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Near-fatal asthma: recognition and management

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Purpose of review

Near-fatal asthma continues to be a significant problem despite the decline in overall asthma mortality. The purpose of this review is to discuss recent advances in our understanding of the pathophysiology, diagnosis and treatment of near-fatal asthma.

Recent findings

Two distinctive phenotypes of near-fatal asthma have been identified: one with eosinophilic inflammation associated with a gradual onset and a slow response to therapy and a second phenotype with neutrophilic inflammation that has a rapid onset and rapid response to therapy. Patients who develop sudden-onset near-fatal asthma seem to have massive allergen exposure and emotional distress. In stable condition, near-fatal asthma frequently cannot be distinguished from mild asthma. Diminished perception of dyspnea plays a relevant role in treatment delay, near-fatal events, and death in patients with severe asthma. Reduced compliance with anti-inflammatory therapy and ingestion of medications or drugs (heroin, cocaine) have been associated with fatal or near-fatal asthma.

Summary

Near-fatal asthma is a subtype of asthma with unique risk factors and variable presentation that requires early recognition and aggressive intervention.

Keywords

asthma, fatal asthma, near-fatal asthma, resistant asthma

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Introduction

Near-fatal asthma (NFA) and fatal asthma represent the most severe clinical presentations of asthma [1–3]. Although there are no universally agreed diagnostic criteria for NFA, it is typically associated with the presence of hypercapnia, acidemia, altered state of consciousness and the development of cardiorespiratory arrest requiring endotracheal intubation and mechanical ventilation [4,5]. NFA subjects typically have at least one asthma exacerbation in the year prior to admission, despite treatment for at least a year with ≥ 1200 $\mu\text{g}/\text{day}$ beclomethasone or equivalent, long-acting β -agonists or theophylline, and with or without oral corticosteroids (≥ 5 mg/day prednisone or equivalent) [6]. Patients with NFA may have one of two distinct patterns of progression (Table 1).

The most common NFA phenotype is characterized by gradual deterioration over days or weeks and often occurs in patients with severe and poorly controlled asthma. It could also occur as a sub-acute exacerbation of asthma symptoms over hours to days [7–10]. Although this type of NFA is responsible for 80–85% of all fatal events associated with asthma, this pattern is generally considered preventable. Postmortem examination reveals extensive airway plugging with gelatinous, dense and tenacious

mucus mixed with inflammatory and epithelial cells, epithelial denudation, mucosal edema, and an intense eosinophilic infiltration of the submucosa [11–20]. A second pattern of NFA is characterized by a history of unstable disease that is partially responsive to treatment. In this type of NFA, patients have hyper-acute or acute asphyxic asthma, in which respiratory failure develops within 2 h of the onset of symptoms. Patients in this group typically have massive allergen exposure as well as emotional distress [21]. Death can be sudden and unexpected [18,22–24]. Patients in this group have been also called brittle asthmatics. They have a faster rate of improvement to therapy and have shorter hospitalizations when compared with the slow-onset NFA [23,24].

Monitoring of peak expiratory flow rates (PEFRs) has led to the recognition of two distinct groups of patients at risk for NFA. The first group comprises patients presenting with hyperacute or asphyxic asthma who have abnormal physiological responses to their airway constriction [23,24]. Within this group, some patients may have blunted hypoxic ventilatory drive and not respond to bronchoconstriction and hypoxemia with hyperventilation, and some fail to perceive worsening bronchoconstriction of the airway (known as underperceivers). This group of patients present with hypercapnia, even during

Table 1 Clinical features of the two known near-fatal asthma phenotypes

	Near-fatal asthma phenotype	
	Gradual onset	Sudden onset
Course	Days	Hours, asphyxic asthma
Incidence	80–85%	15–20%
Airway pathology	Gelatinous mucus plugging	No mucus plugging
Predominant inflammatory cell	Eosinophil	Neutrophil
Response to treatment	Slow	Faster
Hospitalization course	Long	Short
Prevention	Possible	Undetermined*

* Avoidance of acetylsalicylic acid/nonsteroidal anti-inflammatory drugs and daily measurements of peak expiratory flow rates likely reduce incidence.

moderate exacerbations [23]. Although episodes of hypercapnia occur more frequently than the need for orotracheal intubation and mechanical ventilation in all NFA episodes, they do not necessarily imply a poor prognosis [3]. The sudden change in airflow in these patients probably results from acute bronchoconstriction rather than airway inflammation and edema [3].

Pathologic examination in such cases shows absence of mucus plugs in the large majority of patients, and in almost all patients a greater proportion of neutrophils than eosinophils infiltrating the submucosa is observed [3,18,19,21,22].

The second group of patients identified by routine PEFr monitoring consists of patients with marked diurnal variations in PEFr. These patients may have normal PEFrs on intermittent testing but have large fluctuations in flow and may develop sudden NFA attacks. These patients may have severe drops in their PEFr early in the morning (morning dippers) even during hospitalization and require continual monitoring of their PEFr [24].

A recent report by Romagnoli *et al.* [6] found a low prevalence of atopy in NFA, suggesting that mechanisms different from atopy might be more relevant to the pathogenesis of severe asthma. Due to the many differences between NFA and severe asthma in terms of lung function and airway inflammation, NFA may represent a different disease that frequently cannot be distinguished from mild asthma when in stable conditions.

Since virtually all patients requiring hospitalization for asthma can be considered at risk for respiratory failure or death, and the long-term prognosis is poor [3], recognition of risk factors and the understanding of the pathophysiology of NFA are of paramount importance to optimize the evaluation and therapy during their exacerbations and to decrease the rate of fatal events. In both phenotypes, the most important pathophysiological events that lead to death are cardiac arrhythmias and asphyxia followed by

complications of invasive mechanical ventilation such as barotrauma and ventilator-associated pneumonia [25*].

Pathophysiology

Hypoxemia, hypercapnia, lactic acidosis, and dynamic hyperinflation are considered some of the most relevant pathophysiological events in NFA.

Hypoxemia, hypercapnia and lactic acidosis

Airway occlusion due to smooth muscle bronchoconstriction, airway edema, inflammation, and formation of mucus plugs form the pathologic basis of the gas-exchange abnormalities observed in acute, severe asthma and leads to the development of extensive intrapulmonary shunting [26]. Shunt could be absent in patients with effective hypoxic pulmonary vasoconstriction and good collateral ventilation [26]. Mild hypoxia is easily corrected with the administration of relatively low concentrations of supplemental oxygen [27]. Severe hypoxemia correlates well with the degree of intrapulmonary shunt (often caused by atelectasis and mucus plugging) and requires higher concentrations of supplemental oxygen. As the severity of airflow obstruction increases, the initial hypocapnia changes to normocapnia and eventually into hypercapnia due to alveolar hypoventilation or patient exhaustion.

In patients with severe respiratory acidosis due to hypercapnia, a metabolic (lactic) acidosis may coexist. The pathogenesis of lactic acidosis in the acutely severe asthmatic patient remains unclear; however, it may be related to diaphragmatic fatigue or the excessive use of β -agonists.

Dynamic hyperinflation and effects on the cardiovascular system

In the presence of gradual worsening, airway narrowing leads to lung hyperinflation, which increases work of breathing and may be followed by exhaustion. The short expiratory time does not permit the respiratory system to reach static equilibrium volume at the end of expiration and intrinsic positive end-expiratory pressure (PEEP_I) or auto-PEEP ensues. This phenomenon is called dynamic hyperinflation and is directly proportional to minute ventilation and to the degree of airflow obstruction [28].

Dynamic hyperinflation is largely responsible for the significant decrease in systemic venous return. Shifting of the interventricular septum toward the left ventricle during inspiration may lead to left-ventricular dysfunction, incomplete filling and decreased cardiac output. Right-ventricular afterload may increase as a result of the pulmonary hypertension caused by lung hyperinflation. In advanced stages, the absence of pulsus paradoxus indicates ventilatory muscle fatigue and impending respiratory failure.

Risk factors

A history of prior hospital admissions, especially if mechanical ventilation is required, is considered the greatest predictor of NFA [25^{*}]. The results of a systematic review of risk factors associated with NFA conducted by Alvarez *et al.* [29] showed that a history of mechanical ventilation due to asthma and increased use of nebulizers significantly increased the odds of a near-fatal event. All results are summarized in Table 2.

Risk factors may differ between patients with slow-onset or sudden-onset NFA. Patients with asphyxic asthma are more likely to be male, are less likely to report a history of respiratory infection, but may have a massive allergen exposure or major emotional stress precipitating their worsening [30]. Overall, the strongest predictors of NFA are a prior history of a life-threatening episode of asthma or hospitalization for asthma within the past year. Increased use of oral corticosteroids or nebulized β -agonists and underlying psychosocial problems should also be considered significant risk factors. Risk factors for NFA are listed on Table 3 [31,32].

A severity assessment in asthma for The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study group found that the mean age of 1447 patients with severe asthma was 32 years. Sixty two per cent were females, 34% were nonwhite, 69% had education past high school, and 21% smoked [33].

Adherence and compliance to therapy

Lack of utilization of inhaled corticosteroids 2 weeks prior to the onset of symptoms is associated with the development of severe life-threatening asthma. Lack of objective measurements of obstruction which delays seeking medical care and institution of corticosteroid therapy typically results in higher risk for fatal asthma [34,35]. As compared with both severe and mild-to-moderate asthmatics, NFA patients had lower adherence to antiasthma treatment [6].

Table 3 Risk factors for death in patients with near-fatal asthma

Past history of sudden severe exacerbations
Prior intubation and mechanical ventilation for asthma
Prior admission for asthma to an intensive care unit
Two or more hospitalizations for asthma in the past year
Three or more emergency care visits for asthma in the past year
Hospitalization or emergency care visit for asthma within the past month
Use of more than two canisters per month of inhaled short-acting β_2 -agonists
Current use or recent withdrawal from systemic corticosteroids
Poor perception of dyspnea
Presence of other comorbidities such as cardiovascular diseases or chronic obstructive pulmonary disease
Serious psychological problems or psychiatric disease
Low socioeconomic status
Urban/inner-city residence
Illicit drug use
Sensitivity to alternaria

Data from [31,32].

Socioeconomic status

Although socioeconomic status can delay seeking care, whether it truly impacts the natural history of asthma remains unclear. There are articles in the literature both supporting and refuting socioeconomic factors as a major risk for NFA.

Psychological factors and poor perception of dyspnea

Following a systematic assessment of all published studies between 1960 and 2006 on the psychological risk factors associated with NFA or fatal asthma, Alvarez and Fitzgerald [36] could not conclude that psychological factors increase the risk of NFA and fatal asthma due to the significant heterogeneity in the measurement of the psychological factors. Case-control studies by Kolbe *et al.* [37] and by Romero-Frais *et al.* [38] demonstrated that socioeconomic status was inversely associated with the risk of life-threatening exacerbations.

Poor perception of dyspnea is strongly associated with treatment delay, near-fatal events, and death during acute severe asthma [39]. Magadle and colleagues [40] found in 2 years of follow-up that 29 asthmatic patients with poor perception of dyspnea suffered 13 near-fatal

Table 2 Risk factors associated with near-fatal asthma

Risk factor	Statistical measure	
	Odds ratio (\pm 95% confidence interval)	P value
History of mechanical ventilation due to asthma	6.69 (2.80–15.97)	0.0001*
Increased use of nebulizers	2.45 (1.52–3.93)	0.0002*
History of intensive care unit admission	5.14 (1.91–13.86)	0.001*
Increased use of oral steroids	2.71 (1.34–5.51)	0.006*
Increased used of oral theophylline	2.02 (1.03–3.98)	0.04*
History of hospital admission	2.62 (1.04–6.58)	0.04*
Increased use of medications such as β -agonists via metered-dose inhalers	1.67 (0.99–2.84)	0.057
Use of inhaled corticosteroids	1.31 (0.83–2.05)	0.25
Prior emergency department assessment	1.13 (0.43–2.92)	0.810

* Statistically significant.

attacks and six deaths. It is recommended that physicians measure poor perception of dyspnea at least once in all asthmatic subjects.

Alexithymia is a psychological condition characterized by difficulty in perceiving and expressing emotions and body sensations. In a study by the Spanish High Risk Asthma Research Group, the authors found a higher proportion of alexithymia in the NFA group than in the non-NFA group (36 vs. 13%, respectively). Alexithymia, severe persistent asthma and a low level of education were identified as independent variables related to repeated very severe asthma exacerbations [41].

Drugs

Drugs such as aspirin, β -blockers, and nonsteroidal anti-inflammatory agents may predispose to asthma exacerbations. Picado and co-workers [42] and Yoshimine *et al.* [43] have found that in almost 10% of asthma patients who required mechanical ventilation aspirin was the precipitating factor. A strong association between substance abuse and asthma death has been documented previously [44]. The illicit drugs cocaine and heroin, as well as alcohol, are frequently reported.

Smoking/environmental factors

Thirty-five per cent of adult patients presenting to the emergency room with asthma exacerbation are current smokers. Cigarette smoking can decrease responsiveness to steroids and worsen asthma control [45]. Smoking in asthmatics is correlated with increased severity of asthma, and a greater risk for hospitalization for asthma. It is one of the few modifiable risk factors for adverse asthma health outcomes [46]. The fact that asthma admissions peak in late fall but mortality peaks in mid-winter strongly suggests that environmental factors play a significant role in fatal and NFA. Allergens (especially alternaria), food reactions (peanuts, eggs, and milk), thermal inversions (increasing pollutants), and occupational exposures have been shown to trigger NFA [3].

Genetic factors

Genetic polymorphisms are associated with severity of asthma [47,48]. Five potential asthma-susceptibility genes or complexes have been identified using a positional approach [49]. The interleukin-4 gene is linked to IgE level. The interleukin-4 589T allele has been associated with life-threatening asthma and the interleukin-4 receptor α (IL4RA) 576R allele is a risk factor for decreased lung function in asthmatics [50].

Genetics can also determine response to β -agonists as well as corticosteroids. A retrospective genotype-stratified study found that the B16-Arg/Arg allele at the sixteenth amino acid residue of the β_2 -adrenergic receptor is associated with deterioration in pulmonary function with routine

use of β -agonist medication [51]. The ADAM33 gene on chromosome 20p13 was identified as a susceptibility gene for asthma. ADAM33 protein levels correlate inversely with the predicted forced expiratory volume in 1 s (FEV₁) [52]. Tumor necrosis factor- α expression in the airway is related to severity of asthma. The levels of expression of the tumor necrosis factor- α gene and protein are higher in patients with refractory asthma than in the airways of control subjects or patients with mild asthma [53,54–56]. NFA of gradual onset is associated with a greater degree of steroid insensitivity. Their asthmatic inflammatory response is relatively resistant to genetically modulated suppression [57**].

Physical exam

Patients with NFA appear dyspneic at rest, may be unable to lie supine, are unable to talk with sentences or phrases, are agitated and sit upright. They may be diaphoretic. Drowsiness or confusion are always ominous signs and denote imminent respiratory arrest. They are tachypneic (respiratory rate usually >30 breaths/min); tachycardic (heart rate >120 beats/min); there is wheezing throughout both the inspiration and the expiration; accessory respiratory muscles are used; there is evidence of retractions; and pulsus paradoxus is seen at greater than 12–15 mmHg. Although a valuable clinical sign, the absence of pulsus paradoxus should not delay prompt treatment since it may suggest ventilatory muscle fatigue. Along with the disappearance of wheeze and the presence of bradycardia, the paradoxical breathing represents a sign of imminent respiratory arrest [58].

The physical examination of the patient with NFA should be directed to detecting complications as listed in Table 4.

Patient monitoring

Close monitoring of patients with NFA including serial measurements of lung function (peak expiratory flow or FEV₁ at bedside) to quantify the severity of airflow obstruction and its response to treatment is of paramount importance. It should also include blood gas analysis, chest radiography, blood counts, drug monitoring, electrolytes, and electrocardiography.

Lung function

Although lung-function assessment of patients with acute asthma may be challenging, evaluation of PEF or FEV₁ should be done on all patients capable of performing this maneuver. A peak expiratory flow greater than 50 l/min above baseline and a PEF greater than 50% of the predicted rate measured 30 min after initiation of treatment are correlated with excellent prognosis in patients with NFA [25*]. A FEV₁ of less than 25% the predicted value suggests a high risk for the development

Table 4 Complications of asthma

Pneumothorax
Pneumomediastinum
Pneumopericardium
Subcutaneous emphysema
Pulmonary interstitial emphysema
Pneumoretroperitoneum
Tracheoesophageal fistula (in the mechanically ventilated patient)
Cardiac arrhythmias
Myocardial ischemia or infarction
Mucous plugging
Atelectasis
Pneumonia
Theophylline toxicity
Electrolyte disturbances (hypokalemia, hypophosphatemia, hypomagnesemia)
Lactic acidosis
Hyperglycemia

of hypercapnia and hypoxemia, and warrants further assessment with an arterial blood gas.

During NFA events, all airway flow indices are reduced significantly. Patients with normal peak flows, but with intermittent large fluctuations, may develop sudden-onset NFA. Hetzel *et al.* [59] showed that in nine out of 10 cases of respiratory failure occurring after hospitalization of asthmatics, peak flow measurements showed greater than 50% variability.

Attention should be paid to measuring lung function in the severely ill patient since the deep inspiration maneuver involved in PEF_R or FEV₁ measurement may precipitate respiratory arrest by worsening bronchospasm [60]. Patients with an initial FEV₁ of less than 30% the predicted value and less than 10% of the response value in objective measures after 1 h should be considered for admission [61]. In a study by Romagnoli *et al.* [6] no difference was found between patients with NFA, severe persistent asthma, or mild-to-moderate asthma. FEV₁, FEV₁/forced vital capacity ratio and the carbon monoxide diffusion constant (K_{CO}) were lower and residual volume higher in patients with severe asthma as compared with those with mild-to-moderate asthma and NFA. Forced vital capacity was significantly decreased in severe asthma compared with mild-to-moderate asthmatics. Patients with NFA often showed values for partial pressure of arterial oxygen similar to mild-to-moderate asthmatics and higher compared with patients with chronic severe asthma [6].

Measurement of total exhaled nitric oxide (F_eNO) may be an indirect measure of airway eosinophilia [62] and may help in stratifying risk for asthma exacerbation. In a study by Arthur *et al.* [63] of 44 nonsmoking clinically stable asthmatics, they found that a F_eNO of > 28 ppb and FEV₁ < 76% of the predicted value identified 13 stable asthmatics with 85% probability for future exacerbation, whereas nine asthmatics with F_eNO < 28 ppb and FEV₁

> 76% of predicted had a 0% probability of exacerbation [63]. The role of exhaled NO in identifying patients with NFA is unknown.

Blood gas analysis

Although arterial blood gas analysis is useful in the management of patients with NFA, it is not predictive of outcome. Arterial blood gas analysis is indicated whenever oxygen saturation is lower than 90% and if there is no response to therapy, or deterioration [25*].

Respiratory alkalosis with mild hypoxemia is the most common abnormality seen in the early stages of acute, severe asthma. Some compensatory renal bicarbonate secretion is common in slow-onset NFA, which manifests as a non-anion-gap metabolic acidosis. The transition from hypocapnia to normocapnia is an important sign of severe clinical deterioration. Although hypercapnia itself is not an indication for intubation, aggressive therapy may be warranted [56]. After β -adrenergic agonist administration, the presence of transient paradoxical deterioration of gas exchange while flow rates are improving is not uncommon. The presence of metabolic acidosis denotes impending respiratory arrest.

Chest imaging studies

Whereas the chest radiographs in the majority of patients with acute asthma will be normal [64] it is a valuable tool to exclude complications. However, obtaining and interpreting a chest radiograph should never delay initiation of treatment. A comparison of patients with NFA and mild-to-severe asthma with high-resolution computed tomography showed prominence of centrilobular structures in 36% of mild asthma cases, in 70% of moderate-to-severe asthma cases, and in 100% of NFA cases [65]. Neither bronchial wall thickness nor the area of air trapping seemed significantly increased in NFA, as compared with mild or moderate-to-severe asthma. These small airway abnormalities were partially reversible in both groups. Residual prominence of centrilobular structures after long-term inhaled corticosteroid treatment was significantly higher in NFA than non-NFA patients. The results of this study by Lee *et al.* [65] indicate that extensive small-airway abnormalities may be associated with NFA, and that these abnormalities are partially reversible after the successful therapy.

Blood counts, drug-monitoring and electrolytes

Blood counts are indicated in patients with fever and/or the presence of purulent sputum to support the diagnosis of infection as a trigger of NFA. Total and differential cell counts in peripheral blood typically show increased total white blood cells and percentage neutrophils in severe asthma as compared with NFA and mild-to-moderate asthma [6]. Determination of serum theophylline levels is mandatory in every patient under treatment with

theophylline. If the patient is under diuretic therapy or frequently uses β_2 -agonists, electrolyte measurement of potassium, magnesium, and phosphate are indicated.

Electrocardiography

Electrocardiographic changes observed in acute NFA include right-axis deviation, and evidence of right-ventricular hypertrophy that usually resolves within hours of effective treatment [66].

Sputum and blood inflammatory markers

Patients with severe asthma have higher total sputum cell counts when compared with NFA and mild-to-moderate asthmatics [6]. Sputum neutrophil percentage is significantly elevated in severe asthma as compared with mild-to-moderate asthma. Airway neutrophilia has been noted in autopsies of patients with acute asphyxic asthma but the prevalence of sputum eosinophils and neutrophils at baseline in patients with NFA is unclear.

Management

The management of NFA events should be driven by early recognition of deterioration in order to determine the best clinical area to treat the patient.

Hospitalization

The most important prognostic factor in NFA is the acute response to therapy rather than the intensity of the presenting symptoms or the spirometry values [63,67]. Although 4–6 h of treatment in the emergency department is the average time taken to evaluate the disposition of patients [60,68], three out of four patients resolve their bronchospasm within the first 2 h [69]. The remaining patients who fail to respond to aggressive therapy usually require either 24 h of observation or admission to the hospital. Table 5 summarizes some of the factors that may influence the decision to hospitalize or admit an asthmatic patient to the intensive care unit (ICU) [31,58].

Patients with a partial response (peak expiratory flow or $FEV_1 < 60\%$ predicted) after 2 h of continuous nebulization with β_2 -agonists in the emergency department should be considered for admission to the general

medical ward. Patients who fail to respond to therapy (PEFR improved by less than 10–20%) or with persistent hypercapnia, tachypnea (respiratory rate ≥ 30), or altered mental status should be referred to an ICU.

Pharmacologic therapy

The primary therapies for acute severe asthma include oxygen administration, inhaled β_2 -agonists, and systemic corticosteroids. Magnesium, heliox, and subcutaneous β -agonists and theophylline may be useful in refractory cases. Other therapies, including inhaled corticosteroids, leukotriene antagonists, long-acting β -agonists, and anti-IgE therapy, warrant further investigation.

Oxygen

Oxygen via nasal cannula or mask is recommended to maintain oxygen saturation above 90%. Oxygen saturations should be maintained at $>92\%$ in pregnant females and in patients with angina or acute ischemic heart disease.

Inhaled β_2 -agonists

Continuous or intermittent administration of nebulized short-acting β_2 -agonists remains the first line and most effective therapy for reversing airflow obstruction in NFA. These medications induce acute bronchodilatory responses, with rapid onset of action. Continuous nebulization of β_2 -agonists may be more effective in the most severe cases of asthma exacerbations [69–74]. Nebulized β_2 -agonists should continue on a frequent basis until a significant clinical response is achieved. Numerous studies have indicated that administration via pressurized metered-dose inhaler (pMDI) with spacer provides equivalent efficacy to nebulized treatments [74,75]. Seventy per cent of patients respond to between four and eight puffs every 10 min or between 5.0 and 7.5 mg of nebulized albuterol [25*]. Inhaled therapy with β_2 -agonists appears to be equal to or better than intravenous infusion in treating airway obstruction in patients with severe asthma [60,76,77]. Although albuterol is the most frequently administered β_2 -agonist, levalbuterol, an isomer of racemic albuterol, may play a role in refractory asthma [78], particularly in patients with ischemic heart disease or severe tachycardia.

Table 5 Important considerations for hospitalization and intensive care unit admission

Hospitalization [31]	Intensive care unit admission [58]
Duration and severity of symptoms	Respiratory arrest
Severity of airflow obstruction	Altered mental status
Course and severity of prior exacerbations	Serious concomitant cardiac complications
Medication use at the time of exacerbation	
Access to medical care and medications	
Adequacy of support and home conditions	
Presence of psychiatric illness	

Systemic epinephrine and terbutaline

Although the results of a study by Appel *et al.* [79] do not clearly define the role of systemic β -agonists in the treatment of life-threatening asthma, it suggests that subcutaneous administration of epinephrine or terbutaline should be considered in patients unresponsive to continuous nebulized β_2 -agonists, and in those patients unable to cooperate due to alteration of mental status or an inability to tolerate inhaled therapy. Epinephrine may also be delivered in intubated patients not responding to

inhaled therapy during mechanical ventilation. Subcutaneously, 0.3–0.5 ml (1:1000) of epinephrine can be administered every 20 min to a maximum of three doses. Terbutaline can be administered subcutaneously (0.25–0.5 mg) and is the preferred treatment in pregnant females. Subcutaneous administration of epinephrine or terbutaline should not be delayed since it is well tolerated even in older patients with no history of myocardial infarction [80].

Intravenous infusion of terbutaline starting at 0.05–0.10 $\mu\text{g}/\text{kg}$ per min has been utilized predominantly in pediatric patients. It may be considered in the treatment of patients with no response to inhaled or subcutaneous treatment, and in whom respiratory arrest is imminent, or in patients not adequately ventilated despite optimal setting of the ventilator. A recent double blind, randomized controlled trial by Bogie *et al.* [81] evaluated the benefit of intravenous terbutaline in 49 nonventilated children with acute severe asthma who were already on continuous high-dose nebulized albuterol. Although the use of intravenous terbutaline was associated with improvement in the clinical asthma severity score over the first 24 h, shorter use of continuous nebulized albuterol, and shorter ICU stay, the differences were not statistically significant [81].

Anticholinergic drugs

Anticholinergics may be considered in the emergency treatment of asthma, although there is controversy on their ability to offer significant additional bronchodilation [1,82]. Ipratropium bromide has shown improvement of acute bronchospasm induced by β -blockers and monoamine oxidase inhibitors [83]. In patients with an FEV_1 of less than 50% of the predicted level, the combined use of anticholinergics and β -agonists produces an improvement in PEFr and FEV_1 above that produced by β -agonists alone, and decreases the risk of hospital admission [84]. The onset of action typically occurs within 1 min, with peak effects within 20 min. Benefit may persist for up to 48 h. Anticholinergic therapy, if used, should be continued until the patient stabilizes, but should not be added to the patient's chronic-asthma management regimen.

Corticosteroids

Systemic corticosteroids decrease inflammation, increase the number and sensitivity of β -receptors, and inhibit the migration and function of eosinophils [85,86]. Systemic corticosteroids should be administered to all asthmatics presenting to the hospital unless peak flow or FEV_1 is greater than or equal to 80% predicted after 1 h of treatment. Corticosteroids are recommended for most patients in the emergency department, especially those who do not respond completely to initial β_2 -agonist therapy. Corticosteroid administration reduces admission rates,

decreases relapse rates, and may also reduce the number of cases of fatal asthma [60,87,88]. Since benefits from corticosteroid treatment are not usually seen for 6–24 h after administration, therapy should be instituted early. A study by Rodrigo and Rodrigo [89] reported that large doses of inhaled corticosteroids (18 mg flunisolide in 3 h) administered in the emergency department, in addition to β_2 -agonists, did speed the resolution of acute bronchoconstriction. Although the dosing schedule in severe hospitalized asthmatics remains controversial, guidelines recommend 120–180 mg/day of oral prednisone in three or four divided doses. Our approach in the ICU setting is the intravenous administration of 80–125 mg methylprednisolone every 6 h during the initial 24 h of treatment, followed by 60–80 mg every 12 h in improving patients. Once the patient leaves the ICU, they are maintained on 1 mg/kg of oral prednisone for 7–10 days or until the PEFr reaches 70% of their baseline value [33,90]. Since the risk of myopathy is significant, especially in the mechanically ventilated patient, the concomitant use of systemic corticosteroids and paralytic agents should be avoided. Tapering of oral corticosteroids is not necessary in patients who are receiving inhaled corticosteroids and the combined use of the inhaled and oral corticosteroids is recommended during hospitalizations for asthma exacerbation.

Methylxanthines

Methylxanthines are not generally recommended and have not been shown to be beneficial in the emergency department setting [91]. Theophylline has a very narrow therapeutic to toxic index and significant side effects, such as vomiting and tachycardia, can be seen with its use. Several authors, however, consider that theophylline may have a role in asthmatic patients with impending respiratory failure who have failed aggressive therapy with inhaled bronchodilators [92] due to theophylline's properties, including its action on the diaphragm and its anti-inflammatory effects [83,93]. In combination with β -agonists, systemic corticosteroids, and anticholinergics, patients receiving theophylline may show a more rapid improvement in their clinical asthma scores than those receiving placebo [94]. The data on theophylline, however, are mixed and we tend to utilize it only in patients who present on chronic theophylline therapy.

Magnesium sulfate

Magnesium sulfate inhibits calcium channels in smooth muscle and reduces acetylcholine release. A meta-analysis showed no improvement in PEFr or FEV_1 after magnesium administration [95]. A subgroup analysis suggested that patients with an FEV_1 of less than 30% at admission or less than 60% after 1 h of treatment might benefit from 1–2 g of magnesium administered over 30 min intravenously. Current evidence does not support the routine use of magnesium in severe asthma attacks.

Heliox

Heliox is a combination of helium and oxygen at typical ratios of 60:40 or 70:30. Helium is a gas of very low density, which decreases turbulent flow generated by the passage of air through constricted airways. Although randomized control trials have failed to demonstrate sustained improvement in pulmonary function testing or hospital admissions [96,97], some case reports have shown that heliox administration improves ventilation and aerosol-particle deposition to distal airways [98], and decreases pulsus paradoxus, work of breathing, peak airway pressures and PCO_2 in intubated patients [60]. A study by Kress *et al.* [99] showed that administration of an 80:20 mixture delivered via nonrebreather mask was associated with significant improvements in pulmonary functions over the first 3 h of treatment. Future studies may elucidate the role of heliox in severe, life-threatening asthma.

Leukotriene antagonists, leukotriene synthesis inhibitors and anti-IgE therapy

Leukotriene antagonists and leukotriene synthesis inhibitors may have a theoretic role in the therapy of life-threatening asthma since they complement the anti-inflammatory effects of systemic corticosteroids. Camargo *et al.* [100] compared the clinical efficacy of intravenous montelukast plus standard therapy with standard therapy alone in 201 patients with acute asthma exacerbations. Patients receiving intravenous montelukast therapy had improved FEV_1 over the first hour and tended to require fewer β -agonists and to have fewer treatment failures. Since oral montelukast is rapidly absorbed and has few side effects, we have tended to add this agent in patients presenting with severe asthma refractory to standard therapy. The addition of zafirlukast has been shown to reduce the need for hospitalization among patients with acute exacerbation [98,101]. Although reports from the use of omalizumab (anti-IgE therapy) in severe allergic asthma have shown a reduction in corticosteroid use and reduction of symptom scores [102,103], its role in patients with NFA remains unclear.

Anesthetic management

Inhalational anesthetics have only been used sporadically for the treatment of patients with NFA to avoid bronchoconstriction and to induce bronchodilation. Since a relatively small number of asthmatic patients require mechanical ventilation, publications on the use of these inhalational anesthetics and their effects on ventilated asthmatic patients has been limited to case reports [104]. Inhalational anesthetics may cause a decrease in airway pressures and improvement in blood gases [105,106]. A recent update on the anesthetic approach for the asthmatic patient recommends regional over general anesthesia, if feasible, to reduce airway irritation and postoperative complications [107]. If general anesthesia

is chosen, a laryngeal airway mask may be safer than endotracheal intubation. Lidocaine inhalation, alone or combined with albuterol, minimizes histamine-induced bronchoconstriction. Propofol and ketamine may decrease the risk of bronchospasm during anaesthesia induction and nondepolarizing agents such as vecuronium, rocuronium, cisatracurium, and pancuronium do not induce bronchospasm, whereas atracurium and mivacurium result in histamine release in a dose-dependent fashion.

Noninvasive mechanical ventilation

Although the application of noninvasive positive-pressure ventilation (NPPV) has proved to be safe and effective in patients with chronic obstructive pulmonary disease with acute respiratory failure, its use in severe asthma is not clearly defined. NPPV improves alveolar ventilation, relieves dyspnea associated with ventilatory muscle fatigue, and improves gas exchange. Application of NPPV by qualified personnel, in addition to standard therapy, appears to reduce the intubation rate in some patients with NFA [107,108]. A recent retrospective study by Beers *et al.* [109] evaluated the safety, patient tolerance, and possible benefit of bilevel positive airway pressure (BiPAP) in conjunction with β_2 -agonist therapy in the treatment of 83 pediatric patients with status asthmaticus who were refractory to conventional medical therapy. The use of bilevel positive airway pressure resulted in 88% patient tolerance, a 22% reduction of admissions to the pediatric ICU, and a reduction of respiratory rate and improvement in oxygen saturations in 77 and 88% of the subjects, respectively. No adverse events were reported. Although these results are encouraging, in our experience many patients with acute, severe asthma fail to tolerate NPPV.

Mechanical ventilation

Intubation and mechanical ventilation should be considered for patients with progressive deterioration despite aggressive treatment. Mechanical ventilation of patients with NFA is challenging and not without complications. Intubation should be performed by an experienced clinician as soon as signs of deterioration are present. Table 6 lists some of the indications for intubation and mechanical ventilation in patients with NFA.

Table 6 Indications for intubation and mechanical ventilation in near-fatal asthma

Refractory hypoxemia ($P_aO_2 < 60$ mmHg)
Persistent hypercapnia ($P_aCO_2 > 55-77$ mmHg)
Increasing hypercapnia ($P_aCO_2 > 5$ mmHg/h)
Signs of exhaustion despite bronchodilator therapy
Worsening of mental status
Hemodynamic instability
Coma or apnea

P_aCO_2 , partial pressure of arterial carbon dioxide; P_aO_2 , partial pressure of arterial oxygen.

The oral route for intubation is preferred since it allows placement of a larger endotracheal tube size that minimizes airway resistance and maximizes airway clearance. A large part of the morbidity and mortality of patients with NFA may be related to the mechanical ventilation itself rather to the disease process [110]. Regardless of the mode of ventilation selected, mechanical ventilation in NFA should aim to avoid barotrauma, minimize dynamic hyperinflation, maintain adequate oxygenation, and allow some degree of permissive hypercapnia until bronchodilators and steroids improve airflow [111,112]. Pressure control may not be an ideal mode of ventilation for patients with NFA since frequent fluctuations in airway resistance lead to variable tidal volumes and a risk for hypoventilation [113]. The use of extrinsic PEEP to improve patient ventilator synchrony and trigger sensitivity remains controversial [114]. Table 7 lists some ventilator parameters and the recommended settings [115].

A recent study by Mutch *et al.* [116] compared biologically variable ventilation (mechanical ventilation that emulates healthy variation) and conventional control-mode ventilation in an animal model of bronchospasm to determine which approach resulted in better gas exchange and respiratory mechanics. Measurements of physiologic variables and inflammatory cytokines showed that biologically variable ventilation significantly improved gas exchange, was associated with a lower peak inspiratory pressures and greater static and dynamic compliance, and lower total respiratory system resistance compared with conventional ventilation.

Prognosis of patients with near-fatal asthma

Although the mortality rate of patients with NFA has decreased significantly in recent years, it could be as high as 22% [115,117]. Since nearly 10–30% of patients with NFA require mechanical ventilation, early detection of high-risk patients, adequate outpatient therapy, and extremely close observation of these patients in the emergency department may decrease the incidence of

fatal asthmatic attack. Molfino *et al.* [3] showed that patients with NFA are at risk for future fatal or near-fatal exacerbations, but that the survival was significantly improved in patients who complied with inhaled anti-inflammatory therapy, regular peak-flow monitoring, and close medical follow-up.

Conclusion

Recognition of the different subtypes of NFA remains a significant problem in patients with asthma. These subtypes are frequently underdiagnosed and undertreated. Understanding of the risk factors and pathophysiology of NFA allows physicians to identify patients who require aggressive management and follow-up that can significantly reduce the likelihood of a fatal event.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 82).

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Table 7 Initial ventilator settings in near-fatal asthma

Ventilator parameter	Recommended setting
Mode	Pressure or volume-limited ventilation
Respiratory rate	10–12 breaths/min
Tidal volume	8–10 ml/kg
Minute ventilation	8–10 l/min
Positive end-expiratory pressure	0 cmH ₂ O
Inspiratory/expiratory ratio	≥ 1 : 3
Inspiratory flow	≥ 100 l/min
F _I O ₂	Maintain S _a O ₂ /S _p O ₂ > 90%
Pplat	<35 cm H ₂ O

F_IO₂, fraction of inspired oxygen; Pplat, end-inspiratory plateau pressure; S_aO₂, arterial oxygen saturation; S_pO₂, pulse oxymetry saturation. Data from [115].

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