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REVIEW

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Medical and ventilatory management of status asthmaticus

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Introduction

All patients with asthma are at risk of episodic deteriorations in lung function. Asthmatic attacks vary greatly in severity, from those that are mild and easily managed with intensification of anti-asthmatic medications to those that may progress to respiratory failure, sometimes within a matter of minutes.

Status asthmaticus is generally defined in terms of the responsiveness of the asthmatic attack to intensive, medically supervised therapy. Patients who fail to improve significantly despite several hours of hospital-based care (or the equivalent intensity of treatment in another setting) are said to be in "status". Virtually all patients with severe asthmatic attacks requiring hospitalization for continued treatment of their disease can be said to have status asthmaticus, which is an unstable and (potentially) life-threatening condition. This review addresses the special pharmacological and ventilatory considerations pertinent to the management of severe asthmatic attacks and status asthmaticus.

Epidemiology

With the advent of public educational campaigns and increased routine use of anti-inflammatory medication [1], asthma mortality has finally begun to decrease in many parts of the industrialized world with death rates in persons aged 5–34 now less than 1 per 100 000 (Fig. 1) [2]. Although the United States also had a low asthma specific mortality rate of 0.49 per 100 000 persons (5–34 years of age) in 1991, this represented a 42% *increase* when compared to data from 1982 [3]. In the United States there are approximately 500 000 hospitalizations per annum for severe asthma, and at least 4 times as many emergency department visits [3]. The burden of acute severe asthma falls disproportionately onto the shoulders of women and minorities. Asthma is the most common non-obstetric cause of hospitalization in women aged 15–44 in Boston [4], and a review of hospital admissions in southeastern Pennsylvania determined the ratio of female to male patients admitted for asthma to be nearly 3:1 [5]. Deaths attributable to asthma are at least 3 times greater among blacks than whites [3, 6]. In New York City, a direct correlation was reported between the proportion of minority residents in a given neighborhood and the incidence of asthma hospitalizations [7]. Poverty appeared to be an important risk factor, in that median household income was inversely proportional to the incidence of hospitalizations. The same trends have also been observed in Boston [8]. The explanation for the vulnerability of these populations is uncertain, but probably relates to living conditions, comorbid medical problems, availability of medications and health care resources, and patterns of health care utilization.

Patterns of asthmatic attacks

Most patients who seek help in emergency departments report that their symptoms developed within hours, al-

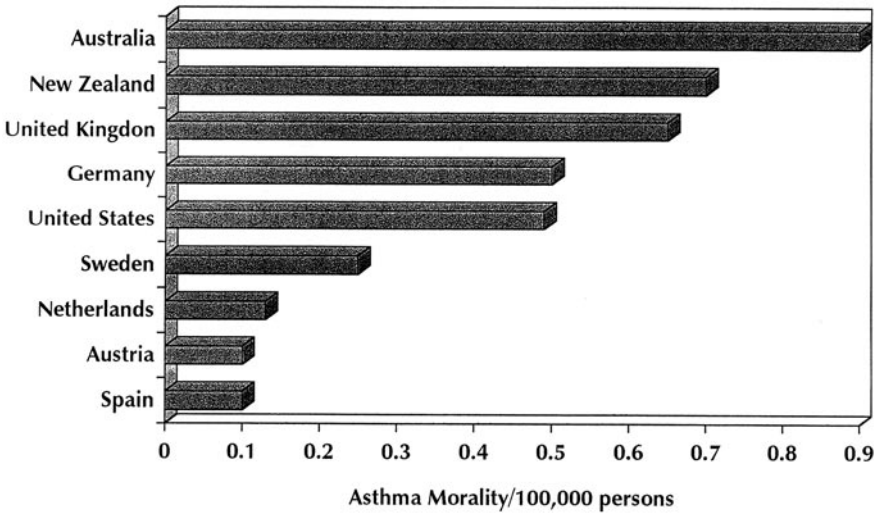

Fig. 1 Asthma mortality rates per 100000 persons aged 5–34 years in selected countries in 1991. International Classification of Disease code 493 was used to determine death rates [1–3]

Table 1 Patterns of respiratory failure in asthma

	Group I acute severe asthma	Group II acute asphyxic asthma
Gender	Women > men	Men > women
Baseline	Moderate to severe airflow obstruction	Normal or mildly decreased lung function
Onset	Days to weeks	Minutes to hours
Pathology	1. Airway wall edema 2. Mucus gland hypertrophy 3. Inspissated secretions	1. Acute bronchospasm 2. Neutrophilic, not eosinophilic bronchitis
Response to treatment	Slow	Rapid

though the duration of airflow obstruction, like the severity, varies considerably. Some patients have decreases in respiratory function that occur gradually or stepwise over several days, whereas others may experience a deterioration from normal lung function to life-threatening obstruction within minutes to hours (reviewed in [9]). Based on reviews of fatal and near-fatal asthmatic attacks, some investigators have identified two distinct patterns (Table 1).

Acute severe asthma

This group, predominantly women, comprises 70% of all patients who progress to respiratory failure [10, 11]. These are usually patients with poorly controlled disease resulting in persistent moderate-to-severe airflow obstruction. Many such patients have a diminished perception of dyspnea that results in greater tolerance of chronic airflow obstruction, thereby placing them at increased risk of severe and potentially fatal asthmatic attacks [12]. Relatively little bronchospasm is present because of aggressive beta-agonist use prior to arrival. Response to treatment, including systemic corticosteroids, is often slow [13]. Increased clearance of airway secretions is said to be an encouraging sign of clinical improvement [14].

Acute asphyxic asthma

This presentation occurs in a minority of patients who rapidly progress to respiratory arrest within 3 hours (and occasionally within minutes) of the first symptoms of an attack [11, 13]. It is described most often in young men. Prior to the attack, symptoms are often mild or completely controlled, but bronchial hyperreponsiveness is heightened [15]. The stimulus for the attack may remain unidentified, although some episodes are associated with exposure to specific allergen [11]. These attacks are predominantly due to acute bronchospasm; neutrophilic infiltration of airways, rather than an eosinophilic bronchitis, has been described. Quick, aggressive treatment with bronchodilators may avert progression to respiratory arrest. Patients requiring intubation often improve rapidly, needing only a brief duration of mechanical ventilation.

Pathophysiology

Understanding the pathophysiology of severe asthmatic attacks is important in the design of effective management strategies that address the abnormalities in gas exchange and hemodynamics, as well as increased airways resistance, that are observed in this setting. Histopathological data gathered post mortem indicate the presence of airway wall edema, hypertrophy of mucus

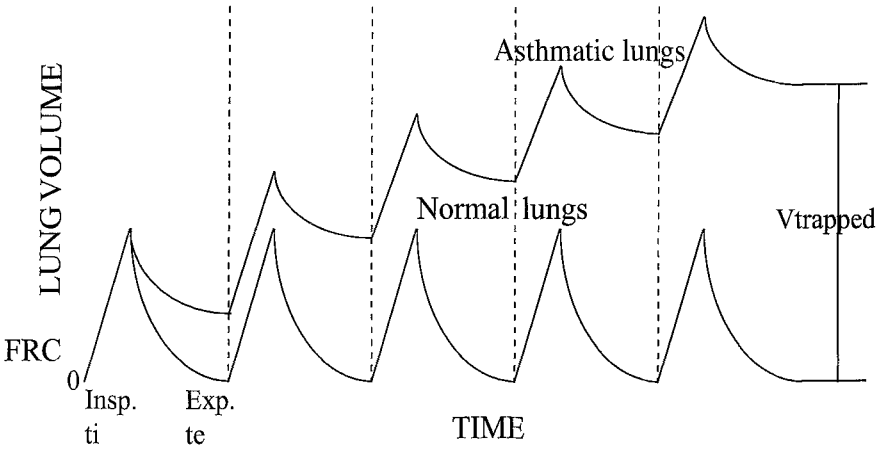

Fig. 2 Mechanism of dynamic pulmonary hyperinflation in the setting of severe airflow obstruction. The next inspiration begins before complete exhalation of the tidal breath, leading to gas trapping and an increased end-expiratory lung volume. The pressure (in excess of atmospheric pressure) within the airways and alveoli at the end of exhalation is referred to as intrinsic or auto-PEEP

glands, and the presence of inspissated secretions with extensive plugging of both large and small airways [16]. These tenacious plugs are comprised of mucus, shed epithelial cells, eosinophils, fibrin, and other plasma proteins. Mucus plugging, cellular infiltration and edema of the bronchial mucosa and submucosa and airway smooth muscle constriction combine to cause large increases in both inspiratory and expiratory airway resistance.

These pathologic changes in the asthmatic airway result in an abnormal distribution of alveolar ventilation ($\dot{V}$) relative to perfusion ($\dot{Q}$) (areas with low $\dot{V}/\dot{Q}$ ratios) and a widened alveolar to arterial gradient for oxygen. Hypoxemia in some degree is therefore common in severely ill asthmatics, but it is generally mild and easily corrected by increasing the inspired oxygen concentration [17]. Evaluation using the multiple inert gas technique has revealed a low frequency of true shunt, with much of the hypoxemia explained by perfusion of units with $\dot{V}/\dot{Q}$ ratios < 0.1. The degree of hypoxemia correlates only weakly with the severity of the spirometric abnormality [18].

Small airway obstruction results in significant alveolar overinflation with areas of diminished local capillary perfusion. Ventilation with reduced perfusion leads to a substantial increase in physiological dead space. During most asthmatic attacks patients are able to increase their minute ventilation to compensate for this wasted ventilation, and they usually present with mild hypocapnia. A normal or elevated arterial carbon dioxide tension ($PaCO_2$) should therefore alert the clinician to impending or actual respiratory failure [19, 20].

Abnormally high airway resistance results in dramatically increased work of breathing. During an asthmatic attack, the inspiratory transpulmonary pressure may be as high as 50 cm H_2O, compared with 5 cm H_2O during normal tidal breathing [21]. Expiration, no longer passive, becomes an active effort to empty the lungs via markedly narrowed airways. Despite this work expiratory flow rates are low, resulting in long expiratory times and incomplete alveolar emptying. A natural consequence is progressive dynamic lung hyperinflation (Fig. 2). This adaptation permits higher expiratory flow than would be possible at low lung volumes, but it also places the inspiratory muscles at a mechanical disadvantage because of their shortened resting length at the start of contraction. As a result of incomplete alveolar emptying, alveolar pressure remains positive at end expiration, the condition of intrinsic positive end-expiratory pressure ($PEEP_i$), leading to further increases in the inspiratory work of breathing (reviewed in [22]).

Circulatory derangements also occur during status asthmaticus. Increased positive thoracic pressure decreases systemic venous return, which is then augmented by vigorous inspiration. As the right ventricle fills during inspiration, the interventricular septum shifts toward the left ventricle and leads to left ventricular diastolic dysfunction and incomplete filling. The large negative intrathoracic pressure generated during inspiration increases left ventricular afterload by impairing systolic emptying. Pulmonary artery pressure may also be increased due to lung hyperinflation, thereby resulting in increased right ventricular afterload. In aggregate, these events accentuate the normal inspiratory reduction in left ventricular stroke volume and systolic pressure, leading to pulsus paradoxus, an exaggerated variation in systolic blood pressure between inspiration and expiration [23]. In severe asthma, a pulsus paradoxus > 10 mmHg indicates a 1-s forced expiratory volume (FEV_1) of less than 1 l [19, 23].

Dynamic hyperinflation places a large workload on the inspiratory muscles. With hyperinflation, lung compliance is reduced, and $PEEP_i$ adds a threshold load. In addition, diaphragmatic blood flow may be reduced (reviewed in [22]). Elevated levels of creatine phosphokinase and circulating lactate are occasionally observed during status asthmaticus [24, 25] and may reflect fa-

tigue of the respiratory muscles. Unless airways obstruction is rapidly reduced, the respiratory muscles cannot sustain adequate tidal volumes and respiratory failure ensues.

Assessment of asthma severity

Objective measurement of airflow obstruction

In patients with an established diagnosis of asthma, serial peak expiratory flow rates (PEFR) can be monitored in lieu of FEV_1. A complete forced expiratory maneuver is usually unnecessary and can even temporarily worsen asthmatic symptoms. Tests of maximal expiratory flow, including both the PEFR and FEV_1, are effort dependent and require patient cooperation to obtain reliable results. PEFR can be used to screen for the likelihood of hypercapnic respiratory failure. In the absence of respiratory depressant medications, hypercapnia does not develop until the PEFR is less than 30% of its predicted value [26]. Therefore, if the PEFR is > 30% predicted, pulse oximetry, rather than arterial blood gas sampling, can be safely used to monitor gas exchange.

Repeated measurements of maximal expiratory flow can be used to assess response to therapy, and to detect deterioration. Thus, patients with an FEV_1 < 30% of predicted on presentation to the emergency department who do not improve to at least 40% after 60 min of intense treatment, require either prolonged management in the emergency department or hospital admission [27]. It is our current practice to measure PEFR at least hourly during emergency department care and then at regular intervals (at least every 8 h in the hospitalized patient) to monitor carefully a patient's progress.

Arterial blood gas sampling

Status asthmaticus is invariably accompanied by (at least) mild hypoxemia. The correlation between FEV_1 and arterial oxygen tension (PaO_2) is weak, especially at presentation [18, 28], but PaO_2 generally declines further with worsening airflow obstruction. Even with severe asthma, significant hypoxemia resistant to supplemental oxygen is unusual, and its presence should prompt the astute clinician to reconsider the diagnosis and search for potential complications of asthma, such as pneumothorax or lobar atelectasis.

Rarely, bronchodilator therapy can result in a transient exacerbation of hypoxemia because of the vascular effects of β-adrenergic agonists. These medications are vasodilators, especially in high dose, and can lead to worsening of the asthma-related V/Q mismatch [29]. With the use of a selective β_2-agonist, this effect is generally minimal and not clinically significant.

With the advent of pulse oximetry, the need for arterial blood gas sampling in severe asthma has become restricted to the detection of abnormal CO_2 levels and acidosis. These are especially important in patients with respiratory distress and a PEFR < 30% of predicted despite initial treatment. Normalization or elevation of $PaCO_2$ may be an early sign of respiratory muscle fatigue, while arterial oxygenation tends to remain relatively preserved until respiratory failure ensues.

Laboratory data

Mild electrolyte abnormalities are common during severe asthma. Hypokalemia (potassium < 3.5 mmol/l) has been detected in 17% of patients [30], although clinically significant reductions are distinctly unusual. Hypokalemia is associated with the use of adrenergic agonists and systemic corticosteroids. Although hypophosphatemia also has been reported, it usually develops as respiratory acidosis is clearing [31]. Elevated creatine kinase levels are common in asthma with respiratory failure requiring intensive care [32] and may be indicative of increased respiratory muscle use [24] or, if the enzyme rise is delayed 2–5 days, a developing myopathy [32].

Leukocytosis and eosinophilia are also common; the former may indicate occult infection but more commonly neutrophil demargination due to systemic corticosteroid or adrenergic agonist therapy. Neither eosinophilia nor an elevated white blood cell count correlates with asthma severity [33].

Sputum examination

Although frequently purulent in gross appearance, asthmatic sputum is most often comprised of eosinophils, not neutrophils. Creola bodies (shed clusters of epithelial cells), Charcot-Leyden crystals (eosinophil lysophospholipase), and Curschmann's spirals (bronchiolar casts) can also be frequently identified on microscopic examination of the sputum [34]. If allergic bronchopulmonary aspergillosis is suspected, a fungal stain can identify branching hyphae.

Chest radiographs

The most common finding on routine screening chest radiography in acute asthma is hyperinflation. On rare occasions, unsuspected barotrauma (pneumothorax or pneumomediastinum), lobar atelectasis, or pneumonia is found. In the emergency department it is reasonable

Table 2 Differential diagnosis of status asthmaticus

Obstructive airway diseases:
Upper airway obstruction
(vocal cord dysfunction, tumor, stricture, or foreign body)
Chronic obstructive pulmonary disease
Bronchiectasis
Bronchiolitis
Cystic fibrosis
Cardiovascular diseases:
Congestive heart failure ("cardiac asthma")
Pulmonary embolism
Severe respiratory infections:
Bronchopneumonia
Severe tracheobronchitis (eg, herpetic)
Parasitic infections (esp. *Ascaris* and *Strongyloides*)
Other:
Vasculitis (allergic angiitis and granulomatosis)
Carcinoid syndrome
Aspiration pneumonitis
Cocaine inhalation
Barotrauma

to reserve chest X-rays for patients with clinically suspected complications. Although most asthmatic patients admitted to the hospital continue to have "routine" chest X-rays, patients with status asthmaticus are unlikely to benefit from admission chest radiography in the absence of certain features predictive of a high risk for radiographic abnormalities (fever, immunodeficiency, antecedent loss of consciousness, or prior thoracic surgery) [35].

Electrocardiography

The electrocardiogram in asthma often indicates sinus tachycardia, while evidence of right heart strain, including right axis deviation and P pulmonale, is less frequent. Atrial and ventricular premature complexes and supraventricular tachyarrhythmias only complicate severe asthma and its treatment, especially high doses of adrenergic agonists and methylxanthines [36]. These findings usually reverse as the asthmatic attack resolves and rarely require specific treatment.

Differential diagnosis

In a patient with severe wheezing and shortness of breath who fails to respond to intensive bronchodilator and corticosteroid therapy, particularly an adult without prior history of asthma, it is important to consider potential diagnostic possibilities other than asthma. Some of the conditions that can mimic status asthmaticus are listed in Table 2. Common confounding diagnoses that require distinct therapeutic approaches include congestive heart failure, upper airway obstruction, and pulmonary embolism.

Medical treatment

Status asthmaticus requires prompt medical treatment and close patient monitoring to identify those with impending respiratory failure. While many national societies have developed guidelines to assist the clinician during the initial management of acute severe asthma [37], critically ill asthmatics may not respond to protocol treatment and in the intensive care unit often require a more individualized approach. This section and the next review the specific medical and ventilatory therapeutic modalities available for use in the treatment of status asthmaticus.

Medical therapies can be broadly categorized into two groups: standard and unproven [38].

Standard therapies

Oxygen

Significant hypoxemia is often present, but can usually be corrected with modest concentrations of supplemented oxygen ($F_IO_2 \leq 0.4$). Restoration of normal arterial oxygen saturation improves hypoxic vasoconstriction and oxygen delivery to the respiratory muscles as well as protecting against hypoxic injury to other organs, such as the heart.

Bronchodilators

Inhaled β_2-agonists should be started immediately on presentation to relieve smooth muscle-mediated bronchoconstriction. Their onset of action is rapid, and side effects, although common, are generally mild and well tolerated. Long-acting inhaled β_2-agonists (e.g., salmeterol or formoterol) are not appropriate in this setting because of their lack of suitability for frequent repetitive administration.

Because severe airways obstruction can markedly reduce delivery and deposition of inhaled medication, larger and more frequent dosing of these agents than is used in the outpatient setting is often necessary for clinical effect (Table 3). A common starting dosage in acute asthma for inhaled albuterol (salbutamol) is 2.5 mg by nebulization (0.5 ml of a 0.5 % solution in 2.5 ml of normal saline) every 20 min for three doses, then approximately hourly as dictated by the patient's clinical course. If severe airflow obstruction persists, albuterol (salbutamol) can be nebulized at higher doses (5 mg) and more frequently (even continuously) [37], unless

side effects, such as tachyarrhythmias or severe tremor, limit administration.

Recent reports indicate that for administration of inhaled β_2-agonists, metered-dose inhalers combined with a spacer are as effective as nebulized solutions in acute asthma of all degrees of severity [39, 40]. In severe asthma, four puffs (400 μg) of albuterol (salbutamol) is as effective as 2.5 mg via nebulization, and three puffs (1.95 μg) of metaproterenol (orciprenaline) is a effective as 15 mg by nebulizer [41] (Table 3). With severe airflow obstruction, most providers still prefer administration via hand-held or mask nebulizer because less patient coordination and supervision are required. Regardless of the chosen mode of delivery, a health care provider (nurse, physician or respiratory therapist) should be present, at least initially, to ensure proper medication use and to observe clinical signs of improvement – or their absence.

In general, systemic administration of β-agonists offers no advantage over the inhaled route of delivery. Subcutaneous epinephrine (adrenaline) or terbutaline may be beneficial when a patient is unable to receive inhaled medications, such as in delirium, coma, or cardiopulmonary arrest, and occasionally when there is an inadequate response to inhaled therapy [42]. For subcutaneous therapy, epinephrine (adrenaline) is the drug of choice. Despite equivalent bronchodilation, terbutaline results in a greater frequency of tachycardia than epinephrine (adrenaline), even in older individuals [43]. The only exception is during pregnancy, because epinephrine (adrenaline) has been associated with congenital malformations and diminished uterine blood flow [44]. Potential complications of parenterally administered sympathomimetics include lactic acidosis, hypokalemia, cardiac arrhythmias, and myocardial ischemia. Again, it should be emphasized that inhaled therapy is the preferred form of treatment for bronchoconstriction in status asthmaticus, even among critically ill patients with hypercapnia, and is less likely to cause cardiac side effects [45–47].

Table 3 Medical treatment of status asthmaticus (MDI metered-dose inhaler)

	Examples	Dosages
First-line therapies		
β_2-Agonists	Albuterol (salbutamol)	2.5 mg in normal saline via nebulizer or 4 puffs (400 μg) by MDI with a spacer q20 min × 3
	Metaproterenol (orciprenaline)	15 mg via nebulizer q20 min × 3 or 3 puffs (1.95 mg) by MDI with a spacer q20 min × 3
	Epinephrine (adrenaline)	0.3 ml 1:1000 solution SC q20 min × 3
Corticosteroids	Prednisone	150–225 mg PO qd in divided doses
	Methylprednisolone	60–125 mg IV q6–8 h
Oxygen		Titrate to keep $SaO_2 > 90\%$
Second-line therapies		
Methylxanthines	Theophylline	Load: 5–6 mg/kg IV over 20–30 min (reduced loading dose in patients already taking theophylline preparations) Maintenance: 0.6 mg/kg/h IV; titrate to serum theophylline concentration 8–15 μg/ml
Anticholinergics	Ipratropium	0.5 mg via nebulizer qh × 3

Corticosteroids

The best time to begin systemic corticosteroids is prior to the development of status asthmaticus, when the patients' usual medications fail to control their deteriorating PEFR and increasing symptoms. Many patients and physicians remain reluctant to intervene with a course of corticosteroids early in worsening asthma because of fear of side effects. The consequence of delay is often progression to severe disease requiring emergency care.

The time to onset of action of systemic corticosteroids is thought to be several hours; the resultant improvement in lung function evolves slowly as airway inflammation gradually resolves. As a result, in status asthmaticus the first dose should be given as soon as possible (in the physician's office or emergency department). Significant improvement with systemic corticosteroids has been difficult to demonstrate during the few hours that the asthmatic patient spends in the emergency department [48–50]. Demonstrable benefit is found among patients after they leave the emergency department, either admitted to the hospital for continued care [51] or after discharge home following significant improvement in the emergency department [52–54].

The optimal dose of systemic corticosteroids remains an open question. Recent reviews have recommended 150–225 mg/day of prednisone or the equivalent (e.g., 40 mg methylprednisolone IV q6h, 125 mg hydrocortisone IV q6h, or 60 mg prednisone PO qg-8h) [49, 55] (Table 3). At least four studies have found oral therapy to be as effective as intravenous in the absence of vomiting [56–59].

Once there has been definite improvement in pulmonary function, the dose of corticosteroids can be reduced to 60–80 mg of prednisone/day in single or divided doses. Systemic corticosteroids should be continued until recovery of lung function to normal or to the patient's own baseline value; as long as 10–14 days of ther-

apy may be necessary. The exact timing and method of withdrawal of steroid therapy (with or without tapering doses) are more art than science, in part because no widely accepted measurement is available to inform the clinician of the status of a patient's airway inflammation. Among patients able to coordinate metered-dose inhalers, inhaled corticosteroids can be continued while the patient also receives oral or intravenous steroids. This practice should reduce patient confusion about how and when to restart their inhaled medication.

High doses of corticosteroids are associated with several adverse side effects, including hyperglycemia, hypokalemia, mood alterations, hypertension, metabolic alkalosis, and peripheral edema. If given in conjunction with a steroidal neuromuscular blocker during mechanical ventilation for respiratory failure, an intensive care myopathy can develop and result in prolonged ventilator dependence (see below).

Second-line therapies

Second-line therapies available as adjunctive bronchodilators for patients failing to improve with conventional β-agonist and corticosteroid therapy include methylxanthines and anticholinergics (Table 3). Risk-benefit analysis for these therapies – whether any additive bronchodilation justifies the potential for increased side effects – continues to be debated.

Theophylline. Numerous studies have found that theophylline is inferior to β_2-agonists as monotherapy for asthma and does not impart additional bronchodilation when high doses of the inhaled β_2-agonists are administered concurrently. Potential non-bronchodilator benefits proposed for the methylxanthines include anti-inflammatory action, improved endurance and accelerated recovery from fatigue of respiratory muscles, and a delayed improvement in lung function not evident during short-term emergency department studies [60, 61]. A meta-analysis of theophylline to treat asthma in the emergency department suggested that there was insufficient evidence to support or reject its use in this setting [62].

Despite the lack of justifying evidence, many clinicians continue to use intravenous aminophylline or theophylline in severely ill asthmatic patients when conventional therapy is slow to bring improvement. Our practice has been to continue oral theophylline in patients chronically taking this medication but not to initiate treatment with theophylline, even in hospitalized asthmatic patients. The usual loading dose for aminophylline is 5–6 mg/kg over 20–30 min, followed by a continuous infusion of 0.6 mg/kg/h. If the patient is already on theophylline, a loading dose is delayed until the serum concentration is known. We use a target serum concentration of 8–15 μg/ml). This range is therapeutic and minimizes the risk of toxicity, such as nausea, anxiety, tremor, palpitations, and tachycardia. Congestive heart failure, liver failure, cimetidine, macrolide antibiotics, and quinolones increase serum theophylline levels by their effects on hepatic cytochrome P450 enzymes.

Anticholinergics. Anticholinergics (e.g., ipratropium bromide and glycopyrrolate) are not first-line agents. They are slower in onset and produce less bronchodilation at peak effect than β_2-agonists. Recent large, prospective, double-blind trials in acute asthma among adults have failed to show a significantly better response to the combination of nebulized ipratropium and albuterol than to nebulized albuterol alone [63, 64]. Ipratropium bromide and glycopyrrolate may be useful adjuncts to β-agonists and corticosteroids in patients whose asthma is not responding to therapy, but we do not favor their routine use in acute, severe asthma. Patients with bronchospasm induced by β-blockers and patients receiving therapy with monoamine oxidase inhibitors may particularly benefit from this class of bronchodilator [65, 66].

Ipratropium bromide can be given by metered-dose inhaler (18 μg/puff) or by nebulization (0.5 mg diluted in normal saline). Optimal dosing is uncertain. A useful strategy in acute severe asthma failing to respond to standard therapy is administration of ipratropium in combination with albuterol (combined in the same nebulizer cup) for three successive hourly treatments. If no benefit is evident, then the anticholinergic can be discontinued.

Anti-leukotriene agents. This new class of medications for control of asthma symptoms consists of agents that block either the synthesis or action of the sulfidopeptide leukotrienes, mediators that are potent bronchoconstrictors and also induce pulmonary vascular leakage and inflammatory cell infiltration of the airways [67, 68]. Although these medications have generated a great deal of excitement, they are only approved in the United States for use in chronic asthma management as disease controllers. Inhibition of pro-inflammatory mediators, such as leukotrienes, is likely to speed resolution of the acute exacerbation, but to date there is no evidence for their efficacy in the management of acute severe asthma in the intensive care unit.

Unproven therapies

Magnesium sulfate

Several small studies have reported a beneficial bronchodilatory effect from intravenous magnesium [69–72] via an unknown mechanism of action. However, larger

prospective studies have failed to show a clear benefit in moderate to severe asthmatic attacks [73]. Except in patients with renal insufficiency, magnesium sulfate is safe when a dose < 2 g is infused intravenously over at least 20 min. At this time, it is difficult to recommend its use in status asthmaticus, except perhaps in the patient with documented hypomagnesemia.

Heliox

Heliox is a blend of helium and oxygen available in mixtures containing 60–80 % helium. Because this mixture is less dense than air, turbulent flow is rendered more laminar, resulting in decreased airway resistance to gas flow [74]. In some patients this effect increases ventilation, decreases the work of breathing, and delays the onset of respiratory muscle fatigue, forestalling the development of respiratory failure. In others, 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. These properties suggest heliox to be ideally suited for patients with acute asyphyxic asthma, but limited clinical data are available on its use in the adult intensive care unit. The role of heliox in acute asthma remains controversial, and it is generally limited to centers experienced in its administration.

Antibiotics

Respiratory infections that trigger asthmatic attacks are almost uniformly viral in etiology. The purulent-appearing sputum of acute asthma most often reflects an increase in airway eosinophils, not neutrophils, and even focal radiographic opacities may be the result of eosinophilic pneumonia or atelectasis secondary to mucus plugging rather than bacterial pneumonia. Therefore, unlike in exacerbations of chronic obstructive pulmonary disease, antibiotics are not a standard treatment in acute asthma. When compared to placebo in a randomized, double-blind study of patients hospitalized with status asthmaticus, amoxicillin neither improved spirometry nor shortened length of hospitalization [75]. We recommend that use of antibiotics be restricted to those patients with fever, sputum that contains neutrophils, or clinical evidence of bacterial pneumonia or sinusitis.

Other

Bronchial lavage, general anesthesia, extracorporeal membrane oxygenation and hypothermia are all unproven therapies in adults with severe asthma. Their use should be reserved for patients who have failed treatment with proven modalities.

Mechanical ventilation

Principles of mechanical ventilation

Airflow obstruction severe enough to require mechanical ventilation is invariably associated with some degree of dynamic hyperinflation. The mechanism of dynamic hyperinflation is shown in Fig. 2. Because expiratory flow is prolonged by increased airway resistance, exhalation of the inspired tidal volume is interrupted by the next breath. As the lung volume at which tidal breathing occurs increases, lung elastic recoil (the driving pressure for exhalation) and small airway caliber increase, resulting in improved expiratory flow (reviewed in [10]). With progressive hyperinflation, an equilibrium point is eventually reached such that all the inspired volume can be exhaled prior to the next inhalation.

This process is adaptive with mild airflow obstruction at lower lung volumes. With severe obstruction, mechanical inefficiency of the inspiratory muscles, decreased lung compliance, and the threshold workload of $PEEP_i$ all come into play as maladaptive factors. In very severe cases, the hyperinflation required for normocapnia may exceed the patient's total lung capacity (TLC) [14]. During spontaneous ventilation, the inspiratory muscles are unable to achieve a maximum lung volume significantly above TLC. In this setting, mechanical ventilation can take over the work of the inspiratory muscles. End-inspiratory lung volumes substantially greater than TLC can only be achieved by positive pressure ventilation, but carry an increased risk of barotrauma and hypotension [76, 77]. During mechanical ventilation, critical factors in determining the degree of dynamic hyperinflation are the inspired tidal volume, expiratory time, and severity of airflow obstruction. Ventilator strategies to minimize dynamic hyperinflation utilize a low tidal volume and maximal expiratory time by increasing inspiratory flow and decreasing respiratory rate.

The decision to intubate

It is obvious that if a patient becomes apneic or markedly hypopneic during a severe asthmatic attack, emergency intubation is mandatory. It is more difficult to decide the need for intubation and mechanical ventilation in a conscious patient who is struggling to breathe, able to cooperate with therapy, but failing to improve despite intensive treatments. Severe dyspnea coupled with respiratory acidosis ($PaCO_2 > 55$ mmHg; pH < 7.28) or rapidly increasing hypercapnia despite appropriate in-

tensive pharmacological management are reasonable indications for initiating assisted ventilation. However, no single numeric criterion can dictate management in the hypercapnic patient with severe asthma. Some hypercapnic patients will respond favorably to aggressive pharmacological treatment with patterns of improvement similar to normocapnic patients [20]. An important factor in the decision concerning intubation is the general appearance of the patient. The fatiguing patient, with respiratory rate and intensity of inspiratory effort decreasing, with speech increasingly difficult and level of alertness likewise declining, will require intubation before the patient with comparable levels of $PaCO_2$ and pH who is alert, cooperative, with stable respiratory effort and willing to continue.

Non-invasive positive pressure ventilation via face mask has been tried as a temporizing measure in acute, severe asthma to avoid the need for intubation [78–80]. Combined with continuous positive airway pressure (to counteract the workload imposed by $PEEP_i$), non-invasive ventilation can decrease the work of breathing and help achieve adequate alveolar ventilation. The technique is difficult to apply, however. The tight-fitting face mask can cause a sensation of claustrophobia in dyspneic patients, patient–ventilator synchrony is often difficult to achieve in the anxious and tachypneic patient, and delivery of medication and expectoration of airway secretions may be hindered. This technique is probably best reserved for use by physicians and respiratory therapists skilled in its application.

When required, orotracheal intubation should be performed by experienced personnel. Upper airway manipulation can result in laryngospasm and worsened bronchoconstriction. Pretreatment with atropine and a topical anesthetic helps to minimize these complications. After the patient is sedated, intubation should be performed with at least an 8-mm tube to permit suction of large mucus plugs. For this reason, nasotracheal intubation should be avoided.

Sedation and paralysis

Effective sedation is crucial to improve patient comfort during intubation and ensure patient–ventilator synchrony. Sedation decreases oxygen consumption ($\dot{V}O_2$) and CO_2 production and helps to control over-exuberant respiratory efforts. Widely accepted sedation protocols are not available. One effective approach at the time of intubation combines a short-acting benzodiazepine (e.g., midazolam) with a short-acting neuromuscular blocker (e.g., succinylcholine). During assisted ventilation, adequate sedation can best be achieved with agents having longer durations of action (e.g., lorazepam and haloperidol) for the duration of intubation and ventilation (reviewed in [38]).

An interesting choice for patients with status asthmaticus is ketamine, an intravenous general anesthetic with analgesic and bronchodilating properties [81]. During intubation, 1–2 mg/kg IV at a rate of 0.5 mg/kg/min results in 10–15 min of general anesthesia without significant respiratory depression [82]. The bronchodilating properties are observed shortly after administration and last roughly 30 min [83]. Ketamine is not without risk because it can cause tachycardia and hypertension (sympathomimetic properties), lower the seizure threshold, lead to delirium (especially upon reemergence from anesthesia), and predispose to aspiration [82]. Only limited clinical data are available regarding the use of ketamine in this setting.

During mechanical ventilation, paralysis should be reserved for well-sedated patients in whom it is difficult to provide adequate ventilation at reasonable inflation pressures. Paralysis will lessen patient–ventilator dyssynchrony and the risk of barotrauma by giving the intensivist control over the patient's minute ventilation. As a result, lung volume and respiratory rate can be optimized to levels that minimize dynamic hyperinflation. Like sedation, neuromuscular blockade will reduce $\dot{V}O_2$, CO_2 production, and lactate accumulation. The preferred paralytics are the non-depolarizing agents, vecuronium and atracurium, which have minimal cardiac toxicity. A potential disadvantage of atracurium is that at high doses it can result in histamine release and worsened bronchospasm [84]. Other potential side effects of paralysis include in increased risk of venous thromboembolism and severe intensive care unit myopathy. This latter condition is particularly common among asthmatic patients simultaneously receiving high doses of systemic corticosteroids [85, 86]. Originally reported with vecuronium, intensive care unit myopathy has now been observed with other paralytic agents as well [87]. The syndrome is difficult to detect during active paralysis although an elevated serum creatine kinase level may be a potential marker for a developing myopathy [87]. As a precaution, laboratory parameters (e.g., creatinine kinase, potassium and phosphate) should be monitored while any asthmatic patient is treated with paralytic agents. In general, the minimal effective dose should be administered, using peripheral nerve stimulation as a guide, and the drug should be withdrawn within 24 h, if at all possible. No specific therapy is available for intensive care unit myopathy should it develop.

Initial ventilator settings

In most instances of respiratory failure, mechanical ventilation is used to restore $PaCO_2$ to normal. In status asthmaticus normocapnia often cannot be achieved without the use of very high inflation pressures and rapid respiratory rates, leading to an increased risk of

barotrauma. A recommended approach in this circumstance is "permissive hypercapnia": the use of relatively low inspired tidal volumes (8–10 ml/kg) and rates of minute ventilation (8–10 l/min) that permit hypercapnia and reduce the risk of barotrauma [10, 38, 88] (Table 4). A high inspiratory flow rate (e.g., 100 l/min) is used to prolong expiratory time. Hypoxemia is corrected by increasing F_IO_2 rather than by applying PEEP, which may further increase the risk for barotrauma by worsening alveolar hyperinflation [89].

Hypotension may complicate the initiation of mechanical ventilation. Positive intrathoracic pressure, sedation, muscle relaxation, and relative hypovolemia can combine to decrease venous return and lead to hypoperfusion. Volume loading the young, cardiovascularly fit asthmatic patient prior to anesthetic induction is usually well-tolerated and lessens the risk of hypotension after intubation. To reduce the adverse hemodynamic effects of $PEEP_i$, an ambu-bag can be used to ventilate the patient with 100% supplemental oxygen at a slow rate while crystalloid is infused (0.5- to 1-l IV bolus over approximately 20 min) to correct hypoperfusion.

Table 4 Initial ventilator settings in status asthmaticus

Setting	Recommendation
Respiratory rate	10–15 breaths/min
Tidal volume	8–10 ml/kg
Minute ventilation	8–10 l/min
PEEP	0 cm H_2O
Inspiratory flow	$\geqslant$ 100 l/min
I:E ratio	$\geqslant$ 1:3
F_IO_2	1.00

Ventilatory management

An approach to mechanical ventilation that minimizes inflation pressure by using relatively low levels of minute ventilation will cause respiratory acidosis. In the absence of increased intracranial pressure, severe respiratory acidosis with very high $PaCO_2$ is generally well tolerated by the sedated patient, with rare instances of cardiac arrhythmias and hypertension [90]. We do not recommend administration of bicarbonate to correct respiratory acidosis in permissive hypercapnia, because the CO_2 released by red blood cell carbonic anhydrase catalysis of bicarbonate cannot be readily excreted via the diseased lungs. When given intravenously as a bolus, bicarbonate results in progressive tissue acidosis despite a more alkaline arterial pH. This intracellular acidosis can be minimized when bicarbonate is given more slowly (infused over $\geq$ 1 h), yet even this strategy does not measurably benefit mechanically ventilated asthmaticus with moderate hypercapnia [91].

Plateau inflation pressure and the level of $PEEP_i$, but not the peak inflation pressure, best reflect dynamic hyperinflation. However, the risk of barotrauma correlates most closely with end-inspiratory volumes, not pressures [77]. Because respiratory compliance varies among individuals and with time, inflation pressures are imperfect predictors of lung volume. The most direct indicators of dynamic hyperinflation are circulatory responses and the end-inspiratory lung volume, but these are cumbersome to measure (reviewed in [10]).

The technique for direct measurement of dynamic hyperinflation requires that patients be paralyzed because a prolonged period of cessation of mechanical ventilation (e.g., 40–60 s) is required. During this interval the patient's arterial blood pressure and central venous pressure will increase if significant dynamic hyperinflation is present [76, 77]. With an in-line volumetric spirometer, the end-inspiratory volume can be quantitated by measuring the volume of exhaled gas (exhaled volume = tidal volume + trapped volume) [10]. An end-inspiratory lung volume > 20 ml/kg above the predicted normal functional residual capacity is associated with an increased risk for hypotension and barotrauma [14]. It has therefore been recommended that ventilatory strategies be chosen that keep the end-inspiratory volume less than this value [10, 14].

As airway obstruction gradually decreases, increased levels of minute ventilation can be achieved with acceptable inflation pressures and degrees of dynamic hyperinflation [14]. When the $PaCO_2$ returns to normal, the level of sedation can be reduced, neuromuscular blockade (if still in place) can be stopped, and the patient is generally ready to be weaned.

Liberation from the ventilator

Once $PaCO_2$ has returned to normal, the patient can be given a trial of spontaneous breathing using a T-piece or CPAP. Depending on the size of the endotracheal tube, inspiratory pressure support between 5 and 8 cm H_2O may be applied to overcome the increased inspiratory resistance of the tubing. If the patient remains alert with stable vital signs and gas exchange after 60–120 min of spontaneous breathing, he/she should be extubated. Thereafter, it is appropriate to continue to observe the patient in the intensive care unit for an additional 24 h after extubation to ensure continued clinical recovery and a safe transfer to the general medical area.

Prognosis after acute severe asthma

Although many experienced clinicians report 0% mortality from status asthmaticus requiring intensive care [77, 92], others have reported a significant (16.5%) in-

hospital mortality [93]. The authors of this latter study observed that the risk of fatal asthma following an episode of respiratory failure remains elevated at 1, 3 and 6 years following hospital discharge [93]. Patients who have experienced a life-threatening attack therefore most likely benefit from close outpatient follow-up with an asthma specialist. Extensive patient education, recognition of early warning signs of an impending asthma attack, written action plans guided by peak flow rate monitoring and symptoms, and the regular use of inhaled corticosteroids with early administration of oral corticosteroids for exacerbations all comprise the intensive outpatient care required by this "at risk" population of asthmatic patients.

Summary

Despite improved understanding of the basic mechanisms underlying asthma, morbidity and mortality remain high, especially in the "inner cities." The treatment of choice in status asthmaticus includes high doses of inhaled β_2-agonists, systemic corticosteroids, and supplemental oxygen. The roles of theophylline and anticholinergics remain controversial, although in general these agents appear to add little to the bronchodilator effect of inhaled β-agonists in most patients. Anti-leukotriene medications have not yet been evaluated in acute asthma. Other therapies, such as magnesium sulfate and heliox, have their advocates but are not recommended as part of routine care.

If pharmacological therapy does not reverse severe airflow obstruction in the asthmatic attack, mechanical ventilation may be temporarily required. Based on our current understanding of ventilator-induced lung injury, optimal ventilation of asthmatic patients avoids excessive lung inflation by limiting minute ventilation and prolonging expiratory time, despite consequent hypercapnia. Unless respiratory function is extremely unstable, the use of paralytic agents is discouraged because of the increased risk of intensive care myopathy. Patients who have suffered respiratory failure due to asthma are at increased risk for subsequent death due to asthma (14% mortality at 3 years) [93] and should receive very close medical follow-up. In general, severe asthmatic attacks can best be prevented by early intervention in the outpatient setting. In the words of Dr. Thomas Petty, "... the best treatment of status asthmaticus is to treat it three days before it occurs" [94].

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