogate indices of dynamic hyperinflation include measurement of the release of the trapped gas, the Pplateau and the PEEPi. Measurement of the trapped gas requires a relatively extended apnoea and collection of the exhaled air, which is the sum of tidal volume and the 'trapped' air above FRC (figure 5a).[139] Measurement of Pplateau is probably the simplest technique for the monitoring of lung hyperinflation.[140] The value of Pplateau is affected not only by the lung but also the chest wall mechanical properties, a point that should be taken into consideration for obese patients or patients who are not paralyzed. Several seconds of end-inspiratory pause are required to allow for the 'equilibration' of lung units with different resistance and compliance. PEEPi is determined after an expiratory port occlusion for a few seconds (figure 5b). Although PEEPi is not synonymous with dynamic hyperinflation (e.g. when expiratory muscle continues to contract after the end of expiration), in cases of passive mechanical ventilation the presence of PEEPi implies dynamic hyperinflation. The presence of PEEPi may be suspected by the flow waveform or the flow volume curve when expiratory flow does

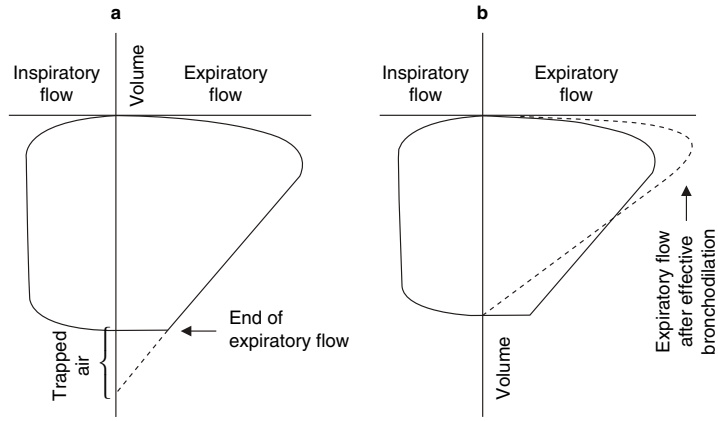

Fig. 4. (**a**) Flow–volume curve of a patient ventilated with volume control mode. Note that the expiratory flow does not zero before the next breath (arrow), indicating that the respiratory system has not reached its equilibrium position (dynamic hyperinflation). Theoretically, the extension of the expiratory flow line to the volume axis corresponds to the 'trapped' volume. (**b**) Flow–volume curve before (solid line) and after (dotted line) effective bronchodilation in a patient ventilated with volume control mode and unchanged settings. Note the increased peak and mid-expiratory flow rate and the attenuation of hyperinflation signs after bronchodilation. Monitoring of respiratory mechanics and recognition of abnormalities in ventilator waveforms can be very useful in the management of mechanically ventilated asthmatic patients.

not zero before the beginning of the next breath (figure 6).

The regression of dynamic hyperinflation, along with clinical improvement, signals the initiation of the weaning process, and a PEEPi <5 cm water is often employed as a useful clinical indicator. By the time the asthma attack has been adequately controlled, the weaning process proceeds without delay. When bronchospasm is relieved and ventilator dependence persists, the clinical suspicion of myopathy should be raised.

6.9.5 Pharmacological Therapy during Mechanical Ventilation

The first line of therapy in ventilated patients remains bronchodilator treatment with a SABA, typically salbutamol (table VI). Administration techniques include nebulizers or MDIs with spacers. Deposition and delivery of inhaled therapy depends on numerous factors, including aerosol characteristics, concentration of the aerosol, electrostatic charge, technique of using the device, host factors, and the ventilator mode and settings. Thus, deposition of radiolabelled aerosols has been shown to vary from 2.2–15.3% for nebulizers to 3.2–10.8% for MDIs.[141,142] The optimal dose administered with an MDI for mechanically ventilated patients is unknown, and many clinicians have advocated higher doses to compensate for factors affecting the deposition of aerosol into the lower respiratory tract. Although in theory this approach appears reasonable, the data are not consistent.[143] A practical approach is to titrate the dose of salbutamol to the level that achieves the most favourable outcome with minimal adverse effects. Such outcomes could be either PEEPi or peak-to-plateau airway pressure gradient. Low inspiratory flow (40 L/min) facilitates deposition, whereas other tips for efficient bronchodilation include efficient suctioning of the endotracheal tube and airway secretions, removing heat and moisture exchange, synchronizing delivery to inspiration and leaving five to six breaths between subsequent puffs (the latter two for MDI with spacer). We tend to use four to six puffs of salbutamol (when using an MDI with a spacer) or 2.5 mg by nebulization every 20 minutes for the first 3 hours until a significant clinical response is achieved or adverse effects appear. A significant proportion of patients (up to one-third in some studies[144]) will not respond to repetitive doses of salbutamol, due to either increased inflammation or mucous plugging. In this situation it is unclear whether mechanically ventilated asthmatic patients with poor response

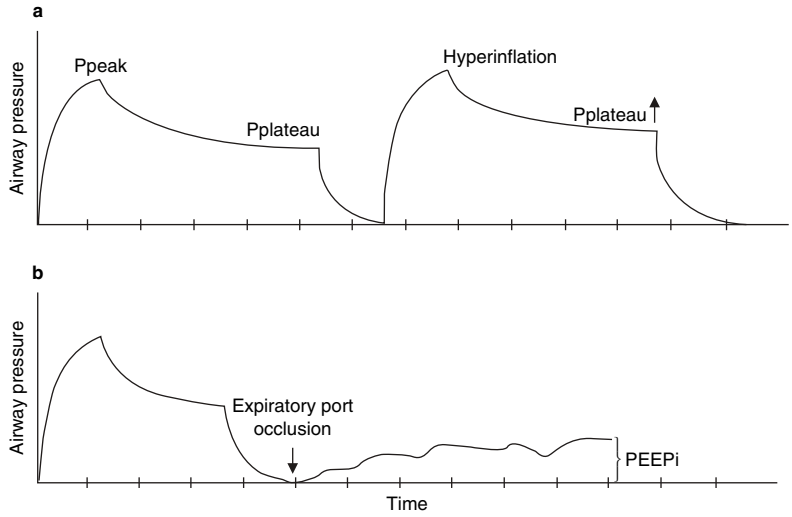

Fig. 5. A prolonged end-inspiratory pause is required for measuring (**a**) plateau pressure (Pplateau) and (**b**) intrinsic positive end-expiratory pressure (PEEPi) in status asthmaticus. Hyperinflation tends to increase Pplateau and PEEPi. **Ppeak** = peak pressure.

benefit from continuing high doses of salbutamol. The effect of levosalbutamol on mechanically ventilated asthmatic patients has not been studied thoroughly. Heliox, as a carrier gas, offers theoretical benefits of delivering inhaled therapy to ventilated asthmatic patients. Increased aerosol delivery for both MDIs and nebulizers by as much as 50% has been demonstrated in a mechanically ventilated model with the use of heliox.[145] Unfortunately, few ventilators have been designed for heliox use, and the rest demonstrate differing performance and the need for careful calibration.[146,147]

Intravenous SABAs have been considered in patients who are unresponsive to treatment with continuous nebulization. Their use is not recommended and they have a place only in desperate situations when all other therapies have failed. Bogie et al.[148] assessed the effect of intravenous terbutaline in a prospective, randomized manner in 49 paediatric patients requiring ICU admission but not intubation. Patients already on continuous high-dose nebulized salbutamol were randomized to intravenous terbutaline or placebo. Although there was a trend for clinical improvement and a decreased need for continuous nebulized salbutamol and length of ICU stay, the differences were not statistically significant. In addition, one patient was removed from the study because of significant cardiac dysrrhythmia, and three patients had elevated troponin values, all of them in the intravenous terbutaline group. Ventilated patients not responding to inhaled SABAs could benefit from subcutaneous epinephrine (0.3–0.5 mL [1 : 1000]) or terbutaline (0.25–0.5 mg). Subcutaneous administration of terbutaline or epinephrine has demonstrated satisfactory tolerability, even in older patients without coronary disease.[149]

Systemic corticosteroids are critical components of management and should be administered to all ventilated asthmatic patients as early as possible. The dose of systemic corticosteroids in mechanically ventilated asthmatic patients remains controversial. Some clinicians recommend a starting dose of methylprednisolone 80–125 mg every 6 hours during the first 24 hours,[53] whereas others (with us among them) tend to be more conservative, administering methylprednisolone 160–240 mg divided into four doses.[150] Clinical studies favouring high[151] or low[152] doses of systemic corticosteroids have not included a significant enough number of ventilated patients in order to reach an evidence-based conclusion, and a meta-analysis investigating whether higher dosages

of systemic corticosteroids (methylprednisolone >360 mg/day) offered a therapeutic benefit was negative in patients with acute asthma requiring hospital admission.[153] Because these drugs suppress, control and reverse airway inflammation, their tapering should proceed with caution, and only in improving patients. High-dose magnesium sulfate therapy (10–20 g over 1 hour) has been reported as effective and safe in five adult asthmatic patients receiving mechanical ventilation,[154] but current evidence does not share the initial enthusiasm. Improvement with magnesium sulfate has been maximal in the most severe subgroup of non-ventilated asthmatic patients (FEV_1 <25%).[155] Thus, the prudent (magnesium sulfate 2 g followed by 2 g more after 20 minutes) administration of a safe and inexpensive drug seems reasonable in refractory ventilated asthmatic patients. Our view is that anticholinergics, inhaled corticosteroids, leukotriene modulators and methylxanthines offer little benefit to the ventilated asthmatic patient, and clinical data favouring their use in ventilated asthmatic patients are lacking. Nevertheless, we continue to administer them in patients already on these treatments, or in cases of inadequate response to SABAs and corticosteroids.

Table VI. Specific pharmacological therapy of ventilated patients with status asthmaticus

Drug	Regimen
Salbutamol	2.5 mg by nebulization continuously or 4 to 6 puffs by MDI with spacer every 15–20 min for the first 3 h, titrated to physiological effect or until serious adverse effects appear
Corticosteroids	Methylprednisolone 40–60 mg IV every 6 h
Magnesium sulfate	2 g IV infused in 20 min, repeated if indicated (total dose 4 g)
Ipratropium bromide	Four puffs (0.8 mg) every 20 min delivered by MDI with spacer, or 0.5 mg per dose every 20 min in nebulized form combined with salbutamol
Theophylline	5 mg/kg ideal bodyweight loading dose over 30 min, followed by an infusion of 0.4 mg/kg/h. Measure blood levels (recommended 8–12 μg/mL), pay attention to interactions
Heliox	80 : 20 or 70 : 30 helium oxygen mix

IV = intravenous; **MDI** = metered-dose inhaler.

6.9.6 Non-Invasive Positive Pressure Ventilation

The potential benefit of non-invasive positive pressure ventilation (NIPPV) in acute severe asthma remains unclear. NIPPV exerts its beneficial role by decreasing the work of breathing and by offsetting PEEPi. The theoretical advantages of NIPPV over intubation include improved comfort, decreased need for sedation, decreased incidence of ventilator-associated pneumonia, and decreased length of ICU and hospital stay.[156] On the other hand, NIPPV carries an increased aspiration risk, and requires increased monitoring resources and nursing workload[157] to ensure an uneventful course. NIPPV might have a role for asthmatic patients with hypercapnic respiratory failure who do not require immediate intubation. Unfortunately, solid clinical data on the effectiveness of NIPPV in this clinical setting are lacking.

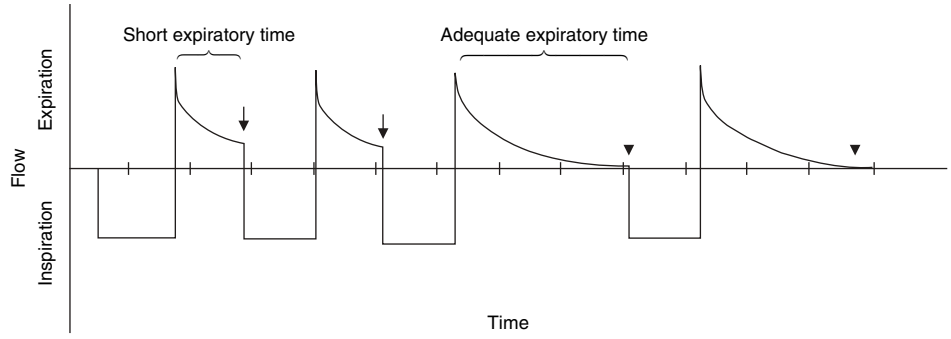

Fig. 6. Flow time tracing of a patient with persistence of flow at the end of expiration (thin arrows for the first two breaths), which indicates dynamic hyperinflation. Prolongation of expiratory time results in effective lung emptying and zeroing of expiratory flow before the next breath (arrowheads).

Meduri et al.[158] reported their clinical experience with 17 episodes of status asthmaticus with hypercapnic acute respiratory failure. NIPPV delivered through a face mask and applying an end-inspiratory pressure of <25cm water resulted in rapid improvement of hypercapnia. The mean duration of NIPPV was 16 hours and only two patients required intubation. In a prospective, randomized manner, Soroksky et al.[159] compared conventional treatment combined with nasal bi-level pressure ventilation with conventional treatment alone in 30 patients with severe asthma attack (FEV_1 <40% predicted) presenting in an emergency department. The addition of NIPPV for 3 hours was associated with improved lung function and faster alleviation of the symptoms.

A recent meta-analysis (finally including only the study by Soroksky et al.[159]) concluded that the routine use of NIPPV in acute severe asthma could not be recommended and remains controversial.[160] A trial of NIPPV could be implemented in selected patients with acute severe asthma following or coincidently with conventional medical treatment, but extreme caution would be required for the early recognition of failure. Specialized personnel and necessary equipment should be readily available to avoid delayed intubation.

6.9.7 Intubated Acute Severe Asthma Refractory to Conventional Management

In mechanically ventilated patients with acute severe asthma, ventilation with heliox decreases airway pressures and resistance and the alveolar-arterial O_2 gradient and improves carbon dioxide elimination, representing an option for those patients with status asthmaticus who continue to worsen on the ventilator.[114,161] Large-scale prospective clinical trials are lacking, so the effect of heliox on the final outcome of mechanically ventilated patients with status asthmaticus is unclear. The use of ventilators not specifically designed for heliox use may result in the delivery of unacceptably low tidal volumes and oxygen mixtures.[162]

Inhalation anaesthesia has been used for patients with acute asthma who are refractory to conventional treatment.[163] Volatile agents such as halothane and isoflurane have bronchodilatory properties and have been used successfully in selected patients.[164,165] They can reduce peak pressure and facilitate carbon dioxide removal, but their action does not last after their discontinuation. Besides the complicated logistics associated with their use, they may cause myocardial depression and arrhythmias, especially in an acidaemic environment. Therefore, their role is limited and they 'buy' time until definitive treatment acts.

Extracorporeal life support (ECLS) could provide adjunctive support for those patients for whom all other treatment modalities have failed. Clinical experience with ECLS in status asthmaticus has been extremely limited, based mainly on case reports or small case series.[166-169] Outcomes for ECLS use in status asthmaticus were recently assessed using an international registry.[170] This cohort of 1257 patients having received ECLS from 120 participating centres included only 24 patients with status asthmaticus. Twenty of them survived to hospital discharge. Complications were noted in 19 patients, including brain death or CNS hemorrhage (three cases) and cardiac arrest (two cases).

Autopsies of patients who have died of asthma often reveal extensive mucous plugging,[171] and interventions such as intense humidification, drainage facilitating positioning, percussion of the chest wall and bronchoscopic lavage have been proposed. Although some of these interventions are popular in routine clinical practice, the evidence supporting them is extremely weak.

7. Conclusions

Acute severe asthma is one of the 'gates' of asthma death. Expertise, perseverance, judicious decisions and practice of evidence-based medicine are of paramount importance for successful outcomes. Current asthma therapy is highly effective in the majority of asthma patients. However, patients with acute severe asthma are often poorly controlled on maximal doses of inhaled therapies and/or systemic corticosteroids, and none of the existing treatments for asthma is disease modifying or curative. This poses a challenge for the development of new treatments based on the variant phenotypes of asthma, drug delivery methods

and drugs targeting specific cell types involved in the pathogenesis of the disease.[172]

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