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The Critically Ill Asthmatic—from ICU to Discharge

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Abstract Status asthmaticus (SA) is defined as an acute, severe asthma exacerbation that does not respond readily to initial intensive therapy, while near-fatal asthma (NFA) refers loosely to a status asthmaticus attack that progresses to respiratory failure. The in-hospital mortality rate for all asthmatics is between 1% to 5%, but for critically ill asthmatics that require intubation the mortality rate is between 10% to 25% primarily from anoxia and cardiopulmonary arrest. Timely evaluation and treatment in the clinic, emergency room, or ultimately the intensive care unit (ICU) can prevent the morbidity and mortality associated with respiratory failure. Fatal asthma occurs from cardiopulmonary arrest, cerebral anoxia, or a complication of treatments, e.g., barotraumas, and ventilator-associated pneumonia. Mortality is highest in African-Americans, Puerto Rican-Americans, Cuban-Americans, women, and persons aged ≥ 65 years. Critical care physicians or intensivists must be skilled in managing the critically ill asthmatics with respiratory failure and knowledgeable about the few but potentially serious complications associated with mechanical ventilation. Bronchodilator and anti-inflammatory medications remain the standard therapies for managing SA and NFA patients in the ICU. NFA patients on mechanical ventilation require modes that allow for prolonged expiratory time and reverse the dynamic hyperinflation associated with the attack. Several adjuncts to mechanical ventilation, including heliox, general anesthesia, and extra-corporeal carbon dioxide removal, can be used as life-saving measures in extreme cases. Coordination of discharge and follow-up care can safely reduce the length of hospital stay and prevent future attacks of status asthmaticus.

Keywords Severe asthma · Status asthmaticus · Near-fatal asthma · Mechanical ventilation

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Introduction

Status asthmaticus (SA) and near-fatal asthma are common medical emergencies faced by critical care physicians. Status asthmaticus is defined as an acute, severe asthma exacerbation that does not respond readily to initial intensive therapy, while near-fatal asthma (NFA) refers loosely to a status asthmaticus attack that progresses to respiratory failure (Fig. 1). Timely evaluation and treatment in the clinic, emergency room, or ultimately the intensive care unit (ICU) can prevent the morbidity and mortality associated with respiratory failure. Fatal asthma occurs from cardiopulmonary arrest, cerebral anoxia, or a complication of treatments, e.g., barotraumas, and ventilator-associated pneumonia. Critical care physicians or intensivists must be skilled in managing the critically ill asthmatics with respiratory failure and knowledgeable about the few but potentially serious complications associated with mechanical ventilation. Bronchodilator and anti-inflammatory medications remain the standard therapies for managing SA and NFA patients in the ICU. NFA patients on mechanical ventilation require modes that allow for prolonged expiration and reverse the dynamic hyperinflation associated with the attack. Several adjuncts to mechanical ventilation, including heliox, general

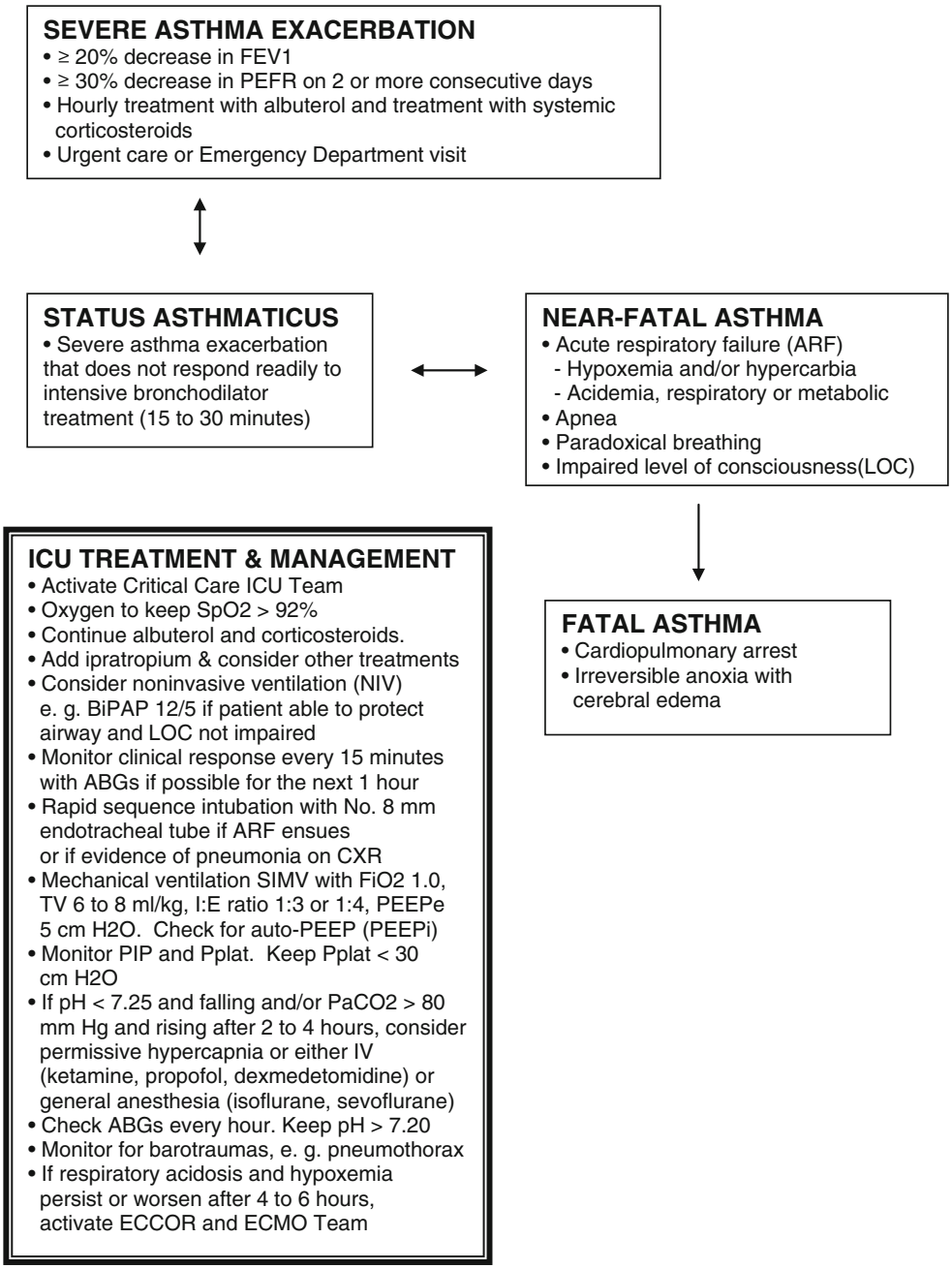

Fig. 1 Deterioration of severe asthma exacerbation: status asthmaticus and near-fatal asthma with suggested ICU treatment and management

anesthesia, and extra-corporeal carbon dioxide removal, can be used as life-saving measures in extreme cases.

Triage of Patients to the ICU

Most asthmatic patients requiring hospital admission do not need ICU-level care. Of the 2 million emergency department visits attributed annually to severe asthma exacerbations, approximately 25% of patients are hospitalized and of these 5% to 10% require the ICU. The majority of hospitalized asthmatics improve while in the emergency department and warrant observation on a ward for a few days (average length of stay 3.2 days) to ensure continued improvement. The number of hospital discharges with asthma as the first diagnosis was 440,000 in 2006 [1]. In an analysis of nearly 30,000 hospital admissions for acute asthma, 10.1% required admission to the ICU and 2.1% required intubation and mechanical ventilation [2]. The intubated patients averaged 4.5 extra days in the hospital and over $11,000 in additional costs as compared to asthma admissions to non-ICU beds. Absolute criteria for triaging acute, severe asthmatic patients are lacking; existing guidelines recommend that patients with PEFR <200 l/

min, a pulsus paradoxus >15 mmHg, use of accessory muscles of respiration, or a <10% improvement in PEFR be monitored in an ICU, but data supporting these recommendations are scant [3]. Clearly, worrisome patients—with a worsening respiratory or metabolic acidosis—should be transferred to an intensive care setting.

Epidemiology of Fatal Asthma

Approximately 11 people die from asthma each day in the USA. Death from asthma in the USA rose from a low of 1,674 in 1977 to 5,667 in 1996 but has steadily declined by at least 30% since 1996 with 3,447 deaths reported in 2007 or 1.1 patients per 100,000 population [4]. Although asthma mortality in the USA is among the lowest in the world, approximately 3,000 to 4,000 asthma-related deaths still occur annually, particularly in African-Americans, Puerto Rican-Americans, Cuban-Americans, women, and persons ≥65 years. The highest at-risk-based death rate was in persons aged ≥65 years (10.5 per 10,000 with current asthma). Males had higher at-risk-based death rates than females (2.3 and 1.8, respectively). For most age groups, males had higher rates than females; only for persons aged ≥65 years was the rate for females (11.3 per 10,000 with current asthma) higher than for males (9.1). Blacks had higher at-risk-based death rates (3.4) than Whites (1.9). This was true for males and females, adults and children, and each age group. Asthma is reported as a contributing factor for nearly 7,000 other deaths each year [5]. It has been suggested that 1% to 7% of severe asthmatics will die each year of their disease, and perhaps 17% of those who survive NFA attacks will eventually succumb to asthma [6].

Mortality rates for NFA patients requiring mechanical ventilation vary from 0% to 22% in reported series over the last three decades, but the rate is probably less than 5% in most settings [7, 8]. In general, the morbidity and mortality of hospitalized patients with SA have decreased significantly and much of the credit is due to the timely assessment and treatment by out-of-hospital providers and better ICU care [9]. Hospital care for asthma is not without problems, of course; patients have died because of inadequate initial observation and treatment and therapeutic measures may cause debilitating complications [10].

Risk Factors for Fatal Asthma

The single largest risk factor for fatal asthma is a history of NFA (Table 1). One study found a 16-fold increased risk of asthma death for patients with a prior history of NFA. Other factors correlate with fatal asthma. Psychiatric illness, for one, is consistently associated with an increased risk of fatal asthma [11]. Similarly, persistent smoking carries a twofold increased risk of death in asthmatics. Another oft-reported risk factor for fatal asthma is frequent short-acting β_2-agonist use [12]. In a case–control study, the use of short acting β_2-agonists conferred a two- to threefold increased risk per bronchodilator canister per month [12].

Patients with SA and NFA may have blunted perceptions of dyspnea. In one study, 11 severe patients had blunted ventilatory responses and lower Borg dyspnea scores compared to mild asthmatics when exposed to hypoxic conditions, suggesting that these patients were unable to recognize their deterioration and impending respiratory failure [13].

Demographics

The majority of adult patients seen in asthma referral clinics are women and this is in contrast to the pediatric population where boys are more prevalent [14]. Furthermore, the age-adjusted mortality rates are significantly higher for women (2.5 vs. 1.9/100,000 population), as they are for African-Americans (3.6 vs. 1.2/100,000), Hispanics, and the elderly [15]. Nearly 65% of asthma deaths are attributed to women, and among African-Americans women have the highest mortality rate, more than 2.5 times higher than that of Caucasian women. Why women make up 60–80% of adult, severe asthma patients is unclear. Genetic predisposition, hormonal effects, and increased prevalence of vocal cord dysfunction and gastroesophageal reflux disease may be contributors in women.

Genetics

Gene polymorphisms are factors in the pathophysiology of severe asthma and possibly fatal asthma. Several studies have outlined the effect of the Gly-16 polymorphism of the β2-adrenoreceptor. Patients homozygous for Gly-16 undergo desensitization and downregulation of this β-receptor

Table 1 Risk factors for fatal asthma

History of near-fatal asthma	Rapid onset of attack ("brittle asthma") [87]
Female gender	Elderly and poor
African-American ethnicity	Psychiatric illness
Puerto Rican-American ethnicity	Blunted perception of dyspnea or inability to distinguish danger from discomfort
Cuban-American ethnicity	β_2-Agonist usage (long/short acting)

response; this genotype is more prevalent in the acute, severe asthma population [16, 17]. In addition, certain polymorphisms for interleukin-4 (IL-4) and its receptor correlate loosely with SA [18]. Variation in one gene, corticotropin-releasing hormone receptor 1 (CRHR1), which is involved in the release of ACTH, was consistently associated with enhanced response to corticosteroids. Genetic variants in CRHR1 may adversely influence the clinical response to corticosteroids and lead to SA. Between 25% and 35% of asthma patients do not respond with a >5% improvement FEV_1 or better asthma control after 6 to 12 weeks of inhaled corticosteroid treatments [19]. Whether this genetic predisposition affects the acute treatment and outcomes of SA and NFA is not known. Other factors that may play a role in predisposition to SA are transforming growth factor β (TGF-β) and 5-lipoxygenase activating protein [20], [21].

Psychosocial and Socioeconomic Factors

Poverty and poor access to medical care correlate with increased risk for fatal asthma. For example, 21% of all asthma deaths among young people in the late 1980s occurred in the inner cities of Chicago and New York [22]. Several hypotheses have been proposed to explain the correlation between socioeconomic status and fatal asthma. Certainly, one of the most important points is that poor patients have inadequate medical care. Risk factors for death from asthma include lack of appropriate anti-inflammatory controller medication, particularly inhaled corticosteroids, inappropriate use of long-acting β_2 agonists without controller medication (s), limited self-management skills, increased exposures to air pollution and indoor allergens (house, dust, mite, cockroach), dietary factors, and drug abuse. Cocaine and heroin users were intubated significantly more often than nonusers for NFA (17% vs. 2.3%, respectively; $p=0.0036$) [23].

Stress

The effect of psychosocial stress on asthma has been demonstrated in several studies. One recent study demonstrated a strong correlation between worsening airway inflammation following antigen challenge during a week of intensive examinations among a university cohort [24]. In the ENFUMOSA [25] study, men with severe asthma reported that stress was a common trigger for exacerbations. Psychiatric illness has also consistently been associated with an increased risk of fatal asthma [11].

H1N1 Infection

During the spring of 2009, a pandemic influenza A (H1N1) virus emerged. In contrast to the traditional host for severe infection, H1N1 appeared to target a more unique cohort of patients. Among these, asthma patients emerged as having a higher risk of infection and resultant respiratory failure [26]. The clinical manifestation of respiratory failure in these patients was more consistent with acute lung injury rather than NFA exacerbation. Except for a few case reports, little is known about how often H1N1 may be responsible for a SA or NFA presentation [27].

Pregnancy

The impact of pregnancy on asthma is reviewed comprehensively in Chapter 9 of this book. Uncontrolled asthma in pregnant asthmatics puts them at a higher risk for complications that can include early labor, hypertension, gestational diabetes, and NFA for mother and fetus. Teenage mothers with asthma face higher risks than older women. Most asthma drugs are safe to take during pregnancy, and a good control of asthma reduces these risks of severe exacerbations to normal levels.

Pregnant asthmatics presenting with severe asthma exacerbations must avoid hypoxia at all costs to prevent fetal anoxia. The threshold to intubate pregnant asthmatics with SA should be very low to prevent and limit hypoxia to mother and fetus [28]. No maternal deaths occurred in 80 pregnancies in 73 women with SA. Infants delivered from gravidas who experienced at least one episode of SA during gestation had decreased birth weights ($p=0.03$) compared with infants delivered from gravidas who did not require emergency therapy or develop SA [29].

Pathophysiology of Near-Fatal and Fatal Asthma

Acute, severe asthma leads to hypoxemia via lung hyperinflation and regional ventilation/perfusion (V/Q) alterations. Studies of patients presenting to the ED with severe asthma attacks using multiple inert gas elimination techniques have shown a bimodal blood flow pattern with a significant portion of the cardiac output perfusing poorly ventilated lungs. Again, a host of inflammatory mediators have been implicated in potentiating this abnormality. Platelet activating factor (PAF), for one, appears to be an important culprit. Inhaled PAF has been shown to induce V/Q mismatching and decrease arterial oxygenation in stable asthmatics by eliciting a capillary leak phenomenon [30, 31]. Additionally, others have shown that perfusion compensates for chronic ventilation abnormalities but does not compensate immediately for an acute change in ventilation [32]. Other local and systemic mediators probably act at the alveolar–capillary interface in SA to generate the profound V/Q abnormalities, and further research in this area is ongoing.

Carbon dioxide retention does not usually develop in SA until the FEV_1 is less than 30% of the predicted value and

one large meta-analysis of severe asthmatics found that only 13% had $PaCO_2$ values>45 mmHg [33]. Increased physiologic dead space associated with the V/Q abnormalities and alveolar hypoventilation secondary to respiratory fatigue both lead to hypercarbia and a heightened respiratory drive.

Asthma is a spectrum of disease and research efforts have attempted to delineate specific biomarkers that might differentiate NFA from milder forms of asthma. Marked airway thickening and a brisk infiltration of neutrophils into the airways are consistent findings in NFA. In cases of fatal asthma, bronchial thickening is 25–300% greater than normal airways, while in NFA patients this is less dramatic [34]. The predominance of eosinophils or neutrophils in the airways of NFA defines two distinct phenotypes and clinical presentations. Recently, Lamblin and colleagues found significantly increased numbers of neutrophils and levels of the neutrophil chemoattractant, IL-8, in bronchoalveolar lavage fluid (BALF) in asthmatics, requiring mechanical ventilation compared to milder patients [35]. In addition, increased matrix metalloproteinase, presumably triggered by neutrophil-mediated epithelial cell injury, was found in the BALF in severe asthmatics [33].

In contrast, Wenzel and colleagues found that the presence of both eosinophils and neutrophils in transbronchial biopsy specimens, rather than neutrophils alone, correlated with the number of NFA events in severe asthma (i.e., patients requiring at least 10 mg of prednisone daily >75% of the year) [36].

This is characteristic of the most common NFA phenotype, marked by a more gradual deterioration over days or weeks in patients with poorly responsive severe asthma [37]. Both phenotypes often have severe airways obstruction and concomitant static hyperinflation. Prevention of NFA may eventually be predicated on identifying predominantly neutrophilic or eosinophilic inflammation phenotypes using screening biomarkers and treatments specific to modulating small airways inflammation, e.g., with 5-lipoxygenase inhibitors, leukotriene receptor antagonists, theophylline, omalizumab, systemic corticosteroids. This discourse presumes that NFA, either predominantly neutrophilic or eosinophilic, is not complicated by infection, e.g., acute pneumonia, bacterial or viral, pulmonary embolism, or drug-induced lung disease.

Two other pathologic features of interest in NFA and fatal asthma are mucus cell hyperplasia and smooth muscle hypertrophy. The contributions of mucous cell metaplasia and mucus secretion are debated. Clearly, in many cases of fatal asthma and SA, mucus plugging with airway cast formation is a critical factor [38]. Airway samples in fatal asthma often reveal a marked infiltration of the mucus glands by mast cells and neutrophils [39]. Smooth muscle hyperplasia is prominent in the larger generation airways and this has been documented in cases of fatal asthma [40]. An excess growth of these myocytes leads to a web-like binder around the airways that are hypercontractile to stimuli. Several inflammatory mediators have been implicated as potential triggers of the smooth muscle hypertrophy, including histamine and Th2 cytokines.

Clinical Evaluation upon Admission to the ICU

SA is a medical emergency and non-intubated SA patients admitted to the ICU require urgent assessment and timely institution of therapy delivered by an intensivist-led critical care team. Patients with signs of respiratory failure—a decreased level of consciousness, shallow respirations, central cyanosis, or other signs of profound fatigue—should be endotracheally intubated urgently. Most patients, however, examined and reassessed by the intensivist during the first hours in the ICU do not require mechanical ventilation.

Much of the relevant physical examination of a SA patient can be obtained from the vital signs and by observation. The most worrisome patients will often be sitting upright, tachypenic, wheezing, and have sternocleidomastoid contraction with respiration. Brenner and colleagues showed a good correlation between patient position and accessory muscle use and a reduction in peak expiratory flow rate (PEFR) and partial pressure of oxygen (PaO_2) [41]. In general, however, physical findings in SA gauge the work of breathing rather than the degree of airway obstruction. Paradoxical breathing signifies impending respiratory arrest from total exhaustion and should prompt immediate endotracheal intubation and mechanical ventilation, not non-invasive mask ventilation (NIV) or continuous positive airway pressure ventilation (CPAP) (Table 2).

Table 2 Indications for intubation

Absolute	Relative
Cardiorespiratory arrest or apnea	Hypercarbia, e.g. $PaCO_2$>50 mmHg or rising >5 mmHg per hour
Acute respiratory failure with PaO_2<60 mmHg or $PaCO_2$>50 mmHg	Worsening respiratory acidosis
Acute chronic respiratory failure	Inability to care for patient appropriately
Decreased level of consciousness	Clinical signs of fatigue, e.g. paradoxical breathing
Hypopneas	Failure to improve with therapy

The vital signs of a patient in SA will consistently include a respiratory rate >30 per minute and a heart rate >120 per minute [42]. Blood pressure can fluctuate depending on the degree of hemodynamic embarrassment due to high intrathoracic pressures. The most worrisome patients are hypotensive because of dehydration and marked lung hyperinflation with impaired cardiac filling. Safe endotracheal intubation in these patients is often a challenge. Perhaps more useful than blood pressure is the pulsus paradoxus. Mountain and Sahn found that hypercapnic SA patients had an increased mean pulsus paradoxus (23 mmHg) compared to normocapnic acute asthmatics (14 mmHg) [43]. It should be remembered that, as respiratory failure progresses, a drop in pulsus paradoxus to near-normal readings may be seen. The remainder of the physical examination should look for possible mechanical complications of SA. Pneumomediastinum and pneumothorax may be identified by observing a deviated trachea, palpating subcutaneous emphysema, or auscultating asymmetric breath sounds or a Hamman's mediastinal crunch.

Assessment of Airway Obstruction

The intensivist should order a peak expiratory flow rate or spirometry in the non-intubated SA patient, if not done recently in the emergency room. Severely compromised patients will be unable to perform the test properly and it should be deferred. SA patients typically have PEFR readings <25% predicted and FEV_1 <20% predicted [44, 45]. In one study of 86 patients presenting with acute, severe asthma, a FEV_1 reading of <1 l (<25% predicted) or a PEFR <200 l/min (<30% predicted) identified all patients with hypercarbia ($PaCO_2$ >42 mmHg) or severe hypoxemia (PaO_2<60 mmHg) [46]. Reductions in PEFR to <33% of normal is as considered life-threatening. One advantage to performing spirometry with a full flow-volume loop is in diagnosing asthma mimics like vocal cord dysfunction or a tracheal tumor that may be admitted to the ICU in extremis.

Arterial Blood Gas Measurement

In SA patients in the ICU, arterial blood gases (ABGs) provide important information in terms of respiratory reserve, metabolic disturbances, and degree of hypoxemia. Respiratory alkalosis is the most common abnormality found during asthma exacerbations [47], but as PEFR and FEV_1 drop to <30% of predicted, hypercarbia and respiratory acidosis develop [46]. It is prudent to remember that acute respiratory alkalosis may signal sepsis, pneumothorax, pulmonary edema, pulmonary embolism, or cerebral edema. Furthermore, concomitant lactic acidosis occurs in up to 28% of SA patients with elevated $PaCO_2$ levels [47]. The lactate production presumably stems from overload of the thoracic cage muscles and tissue hypoxia. ABGs should be obtained early in the ICU course of SA patients.

Chest Radiography

As with ABGs, chest radiographs (CXRs) are not routinely performed in all SA patients in the emergency room. Abnormal CXR findings other than hyperinflation or subsegmental atelectasis in all asthma exacerbations is <5% [48]. Complications from barotrauma in SA patients, however, are sufficiently prevalent to justify routine chest radiographs in this population. A review of 54 admission CXRs on hospitalized asthmatics found that 20 (34%) were felt to have major abnormalities that warranted attention [49]. Most of these major abnormalities were focal infiltrates, and only one patient was found to have a pneumothorax. In the ICU asthmatic population, routine CXRs appear clinically useful. Acute pneumonia, viral, bacterial or fungal can complicate SA and cause adult respiratory distress syndrome to occur with a very high mortality. Influenza A (H1N1) pneumonias were reported in obese asthmatics taking oral prednisone for severe asthma exacerbations prior to their acute presentation to the hospital [50] (Fig. 2).

Other Studies

Few other studies need be obtained in evaluating patients with SA in the ICU. Electrocardiograms in middle-aged patients or those with suspected ischemic heart disease is standard. Screening laboratory chemistries may reveal hypokalemia

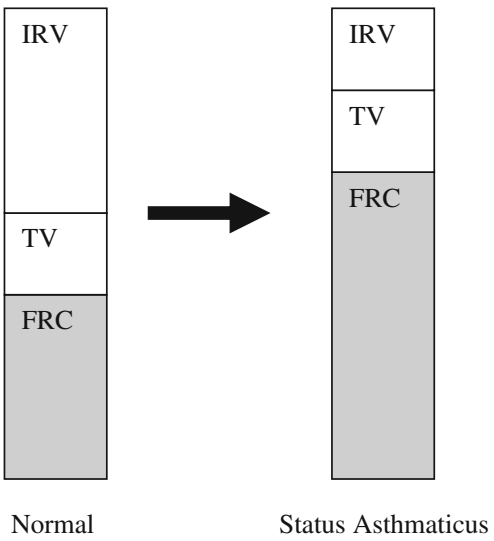

Fig. 2 Effect of dynamic hyperinflation on lung volumes—normal and status asthmaticus. *FRC* functional residual capacity, *TV* tidal volume, *IRV* inspiratory reserve volume

related to aggressive β_2-agonist usage or abnormalities in sodium and glucose, suggesting concomitant illness. A complete blood count could reveal signs of an acute infectious process, but this will be infrequent. Moderate (absolute eosinophil count 1,500 to 5,000 cells/mm^3) to severe peripheral eosinophilia (absolute eosinophil count >5,000 eosinophils/mm^3) should raise concern for allergic bronchopulmonary aspergillosis with massive mucous plugging, Loffler's syndrome, and Churg–Strauss syndrome. In general, specific laboratory tests and studies should be ordered only if other diagnoses or contributing factors are under consideration.

Initial ICU Management

As with most ICU patients, treatment of patients with SA continues in parallel with their ongoing assessment and diagnostic evaluation. Timely intervention is necessary if intubation and mechanical ventilation are to be avoided. The cornerstones of SA treatment are oxygen, bronchodilators, corticosteroids, and, if necessary, ventilatory support.

Oxygen

Modest hypoxemia is common in severe asthma exacerbations, but a PaO_2 <55 mmHg is rare [3]. Supplemental oxygen should be administered to improve the hypoxia caused by (V/Q) mismatch, airway plugging, and atelectasis; oxygen therapy may ameliorate some of the symptoms of air hunger. In the majority of SA patients, inspiratory fraction of oxygen (FiO_2) levels of 30–50% will correct the hypoxemia; failure to do so should prompt an investigation for pulmonary parenchymal or vascular disease. One hundred percent oxygen may increase $PaCO_2$ levels by 5–6 mmHg and, infrequently, may suppress the respiratory drive in SA patients [51]. Physicians should refrain from routinely administering unnecessarily high oxygen concentrations without close patient monitoring.

Bronchodilators

The cornerstone of acute asthma management, bronchodilators have several modes of delivery, mechanisms action, and potential complications. Delivery of the short-acting beta-agonist albuterol by intermittent inhalation is the most common therapy for acute asthma. While delivery of the short-acting beta-agonists by dry powder, nebulization, or meter dose inhalation are effective in severe acute asthma; each modality can offer distinct advantages [52]. Delivery by nebulization provides adequate drug delivery in a wide range of clinical settings: the infant by mask delivery and the tachypenic adolescent or even the intubated patient with respiratory failure. Nebulized delivery may decrease some of the adverse effects (e.g., tachycardia) as compared to oral or systemic delivery. Delivery by metered dose inhaler (MDI) with the use of a spacer has also been effectively employed in acute settings but is often more cumbersome, particularly in the anxious or uncomfortable patient. In the calm, cooperative patient, delivery of beta-agonist by MDI may provide a more rapid and efficacious delivery to the airways. In the acutely ill patient with SA or NFA, aerosol delivery remains the mode of choice.

Delivery by continuous nebulization may offer distinct advantages to intermittent dosing. Even with similar per-hour dosing (e.g., 0.5–1.0 mg/h vs. 2.5 mg every 2–4 h), continuous nebulization, in some studies, shows a more rapid clinical improvement with a decreased medical personnel workload than intermittent administration [39, 52–54]. The addition of heliox as a carrier gas may also improve drug delivery in SA [55].

Alternatively, systemic delivery (e.g., subcutaneous terbutaline) may offer a more reliable dosing in the profoundly ill or pregnant patient. Systemic beta receptor antagonism using subcutaneous epinephrine can be effective and may forestall respiratory failure in selected cases but with the potential for significant adverse cardiovascular effects. Epinephrine with its significant alpha adrenergic stimulation may initially reduce edema by decreasing blood flow but can also promote delayed airway edema and should be used with extreme caution in patients with a coincident cardiac disease.

Anticholinergics or antagonists of relevant muscarinic receptor subtypes in the tracheobronchial tree are emerging as an important bronchodilator therapy for persistent asthma. Whether the addition of an inhaled ipratroprium, 0.5 mg every 6 h, to albuterol is superior to the albuterol-treatment alone in SA or NFA is not known. The benefits for adults are less certain, but in critically ill asthmatics who have COPD physiology with a FEV_1<50% predicted, the addition of ipratropium to albuterol improved FEV_1 to a greater degree than albuterol alone and, most importantly, decreased the need for hospitalization [53], [56].

Systemic Corticosteroids

Intravenous (IV) methylprednisolone, 60 mg every 6 h, is administered to the critically ill asthmatic for the first ICU day. This should be instituted at the same time that albuterol is given. There is typically a 6- to 24-h delay in clinical response to corticosteroids in SA and NFA, but they have been shown to reduce fatal asthma. If the patient improves within 24 h, the dose of methylprednisolone is decreased to

60 mg every 12 h for the next day or two after which prednisone 1 mg/kg is substituted or no greater than 60 mg daily for 2 days, followed by a drop to 40 mg for the next 3 days. If improvement continues, the patient may be discharged from the hospital with a prednisone taper, i.e., 30 mg for 3 days, 20 mg for 3 days, and 10 mg for 3 days. Follow-up in clinic is imperative to prevent SA relapse and assess asthma control.

Methylxanthines

The methylxanthines, theophylline and aminophylline, are less specific bronchodilators and some evidence showing that they improved diaphragmatic contractility may be of utility in a failing patient [55]. Nonetheless, given the higher risk of adverse cardiac events, narrow therapeutic dosing windows, and lack of proven additional efficacy, these are not commonly used.

The most common side effects of beta-agonists are tachycardia and jitteriness. Serious cardiac dysrhythmias are uncommon when using selective beta-agonists. Salpeter reports an attributable heart rate increase of just over nine beats per minute [57]. The decreases in serum potassium levels—on average 0.36 mmol/l—do not usually warrant intervention [57].

Other Therapies

Leukotriene receptor antagonists such as montelukast have demonstrated efficacy in chronic asthma, but their efficacy in acute asthma is emerging. In a randomized, double-blind, parallel-group pilot study, adults with moderate to severe acute asthma received standard therapy plus either intravenous montelukast (7 mg) or matching placebo. A total of 583 adults with acute asthma were treated with standard care within a 60-min screening period. Patients with $FEV_1 \leq 50\%$ predicted were randomly allocated to intravenous montelukast 7 mg ($n=291$) or placebo ($n=292$) in addition to standard care. This double-blind treatment period lasted until a decision for discharge, hospital admission, or discontinuation from the study. The primary efficacy endpoint was the time-weighted average change in FEV_1 during 60 min after drug administration. Secondary endpoints included the time-weighted average change in FEV_1 at various intervals (10 to 120 min) and the percentage of patients with treatment failure (defined as hospitalization or lack of decision to discharge by 3 h post-administration) [58].

Montelukast significantly increased FEV_1 at 60 min post-dose. Similar improvements in FEV_1-related variables were seen at all time points (all $p<0.05$). Although treatment failure did not differ between groups (OR 0.92; 95% CI, 0.63, 1.34), a prespecified subgroup analysis suggests a likely benefit for intravenous montelukast. This benefit was observed at 10 min and over 2 h following intravenous therapy. Patients treated with montelukast tended to receive less ß2-agonists and have fewer treatment failures than patients receiving placebo. The tolerability profile for montelukast was similar to that observed for placebo, and no unexpected adverse experiences were observed. Unavailable for use in the USA, intravenous montelukast in addition to standard therapy causes a rapid benefit and is well tolerated in adults with acute asthma [58].

Magnesium is a purported bronchodilator which works by inhibiting calcium channels in bronchial smooth muscle and blocking parasympathetic tone in the tracheobronchial tree. Nebulized inhaled magnesium sulfate (95 mg of magnesium sulfate in 3 ml of saline or a 3.2% solution nebulized every 20 min for a total of four doses) in addition to β_2-agonist in the treatment of an acute asthma exacerbation appears to demonstrate bronchodilator benefits between 10 and 90 min in a meta-analysis of six trials involving 296 patients in the Cochrane Library. A trend towards benefit in fewer hospital admissions was found [59, 60].

IV magnesium sulfate infusion (1 to 2 g over 20 min) appeared to provide little overall clinical benefit in a meta-analysis of seven trials (five adult and two pediatric) involving 665 patients. While the routine use of IV magnesium was not recommended, severe acute asthma patients who received magnesium were able to significantly avoid hospitalization compared to placebo (O.R. 0.10, 95% confidence interval 0.04 to 0.27) and had improved FEV_1 by 9.8% over several hours [61].

Inhaled heparin and inhaled furosemide have been proposed as immune-modulating adjunctive therapies in the treatment of asthma [62]. The few clinical trials using heparin (inhaled or intravenous) show a decrease in hyper-responsiveness when used as a pretreatment. No discernible respiratory benefit has been shown in the acute asthmatic. Inhaled furosemide has shown mixed results. As with heparin, pretreatment decreases hyper-responsiveness and some case series' data show that in refractory cases of acute asthma inhaled furosemide was associated with a clinical improvement [62].

Non-invasive Ventilation

Non-invasive mask ventilation or continuous positive airway pressure ventilation may be attempted in select patients with severe asthma attacks in the ICU. NIV decreases morbidity and mortality in COPD, but data are limited in asthma. NIV has been shown to decrease the need for mechanical ventilation in some asthmatics with acute respiratory acidosis [63]; however, it should not be used in patients in respiratory distress, patients with altered level of consciousness, or patients with hemodynamic instability and impending cardiorespiratory arrest. Patients who deteriorate while on NIV should be promptly intubated and placed on mechanical ventilation.

Intubation

The decision to endotracheally intubate and mechanically ventilate a SA patient may be made urgently but, preferably, is made electively in patients who are failing to respond to treatment and are fatiguing. Intubation and initiation of mechanical ventilation of NFA patients is challenging and must be performed by skilled intensivists or anesthesiologists. Hypotension (20–40% of cases), arrhythmias, barotrauma, laryngospasm, worsening bronchospasm, aspiration, and seizures will be encountered in the peri-intubation period in near-fatal asthma patients [42, 64]. Excessive bag ventilation should be avoided because of the risk of pneumothorax. While awake, nasotracheal intubations may be preferred in these tenuous patients; orotracheal artificial airways are preferred for prolonged management. Orotracheal tubes of at least 8.0 mm in diameter significantly decrease inspiratory airway resistance and allow for suctioning of secretions and bronchoscopy

Rapid-sequence intubation protocols should be used. Ketamine, etomidate, or another sedating agent can be used with a non-depolarizing neuromuscular blocking agent (NMBA) such as rocuronium. There are risks with NMBA during mechanical ventilation and a full understanding of their side effects is required and is discussed later.

Goals of Mechanical Ventilation

The goals of mechanical ventilation are to provide adequate supplemental oxygen to prevent anoxia and organ ischemia, reduce the work of breathing by the critically ill asthmatic, prevent severe acidemia, respiratory, or metabolic, i.e., pH< 7.20, or allow permissive hypercapnia to prevent ventilator-induced lung injury, including barotraumas. Central to preventing barotraumas is to control dynamic hyperinflation and persistent bronchospasm. The determinants of dynamic hyperinflation are minute volume (respiratory rate − tidal volume), expiratory time, inspiratory to expiratory ratio (*I*:*E*), and airway resistance. Understanding that the pathophysiology of SA and NFA changes significantly after intubation and institution of mechanical ventilation is key to survival and recovery from NFA.

Physiology and Mechanical Ventilation

Near-fatal asthmatic patients that require intubation and ventilation have very high airway resistance and significant distal airway mucous plugging that lead to the obstruction of airflow during expiration. Severe airflow obstruction that has developed over days causes significant dynamic hyperinflation and increased intrathoracic pressures at the end of expiration (intrinsic positive-end expiratory pressure, PEEPi). The inspiratory capacity (IC) of the near-fatal asthmatic patient is reduced as the residual volume of the lung steadily increases and the patient breathes near the limits of their total lung capacity (Fig. 3). At these lung volumes, there is a mechanical disadvantage of the respiratory muscles as the diaphragm flattens, the thoracic muscle fibers stretch, and dead space increases. Overall, the severe asthmatic patient has high ventilatory demands and is at a significant mechanical disadvantage to breathe. Fatigue in these patients seems inevitable but, surprisingly, many patients with this physiology improve and do not require intubation.

NFA patients may worsen in the hours immediately after intubation. Hypotension often results from a combination of sedative and neuromuscular blocking agents, in the setting of high intrathoracic pressures. Intravascular volume supplementation prior to and immediately after intubation can prevent this expected complication. Furthermore, ventilation may be compromised further if sedation is inadequate in the patient awakening from anesthesia or if the initial ventilator settings provide excessive minute ventilation (Table 3). In either situation, dynamic hyperinflation and gas exchange worsen and barotrauma may result.

Pneumothorax, Pneumomediastinum, and Pneumopericardium

The occurrence of life-threatening pneumothorax with asthma is rare. High intrathoracic pressure and hyperinflation are thought to lead to parenchymal or distal airway injury. In the case of pneumomediastinum, “trapped” air tracks along the bronchial tree to the confluence of the pulmonary and mediastinal reflections where small rents or tears allow communication to the mediastinum. Pneumothoraces may arise through rents in the parenchyma caused by subsegmental over-distension distal to mucus plugs or severe airway inflammation. Massive auto-PEEP while on mechanical ventilation can go unrecognized immediately after intubation during the early minutes of mechanical ventilation when the patient is either still paralyzed or heavily sedated. Profound hypotension may be the only clue until auto-PEEP is actually measured on the ventilator. Neuromuscular blockade can aggravate dynamic hyperinflation and auto-PEEP after intubation by paralyzing the diaphragm and accessory muscles of respiration.

In the mechanically ventilated patient, pneumothoraces warrant tube thoracostomy for decompression and prevention of tension pneumothorax. When mediastinal air is present, cardiac tamponade, albeit rare, should be considered and would warrant intervention.

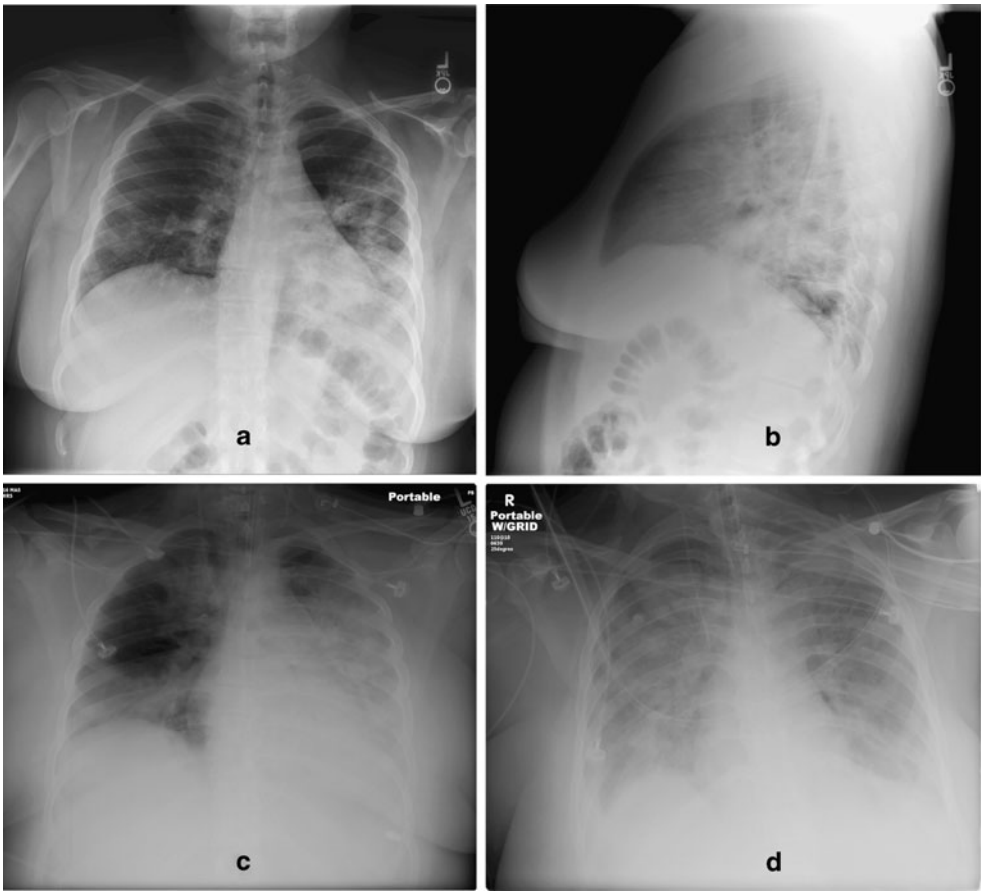

Fig. 3 Progression of near-fatal asthma with H1N1 confirmed pneumonia to frank adult respiratory distress syndrome in a 25-year-old woman with asthma and obesity. **a**, **b** Chest X-ray upon arrival to the ICU from the Emergency Department. **c** Progression of left lower alveolar densities to involve the left upper lobe and the right lower lobe. Endotracheal tube inserted for mechanical ventilation. **d** Bilateral diffuse air space densities. The patient expired despite critical care support and ECMO

Setting the Ventilator

The intensivist must pay close attention to the ventilator parameters in newly intubated SA patients. Junior or in-training physicians err frequently in setting the initial ventilator variables in severe asthma patients. Errors occur because physicians attempt to correct the hypercarbia and acidemia too quickly and fail to recognize the extent of the dynamic hyperinflation. The key goal at this time is to maximize the time for expiration and target a low-minute ventilation strategy.

Table 3 Suggested initial ventilator settings

Modes	Synchronized, intermittent mandatory ventilation
	Volume control with decelerated waveform
	Pressure control ventilation
Rate	8–12 breaths/min
Tidal volume	6–8 cc/kg ideal body weight
Minute ventilation	8–10 l/min
I:*E*	1:3–1:4
Plateau pressure	<30 cmH_2O
PEEP	<5 cmH_2O
FiO_2	100%

A low-minute ventilation strategy (8–10 l/min) aims to permit time for expiration, decrease air trapping, and reduce $PEEP_i$. The ICU physician should accept a moderate degree of hypercapnia with this strategy and $PaCO_2$ levels <100 mmHg are usually well tolerated in the first day [43, 65]. One exception to this is in patients who have suffered a cardiorespiratory arrest at the time of presentation. In these patients, $PaCO_2$ levels should be normalized, if possible, to prevent cerebral vasodilatation and cerebral edema.

Controlled modes of ventilation are favored over support modes when initiating mechanical ventilation. Patients have an impressive drive to breathe because of the elevated $PaCO_2$ levels and acidemia and may require deep sedation initially in order to breathe synchronously with the controlled modes. Two common modes of ventilation used in this setting are synchronized intermittent mandatory ventilation (SIMV) and assist-controlled ventilation. In both modes of ventilation, the respiratory cycle may be limited by pressure (pressure control) or flow (volume control). Pressure-limited forms of mechanical ventilation are favored by some intensivists in this setting because peak airway pressures do not vary as they do in volume control modes but minute ventilation is less tightly controlled. One way to decrease the variability of peak pressures is to set the flow in a decelerated waveform. This

can be set on certain ventilators even if the set mode is flow-limited or volume-controlled. In a recent study that described the 10-year experience of a tertiary referral hospital, the vast majority of patients that required mechanical ventilation had flow-limited modes of ventilation where the flow was delivered with a decelerated waveform [66]. It is imperative to identify and prevent progressive dynamic hyperinflation during mechanical ventilation in a SA or NFA patient who already may have significant dynamic hyperinflation in addition to baseline static hyperinflation. Failure of the flow (L/min) ventilator graphic to return to baseline should prompt lengthening of the expiratory time or a decrease the I:E ratio and/or add extrinsic PEEP to reduce the patient's work of breathing to exhale trapped air ("acute air constipation") in the lungs (Fig. 4).

A relatively low-minute ventilation of 8 to 10 l/min can be achieved by targeting tidal volumes of 7–10 cc/kg of body weight and a respiratory rate of 10–14 breaths/min. The inspiratory to expiratory ratio (*I*:*E*) in the respiratory cycle should be between 1:2 and 1:4. In SIMV, inspiratory flow rates of 100 l/min allow for a prolonged expiratory phase. Plateau pressures should remain <35 cmH_2O to prevent barotrauma and the set PEEP should be 0 to 5 cmH_2O initially. FiO_2 should be decreased from a level of 1.0 over the first several hours. If near-fatal asthmatics continue to require FiO_2 > 0.55, the intensivist should search for a concomitant process, such as pneumonia or pulmonary embolism.

Auto-PEEP or intrinsic PEEP should be measured every 6- to 8-h shift in the ICU, if not more frequently initially, and the extrinsic PEEP (PEEPe) should be increased to match PEEPi to allow exhalation of trapped air in the lungs and to reduce patient–ventilator dissynchrony. In our experience, the PEEPe applied is typically between 5 and 10 cmH_2O. The transitory use of high PEEPe (> 10 cmH_2O) to reduce baseline hyperinflation at the beginning of mechanical ventilation or

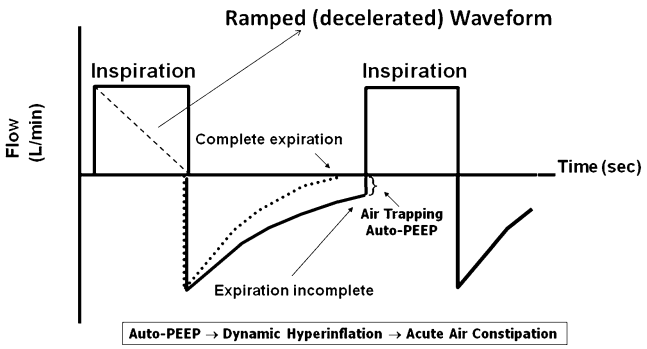

Fig. 4 Ventilator graphic illustrating air trapping and auto-PEEP during volume control mechanical ventilation. It is important to increase the expiratory time, reduce the *I*:*E* ratio to 1:3 or 1:4 and/or add external PEEP to permit the patient to completely exhale before the next breath. A ramped waveform is also diagramed and may be used with certain volume control modes to minimize high peak pressures

ventilation with very low respiratory rates, e.g., two to three breaths for several minutes, can allow auto-PEEP to dissipate.

FiO_2 should be decreased from a level of 1.0 to 0.50 over the first 2 h. If a FiO_2>0.55 is required, the intensivist should immediately determine for a concomitant disorder worsening V/Q mismatching or an intrapulmonary shunt from atelectasis, such as pneumonia, pulmonary embolism, or pulmonary edema.

On these initial ventilator settings—with aggressive bronchodilator and steroid therapy—airway resistance and lung compliance will improve during the first 24 h and hypercapnia will correct easily. The average duration of intubation in most studies of NFA is 3 days; some patients, however, prove refractory to standard medical therapy and ventilator support [63, 67]. Three adjuncts to standard mechanical ventilation that have been explored in severe asthma include general anesthesia, inhaled helium–oxygen mixtures, and extracorporeal CO_2 removal.

Adjuncts to Standard Mechanical Ventilation

General Anesthesia

The inhaled general anesthetics (halothane, sevoflurane, and isoflurane), and intravenous anesthetics (ketamine and propofol) have been used in SA cases with continued clinical decline despite mechanical ventilation and aggressive bronchodilator therapy. The rationale for general anesthesia is to further promote bronchodilation, decrease metabolic demand, and eliminate ventilator–patient dissynchrony.

Anesthetic gases are modestly potent, rapidly acting bronchodilators and pulmonary vasodilators [68]. A beneficial effect with decreased airway pressures and improved gas exchange should be evident within several hours. If no effect is seen in this time period, it is unlikely to work. Finding a ventilator that can handle anesthetic gases (such as the Siemens Servo 900) is problematic and, overall, this rescue modality has become less popular with the use of other bronchodilating intravenous sedatives, like propofol and ketamine.

Propofol is a unique anesthetic agent with an effectively short biological half-life. As with gas anesthesia, propofol affords bronchodilation in addition to the beneficial anesthetic properties. Potential adverse effects include hypotension on initial administration and metabolic acidosis (propofol infusion syndrome) with prolonged use [69].

Ketamine, a dissociative anesthetic, has been successfully used for severe asthma in both children and adults. Ketamine can cause bronchorrhea and bronchodilation—both of which may be beneficial in NFA. The potential serious adverse effects of hypertension and tachycardia must be considered

prior to dosing and during use. Ketamine's notorious dysphoria and hallucinations are usually managed with coincident benzodiazepine administration.

NMBAs are often used during tracheal intubation and allow for complete control during mechanical ventilation. However, NMBAs do not promote bronchodilation nor do they treat the airway inflammation associated with asthma. The use of NMBAs in patients with asthma should be minimized or avoided altogether when possible. Other more efficacious modes of therapy often obviate the need for NMBAs. When used in combination with corticosteroids, NMBAs are associated with a relatively high risk of drug-induced prolonged weakness [70, 71]. The risk of prolonged weakness is correlated with the dose and duration of NMBA and corticosteroids [72]. All NMBAs seem to be implicated [73]. Patients with NMBA myopathies may take months to recover normal muscle function [74].

Helium–Oxygen

A helium:oxygen gas (Heliox) mixture of 70:30 or 80:20 decreases resistance to airflow in obstructed large airways because helium is not as dense as nitrogen and may provide better drug delivery. It is an excellent option in upper airway obstruction and can be useful in SA. When used in the emergency department in SA, heliox may improve PEFR faster than standard therapy, decrease the pulsus paradoxus, and help prevent the need for intubation in some patients [75]. Heliox can improve ventilation in intubated NFA patients, in some instances [76]. Oxygen requirements need to be less than 30% FiO_2 for this modality to be tried. Unfortunately, most ventilators are not calibrated for heliox gas. Still it remains an option for near-fatal asthmatics who continue to worsen on the ventilator.

Extra-corporeal Techniques

Perhaps, the last intervention that can prove life-saving in near-fatal asthmatics with worsening gas exchange and acidemia is extra-corporeal CO_2 removal. This technique mirrors that of the more common extra-corporeal membrane oxygenation (ECMO) in that patients are placed on bypass to provide gas exchange [77]. Numerous reports document the success of this life-saving technique in severe asthmatics on mechanical ventilation and should be considered, if available and appropriate [78].

Sedation

The use of sedatives in asthma patients has a long history. William Osler describes his use in 1892 in *The Principles and Practice of Medicine*: "In a child with very severe attacks, resisting all the usual remedies, the treatment by chloroform gave immediate and permanent relief.… The sedatives antispasmodics… belladonna, henbane, strabonium and lobelia, may be given in solution or used in the form of cigarettes".

Most patients with acute asthma will benefit from anxiolysis and those with NFA require sedation (Table 4). Reducing the anxiety of air hunger and illness may allow for a better delivery of medical care, decrease ventilation requirements, and even obviate the need of mechanical ventilation. Short-acting benzodiazepines (e.g., midazolam or lorazepam) allow for careful titration to effect with subsequent continuous or scheduled bolus delivery. While standardized administrations are not established, it is reasonable to adopt a daily interruption strategy as tested by Kress [79]. Dosing is initiated incrementally and interrupted on a daily basis. The length of stay and length of time on ventilator are decreased using this method.

Dexmedetomidine was introduced in the USA in 1999 and is as effective as propofol and midazolam for sedation of the critically ill. It is a rapid and short-acting α_2-agonist with anxiolytic, anesthetic, and analgesic properties approved by the FDA for use in the ICU for no more than 24 h. A loading dose is not recommended as patients commonly experience hypotension. An infusion of dexmedetomidine 0.2 mcg/kg/h can be titrated to 0.8 mg/kg/h to achieve a sedation score 3 to 5 on the RSS. The distribution half-life is 6 min and elimination half-life is 2 h, metabolized by the liver and metabolites excreted in the kidneys. This drug causes conscious sedation by stimulating the locus caeruleus in the brain stem which controls the sleep–wake cycle. Sedation results from inhibition of the sympathetic vasomotor center of the brain. Unlike propofol and midazolam, which act on γ-aminobutyric acid system and sedates by clouding conscious-

Table 4 Ramsay Sedation Scale

1	Anxious and agitated or restless or both
2	Cooperative, oriented, and calm
3	Responsive to commands only
4	Exhibiting brisk response to light glabellar tap or loud auditory stimulus
5	Exhibiting a sluggish response to a light glabeller rap or loud auditory stimulus
6	Unresponsive

ness, dexmedetomidine produced cooperative conscious sedation by reducing sympathetic activity and arousal. ICU patients given dexmedetomidine remain awake but calm. There is no respiratory depression and it does not interfere with liberating patients from mechanical ventilation in the manner propofol and midazolam do. Hypotension (30%), hypertension (16%), bradycardia (8%), and hypoxemia from hypoventilation (6%) can develop from its use [80].

Dexmedetomidine has not been studied extensively in SA or NFA. Intravenous dexmedetomidine completely blocked histamine-induced bronchoconstriction in dogs. Therefore, dexmedetomidine might be beneficial to decrease airway reactivity in critically ill asthmatics [81]. Two cases of NFA were treated with dexmedetomidine to facilitate NIV. One hour after the institution of NPPV, patients tolerated NIV, with the mask ventilation and respiratory symptoms markedly improved. RSS score was maintained at 2 or 3 during the continuous dexmedetomidine infusion. Patients were successfully weaned from NIV by reducing the inspiratory PAP. Dexmedetomidine helped the agitated patients cooperate with mask ventilation without inducing respiratory depression [82].

Liberation from the Ventilator, Tracheotomy

The majority of intubated near-fatal asthmatics will be liberated from mechanical ventilation with a mean time to extubation of 3.5 days. Once the patient's airway resistance decreases, airway obstruction improves, and hypercarbia resolves, the patient can be switched to a spontaneous support mode of ventilation. Patients unlikely to tolerate extubation can be identified by performing a spontaneous breathing trial of 30 to 60 min on a CPAP of 5 cmH_2O or a T-piece with supplemental oxygen [83]. Patients require close observation immediately post-extubation for worsening bronchospasm and can usually be transferred out of the ICU after 24 h.

Tracheotomy will be required in few NFA patients. NFA patients that have concomitant conditions such as brain injury from an out-of-hospital arrest or lung injury from ventilator-associated pneumonia may require prolonged ventilator support and are more apt to have a tracheotomy performed. The optimal time to perform tracheotomy in NFA patients is not well defined, but the timing should not differ significantly from that of other patients with acute chronic lung injury. The mortality rates for NFA patients requiring mechanical ventilation longer than 3 weeks appear worse than those of COPD and adult respiratory distress syndrome.

Transition out of the ICU and Discharge

Within 12–24 h of reversal of respiratory failure or liberation from mechanical ventilation, most NFA of SA cases may be cared for outside of an intensive care unit setting. Medications previously administered parenterally may be changed to oral dosing. Acute corticosteroid therapy is typically administered for 5–7 days. Further dosing is adjusted based on the prior-to-admission asthma status and level of therapy. Oral prednisone is typically administered for an additional 10 to 12 days, e.g., prednisone 40 mg for 3 days, 30 mg for 3 days, 20 mg for 3 days, and 10 mg for 3 days. Educating the patient about and implementing a "stepped up" asthma management plan similar to those recommended by the oral prednisone is typically administered for an additional 10 to 12 days, e.g., prednisone 40 mg for 3 days, 30 mg for 3 days, 20 mg for 3 days, and 10 mg for 3 days.

Hospital discharge requires stabilization of asthma symptoms, demonstrated tolerance and understanding of the written asthma action plan, and confirmation of outpatient post-discharge plan, preferably to a chronic disease management program with an asthmatologist and certified asthma educator to reinforce lessons learned in the hospital [84]. With these elements assured, full resolution of asthma symptoms prior to discharge is not necessary [85]. With asthma education and reliable discharge plans and follow-up, asthmatics may have a shorter length of hospital stay without an increased readmission rate [86].

Summary

Once recognized, severe asthma and near-fatal asthma are clearly life-endangering diagnoses. The early diagnosis of high-risk individuals, through recognition of the physical signs of progressive respiratory decline and institution of aggressive therapy, may forestall respiratory failure and the need for mechanical support. Once respiratory failure occurs, successful patient management includes the careful use of mechanical ventilation—which may require long expiratory times and permissive hypercapnia. Pharmacotherapy, in addition to beta-agonists and corticosteroids, with sedatives or even general anesthetics offers further techniques to improve impaired respiratory physiology. After clinical improvement is established, patients will need to maintain a higher level of asthma care to help decrease recurrences of SA or NFA.

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