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Near fatal asthma: treatment and prevention

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Summary
Near-fatal asthma (NFA) is described as acute asthma associated with a respiratory arrest or arterial carbon dioxide tension greater than 50 mmHg, with or without altered consciousness, requiring mechanical ventilation. Risk factors for near fatal asthma have not been fully elucidated. In 80-85% of all fatal events, a phenotype, characterized by eosinophilic inflammation associated with gradual deterioration occurring in patients with severe and poorly controlled asthma, has been identified. Regarding to the management, acute severe asthma remains a significant clinical problem, which needs to be identified to facilitate early and appropriate therapeutic interventions. The assessment relies on clinical signs, but additional information might be obtained from chest radiography or blood gas analysis. No investigation should delay the initiation of appropriate therapy. The goals of therapy are the maintenance of oxygenation, relief of airflow obstruction, reduction of airways edema and mucus plugging (with Increased use of medications such as beta-agonists via metered dose inhalers and nebulizers, oral and/or intravenous (other than by inhalation) corticosteroids and oral or intravenous theophylline) whereas supporting ventilation as clinically indicated. Of course, the emergency physician needs to consider the wide range of potential complications, as attention to these problems when managing severe acute asthma might significantly improve outcome. An understanding of the available agents and potential pitfalls in the management of NFA is mandatory for the emergency physician.

Background

Asthma is a significant public health problem that is increasing in prevalence and is associated with relevant morbidity and financial costs (1,2). There is suggestion that asthma-related deaths are decreasing, but a significant minority of individuals presents with severe asthma and have persisting daily symptoms, and exacerbations despite compliance with high doses of inhaled steroids and additional treatment. For this small part of the asthmatic population, the exacerbation can become fatal or near-fatal (1-10). These observations appear to be paradoxi-

cal with the increasing knowledge of asthma pathogenesis and treatment that is currently available. Near-fatal asthma (NFA) is described as acute asthma associated with a respiratory arrest or arterial carbon dioxide tension greater than 50 mmHg, with or without altered consciousness, requiring mechanical ventilation (8). Two distinctive phenotypes of NFA have been identified. The most common phenotype, responsible for 80-85% of all fatal events, is characterized by eosinophilic inflammation associated with gradual deterioration over days or weeks occurring in patients with severe and poorly controlled asthma, and is slow to respond to therapy. This phenotypic pattern is generally considered preventable. The second phenotype, with neutrophilic inflammation, has both rapid onset and response to therapy (4,7,11).

Risk factors

Remodeling in asthma refers to structural changes in large and small airways, consisting of subepithelial fibrosis, increased vascularity, increased airway smooth muscle mass, and goblet cell hyperplasia of proximal and distal airways. Remodeling was believed originally to be the cause of refractory asthma, that is, asthma that fails to respond to optimal treatment and is characterized by persistent airflow limitation. A history of intensive care admission or mechanical ventilation is a well-documented indicator of subsequent NFA (12). Gelb et al. found that in NFA patients the sensitivity for the presence of moderate and/or severe obstruction was 90%, the specificity was 61%, the positive predictive value was 41%, and the negative predictive value was 95%. The sensitivity for an abnormal loss of lung elastic recoil (i.e., less than the predicted normal mean _1.64 SD) was 100%, the specificity was 79%, the positive predictive value was 59%, and the negative predictive value 100% for NFA patients (13). Using TLC percent predicted as a surrogate for elastic recoil, the sensitivity for TLC of > 115% predicted was 70%, the specificity was 70%, the positive predictive value was 88%, and the negative predictive value was 41% for NFA patients (13). Using the ratio of FEV1 percent predicted to TLC percent predicted of < 0.70, the sensitivity was 90%, the specificity was 78%, the positive predictive value was 56%, and the negative predictive value was 96% for NFA patients (13). The unexpected loss of lung elastic recoil in patients with chronic persistent asthma, and its significant physiologic contribution to adverse clinical complications including NFA, are novel prospective observations. This loss of lung elastic recoil was associated with increasing age, duration of asthma, and severity of expiratory airflow limitation, using postbronchodilator FEV1 percent predicted as the signal. Additionally, normal transdiaphragmatic pressures, despite the presence of hyperinflation in patients with NFA, extend similar observations about asthmatic patients without NFA (6,14). Postmortem series show pathological presence of inflammatory cells, mucus plugging, shedding of airway epithelium, airway oedema and smooth muscle hypertrophy (6,14). Airway obstruction in severe asthma that does not respond to conventional therapy, may be caused by mucus plugging (6,14). Evidence for the management of mucus plugging in adult patients with severe near fatal asthma is sparse. Chia et al. describe a patient with fatal asthma who responded dramatically to DNase following bronchoscopy and lavage after failing other therapies in a case report, and believe that the combined use of rhDNase, bronchial toileting and aggressive physiotherapy, on top of mechanical ventilation strategies and intravenous bronchodilators, helped turn the corner (15).
More recently Serrano-Pariente et al. analysed 179 asthmatics patients admitted to the hospital for an episode of NFA. Three clusters of patients with NFA were identified: cluster 1, the largest, including older patients with clinical and therapeutic criteria of severe asthma; cluster 2, with an high proportion of respiratory arrest, impaired consciousness level and mechanical ventilation; and cluster 3, which included younger patients, characterized by an insufficient anti-inflammatory treatment and frequent sensitization to Alternaria alternata and soybean (7).

Assessment

In a study of asthma patients admitted with a near-fatal episode, two-thirds of subsequent severe attacks or deaths occurred within 1 year of the previous life-threatening admission (16). The immediate assessment of patients with asthma should include the degree of respiratory distress (ability to speak, respiratory rate, use of accessory muscles, air entry), degree of hypoxia (cyanosis, pulse oximetry, level of consciousness) and cardiovascular stability (arrhythmias, blood pressure). Accessory muscle use, wheeze and tachypnoea might diminish as the patient tires (17) **(table 1)**. The clinical examination might be misleading; occasionally asthmatics with poor perception of the severity of their asthma appear deceptively well, despite severe decrements in lung function. Although the assessment relies on clinical signs, additional information might be obtained from chest radiography or blood gas analysis. No investigation should delay the initiation of appropriate therapy. On chest radiography, an episode of acute asthma is characterized by hyperinflation of the lungs. Physiologically abnormal distribution of ventilation, perfusion and altered gas exchange. Expiratory flow limitation with incomplete expiration leads to hyperinflation of the lungs, adding to the elastic burden of the thorax. Passive elastic recoil is no longer sufficient to achieve effective expiration, and expiratory muscles are then actively involved in expiration (4,12). Progression of dynamic hyperinflation is associated with a higher intrathoracic pressure at the end of expiration (intrinsic Positive End Expiratory Pressure - iPEEP or auto-PEEP). Hyperinflation and higher intrathoracic pressures mean the respiratory muscles

Table 1 *- Markers of severe asthma.*

Inability to speak in full sentences
FEV1 < 40%, predicted or PEF < 40% of best or predicted (< 25% in life-threatening asthma)
Oxygen saturations < 90-92%
PaO2 < 60 mmHg - PaCO2 > 45 mmHg
Use of accessory muscles or tracheal tugging
Pulsus paradoxus (> 15 mmHg decrease with inspiration). With severe muscle fatigue might be absent
Quiet chest on auscultation
Patient seated upright and unable to lie supine
Cyanosis and sweating
Confusion or decreased level of consciousness - Hypotension or bradicardia

Table 2 *- Asthma complications.*

Pneumothorax
Pneumomediastinum - Pneumopericardium
Pulmonary interstitial emphysema
Pneumoretroperitoneum
Cardiac arrhythmias
Myocardial ischaemia or infarction
Mucus plugging - Atelectasis - Pneumonia
Electrolyte disturbances (hypokalaemia, hypomagnesaemia, hypophosphataemia)
Lactic acidosis - Hyperglycaemia
Theophylline toxicity

start at greater stretch (hence less efficient, more fatiguable), and greater inspiratory effort is needed to commence flow into the lungs, which also increases work of breathing (4,12). Barotrauma, which refers to the adverse effects of this increased intra-lung pressure on both the lung structure as well as that transmitted to the vascular structures, can result in bullae rupture, pneumothorax and reduced venous return with hypotension. Blood gas analyses might reveal respiratory alkalosis, hypoxaemia and hypocarbia. Generally, asthma attacks are not characterized by marked arterial desaturations until very late in life-threatening episodes. Hypercarbia occurs in 10% of cases presenting to the ED (4,12). These patients have greater airway obstruction and respiratory rate than non-hypercapnic patients. A quiet chest on auscultation, inability to talk and cyanosis suggest the presence of hypercarbia. The finding of normocarbia in acute asthma should also be viewed as a sign of impending respiratory failure that requires aggressive treatment, Patients who fail to respond to therapy (PEFR improved by less than 10-20%) or with persistent hypercapnia, tachypnoea (respiratory rate _30), altered mental status, arrhythmias or significant comorbidities should be referred to the ICU (4). The emergency physician also needs to consider the wide range of potential complications, as attention to these problems when managing severe acute asthma might significantly improve outcome **(table 2).**

Therapy

The goals of therapy are the maintenance of oxygenation, relief of airflow obstruction, reduction of airway o edema and mucus plugging whereas supporting ventilation as clinically indicated. High-flow oxygen has been assumed to be harmless, and is often used in the treatment of patients with acute asthma (18). Hypoxaemia in asthma results from ventilation / perfusion mismatching and is thus usually easily corrected with modest increases in the fraction of inspired oxygen (e.g. 1-3 L/min via a nasal cannula or mask). Uncontrolled oxygen has been postulated to correct the effects of hypoxaemia and to compensate for any trend towards a fall in arterial oxygen tension associated with b2-agonist therapy (19). Short-acting, inhaled b2-agonists are the drugs of choice for treating acute asthma. Their onset of action is rapid and their side-effects are well tolerated. Salbutamol, the most frequently used b2-agonist in ED around the world, has an onset of action of 5 min and a duration of action of 6 h. b2-agonists have been described as rescue therapy for use in patients unresponsive to inhaled bronchodilator and systemic corticosteroid therapy, or when the inhaled route is not practical (20). The safety profile of short-acting-β2-agonists has been questioned due to possible detrimental effects on asthma control. Recent evidence and meta-analysis suggest an increased risk for cardiovascular complications in patients using β2-agonists (21,22). There is evidence suggesting that the frequent use of these drugs might increase the risk of premature death. The hypothesis that β2-agonists can have fatal adverse effects was first demonstrated in the late 1960, when Inman and Adelstein reported a 30-700% increase, depending on age, in asthma death in patients using pressurized aerosol containing, most often, isoprenaline (23). The excess mortality was attributed to overdosing but β-agonists came into focus again in the 1980, when more selective β2-agonists were introduced in metered-dose inhaler. A dose-dependent risk of death from asthma was reported, with increased up to 29-fold with the use of β2 agonists (24). Afterwards, large, randomised, double-blind

trials have been performed to test the hypothesis that the use of LABAs in asthmatic patients is associated with an increased risk of death (25). At present, patients with asthma should be initiated and maintained on sufficiently high doses of inhaled corticosteroids and only patients whose asthma cannot be controlled should receive additional β2-agonists on a regular basis in addition, LABA should be withdrawn from patients who do not profit from their use (1). The need for reliever medication, such as the inhaled short-acting β2-agonists (SABA) albuterol, along with daytime symptoms, nighttime waking and activity limitations, is used to assess symptom control in asthma and to estimate the risk of future exacerbations (1).

The inclusion of reliever inhaler use in assessment of asthma control in adults, used on evidence that overuse of SABA medication is associated with poor symptom control, increased risk of exacerbations and death from asthma (26).

Adrenaline has been used both as a nebulized solution and intravenously. There are theoretical advantages to the preferential use of i.v. adrenaline as opposed to pure b2-agonists in acute severe asthma. Although bronchoconstriction is the major pathology in asthma, airway oedema might also make a significant contribution. Both the a-agonist and β-agonist effects of adrenaline might be beneficial, with the a-effect decreasing oedema and the b-effect responsible for bronchodilation. Anticholinergics agents block muscarinic receptors in airway smooth muscles, inhibit vagal cholinergic tone and result in bronchodilation. Ipratropium bromide has a mild additional bronchodilating effect when added to b-agonists, that might only be significant in severe asthma (20). Because anticholinergic agents and b2-agonists exert effects by different mechanisms, affect different-sized airways and have different pharmacodynamic and pharmacokinetic properties, the combined use of them is rational and is likely to result in improved bronchodilation. Corticosteroids have been shown to improve asthma symptoms by reducing airway inflammation, airway reactivity and decrease airway secretions. In addition to their anti-inflammatory effect, steroids increase the number and sensitivity of b-receptors on the bronchial smooth muscle (28,29). Objective improvements in airflow obstruction have usually not been demonstrated during the first 6-12 h of treatment with corticosteroids in acute asthma (30). Corticosteroids are recommended for most patients in the ED, particularly in those who do not respond completely to initial b2-agonist therapy. Corticosteroid administration reduces admission rates, decreases relapse rates and might also reduce the number of cases of fatal asthma. Because benefits from corticosteroid treatment are not usually seen for 6-24 h after administration, therapy should be instituted early. Low dose corticosteroids (_80 mg/day of methylprednisolone or _400 mg/day of hydrocortisone) appear to be adequate in the initial management of adult patients (31). Higher steroid doses do not appear to offer a therapeutic advantage, and because the risk of myopathy is significant, especially in the mechanically ventilated patients, the concomitant use of systemic corticosteroids and paralytic agents should be avoided if at all possible. Importantly oral and i.v. routes of corticosteroid administration are equally efficacious with respect to rate of resolution of airflow limitation (32). The parenteral route is required in patients unable to take oral medication (intubated) or if absorption might be compromised (e.g. vomiting). There is some suggestion that for patients with severe symptoms, i.v. corticosteroid therapy might have an early effect (within 1-6 h) by reversing b2-receptor downregulation seen in chronic b2-agonist use (33). The use of i.v. aminophylline was associated with a higher incidence of adverse effects compared with standard care alone (34). Whether aminophylline has a place as an additional therapy after treatment with established medications such as inhaled b-agonists, systemic corticosteroids and i.v. magnesium remains uncertain. At the current time routine use of aminophylline in severe asthma cannot be recommended. Magnesium might be effective in acute asthma through a variety of mechanisms. This cation is an important cofactor in many intracellular enzymatic reactions. Magnesium has been shown to relax smooth muscle and might be involved with inhibition of smooth-muscle contraction. As an explanation for the effects of magnesium in acute asthma this is perhaps overly simplistic. Magnesium is involved in acetylcholine and histamine release from cholinergic nerve terminals and mast cells, respectively. Furthermore, the ability of magnesium to block the calcium-ion influx into the bronchial smooth muscle might have therapeutic benefit in severe acute asthma (35). A single dose of i.v. MgSO4 administered to patients with severe acute asthma has been shown to be effective. A multicentre trial demonstrated that 2 g of i.v. magnesium sulphate administered as an adjunct to standard therapy, improved pulmonary function in patients presenting to the ED with severe asthma. i.v. (36). Montelukast in addition to standard therapy produces rapid benefit and is well tolerated in adults who have acute asthma. Patients with severe bronchospasm requiring mechanical ventilation and not responding to conventional bronchodilator therapy might benefit from an inhaled volatile anaesthetic agent with bronchodilating properties such as halothane, enflurane or isoflurane (37-41). Use of these agents might result in hypotension and cardiac dysrhythmias, especially in hypoxic patients. Administration is complex and requires either an anaesthetic machine or alternative heat moisture connector device. For practical reasons this therapy is better reserved for use in the ICU. Despite appropriate therapy, there continues to be a small group of patients who deteriorate or those who present in extremis and require mechanical ventilation. The rate of intubation in patients with acute severe asthma is low at 3-8% (42). Surprisingly, only a few reports have described the use of

non-invasive ventilation (NIV) in patients with acute severe asthma (43,44). The positive pressures employed in the studies to date are generally less than 15 cm H_2O, and whether CPAP or BiPAP is the optimal approach remains unknown. Although there are some similarities between asthma and chronic obstructive pulmonary disease, in asthma CO_2 retention occurs late in the exacerbation and by that time the patient is often exhausted and has difficulty tolerating the NIV mask. Furthermore, patients with severe acute asthma are usually tachypnoeic and might struggle to coordinate their breathing with that of the machine and therefore find BiPAP uncomfortable. Mucous production is a feature of severe acute asthma and NIV can exacerbate sputum retention, and it is important that this is borne in mind when implementing NIV. A Cochrane review performed in 2005 concluded there are promising results in favour of the use of NPPV in severe acute asthma; however, the regular use of NPPV in status asthmaticus still remains controversial. Until large randomized controlled trials are completed, this therapy should be restricted, and routine clinical use cannot be recommended (45).

Invasive ventilation

Deteriorating consciousness, severe exhaustion and cardiopulmonary arrest are absolute indications for intubation and mechanical ventilation. Severe hypercapnia, acidosis and fatigue might not warrant immediate intubation, but rather aggressive and continuous bronchodilator therapy. Intubation and mechanical ventilation in the asthmatic should not be embarked upon lightly. Once it is apparent that invasive ventilation is required, experienced help should be sought. The optimal means of intubation is usually direct laryngoscopy, following rapid sequence induction. The best agents to use are those most familiar to the operator. Induction might effectively be achieved with propofol or thiopentone; however careful dosage adjustment is required for potential haemodynamic compromise. The asthmatic patient is often volume-depleted, with induction resulting in both loss of sympathomimetic tone and drug-induced vasodilation. Additional to this, the development of intrinsic PEEP with an inappropriate ventilation strategy might rapidly result in catastrophic circulatory collapse. In this regard ketamine with its sympathomimetic and bronchodilating properties has been advocated by many as the induction agent of choice (46). Inhalational volatile induction is attractive given the bronchodilating properties of these agents, and it might obviate the need for paralysis. It however requires specialized anaesthetic skills and equipment to be available in the emergency room, as transfer of such critically ill patients would be ill advised. Following induction, maintenance with fentanyl and midazolam is appropriate. Fentanyl is the opiate of choice because it inhibits airway reflexes, causes less histamine release than morphine, but on rare occasions can induce chest wall rigidity with rapid bolus dosing (47). Ongoing paralysis might initially be required to facilitate ventilation; however, because of the significant risk of critical illness polyneuromyopathy (especially given the combination with steroids), neuromuscular blockade should be withdrawn as soon as possible. The incidence of myopathy in asthmatics on long-term nondepolarizing neuromuscular blocking agents has been reported as high as 30% (48). The mode of ventilation might be a crucial factor for a successful outcome of NFA. Mechanical ventilation is often difficult because the obstructive defect might result in dynamic hyperinflation. This might then lead to barotrauma, volutrauma or catastrophic haemodynamic compromise secondary to impairment of venous return. Regardless of the mode of ventilation selected, the goals of mechanical ventilation are to maintain adequate oxygenation, minimize dynamic hyperinflation, avoid barotrauma and accept some degree of hypercapnia until bronchodilators and steroids improve airflow. Outcome is improved in mechanically ventilated asthmatics by limiting airway pressure using a low respiratory rate and tidal volume, whereas permitting a moderate degree of hypercarbia and respiratory acidosis (49). Hypercarbia has not been found to be detrimental, except in patients with severe myocardial depression. Moderate degrees of hypercarbia with an associated acidosis (pH 7.15-7.2) are generally well tolerated. To prolong the expiratory time and allow adequate time for expiration, the breath rate can be reduced, or inspiratory time decreased thereby extending the inspiratory to expiratory (I:E) ratio to much greater than 1:2. Expiration should ideally be observed both clinically and on the ventilator graphics to be complete before the next breath is delivered. Pressure control ventilation might not be an ideal mode of ventilation for patients with NFA, as frequent fluctuations in airway resistance lead to variable tidal volumes and a risk of significant hypoventilation. The use of extrinsic PEEP remains controversial, in mechanically ventilated paralysed patients, and Tuxen found it to be of no benefit at low levels and detrimental at high levels, because the decrease in gas trapping was replaced by a rise in functional residual capacity (50). It should be noted that very large tidal volumes were used in the present study. Extrinsic PEEP might prevent airway collapse by splinting the airways open (51); however, as a general rule, extrinsic PEEP should not exceed intrinsic PEEP, and ongoing clinical assessment for the presence of gas trapping and magnitude of FRC are mandatory. Ensuring adequate humidification of inspired gas is particularly important in the ventilated asthmatic, to prevent further thickening of secretions and drying of airway mucosa that might stimulate further bronchospasm. Finally, it should be noted that mechanical ventilation might compromise delivery of aerosolized bronchodilators. Drug delivery might vary from 0% to 42% in ventilated patients, and it is therefore important

to ensure compatibility between the delivery system and ventilator circuit used (52).

Table 3 *- Initial ventilator settings in paralysed asthmatic patients.*

FiO2 1.0, then titrate to keep SpO2 > 94%
Tidal volume 5-6 mL/kg
Ventilator rate 6-8 breaths/min
Long expiratory time (I:E ratio > 1:2)
Minimal PEEP _5 cmH2O
Limit peak inspiratory pressure to < 40 cmH2O
Target plateau pressure < 20 cmH2O
Ensure effective humidification

Conclusion

Acute severe asthma remains a significant clinical problem, which needs to be identified to facilitate early and appropriate therapeutic interventions. In this regard the identification of patients with a specific NFA phenotype could be helpful to prevent future severe asthma exacerbations. An understanding of the available agents and potential pitfalls in the management of NFA is mandatory for the emergency physician.

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