



CME Review

Beyond the guidelines: Fatal and near-fatal asthma

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SUMMARY

While asthma is extremely common, fatal and near fatal asthma is rare and often preventable if there is early recognition of symptom progression and appropriate intervention. In the past decade, asthma mortality has progressively declined in association with the widespread use of inhaled corticosteroids and asthma care plans. Management of life threatening asthma requires patient education to ensure the proper use of medications and to enable the patient to recognize when additional therapy for poorly controlled asthma is required. There is some evidence that suggests that the overly aggressive use of asthma medications when treating a severe exacerbation may contribute to morbidity. Because of the risks of air trapping and barotrauma associated with partial airway obstruction, it is best to avoid mechanical ventilation if possible but when this is used, low tidal volumes, longer exhalation times, and permissive hypercarbia can minimize these risks. There is the promise that a better understanding of asthma immunology and severe asthma “phenotypes” will lead to better prevention and therapy.

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INTRODUCTION

According to the National Health Interview survey of 2006, approximately 13.5% of American children have been diagnosed with asthma at sometime in their life¹. In the United States, during the 3-year period 2001 to 2003, there was average annual asthma mortality of 4,210 although only 200 of these deaths from asthma occurred in infants and children under 18 years of age².

In children, asthma is often an allergic disease with exacerbations triggered by exposure to allergens, irritants such as tobacco smoke, and virus infections. The result of these exposures can be cumulative as well as synergistic. The severity of an exacerbation depends on the duration and quantity of the exposure, the immune response to the trigger, and the availability and appropriate use of asthma medications. Reducing exposure to allergens and irritants, monitoring of disease severity, early intervention when needed, and the appropriate use of medications such as inhaled corticosteroids (ICS) can dramatically decrease the risk of death from asthma³.

RISK FACTORS FOR NEAR FATAL ASTHMA

Risk factors for severe asthma include a previous severe asthma exacerbation such as an intensive care unit (ICU) admission, two or

more hospitalizations over a year, three or more emergency department visits in the past year, hospitalization for asthma in the past month, difficulty perceiving the severity of asthma symptoms, and the use of two or more pressurized metered dose inhaler (pMDI) canisters of short acting beta agonists in the past month^{4–6}. In children, recurrent life-threatening asthma has been associated with obesity, low income, and non-Caucasian race⁷ [Table 1].

Severe and near fatal asthma has been reported to be more common in those diagnosed as having asthma before the age of five years⁸. Teenagers appear to be at greater risk according to some studies⁹. This may be because of greater risk taking behavior which can include nonadherence to therapy.

The need for ICS is associated with an increased risk for near-fatal asthma¹⁰. It has also been shown that the risk of a severe asthma exacerbation requiring intervention with oral corticosteroids is inversely proportionate to the degree of adherence with ICS therapy^{8,11}. Using the Saskatchewan Health database, Suissa and colleagues documented that in patients with asthma who were prescribed ICS, the risk of dying from asthma was inversely related to how consistently the patient filled their prescribed ICS³. Severe asthma exacerbations are associated with a more rapid decline in lung function but this can be attenuated by the inhalation of low doses of ICS¹².

Poor access to medications and medical care also contributes to asthma severity. Household chaos probably increases the likelihood of exposure to aero-irritants and allergens while decreasing medication adherence¹³. Severe and fatal asthma has also been associated with psychiatric disease in patients or in their caregivers^{14–16}. Presumably this decreases adherence and the likelihood of seeking help.

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Table 1
Risk factors for death from asthma

Asthma history
Previous severe exacerbation (e.g., intubation or ICU admission for asthma)
Two or more hospitalizations for asthma in the past year
Three or more ED visits for asthma in the past year
Hospitalization or ED visit for asthma in the past month
Using > 2 canisters of SABA per month
Difficulty perceiving asthma symptoms or severity of exacerbations
Other risk factors: lack of a written asthma action plan, sensitivity to <i>Alternaria</i>
Social history
Low socioeconomic status or inner-city residence
Illicit drug use
Major psychosocial problems
Comorbidities
Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease
Obesity

Key: ED, emergency department; ICU, intensive care unit; SABA, short-acting beta2-agonist

Delay in seeking medical attention contributes to asthma mortality. This may be due, in part, to persons with chronic asthma having blunted recognition of an exacerbation. Children who have had life threatening asthma have impaired perception of inspiratory and expiratory loads and poor perception of dyspnoea which can lead to delay in diagnosis and treatment^{17,18}. Hypoxemia can also blunt the sensation of dyspnoea¹⁹.

There are several genetic risk factors associated with severe asthma including polymorphisms of ADAM33 encoding the disintegrin and metalloproteinase domain-containing protein 33²⁰. ADAM33 has been identified as an “asthma susceptibility gene” suggesting that ADAM33 antagonists may be of benefit to those carrying specific gene polymorphisms. Another example is the observation that patients who carry the Arg/Arg polymorphism of the beta agonist receptor may be at increased risk from adverse effects of beta agonists²¹. However these findings are controversial^{22,23}.

PHYSIOLOGY AND PHENOTYPES

Near fatal asthma is associated with dyspnoea and progressive hypoventilation resulting from hyperinflation and mismatch of ventilation and perfusion. Persons with severe asthma breathe at higher lung volumes while at the same time ineffectively ventilating portions of their lung. Airway inflammation and vascular leak can also contribute to respiratory failure during a severe asthma attack. This can be worsened by fluid overload especially as patients with severe acute asthma are at risk for the syndrome of inappropriate antidiuretic hormone secretion²⁴.

Persons who die of asthma usually have severe airway mucus obstruction^{25,26}. There is evidence that this is associated with abnormal mucin structure²⁷ and surfactant breakdown due to secretory phospholipases A2^{28,29}. There is no proven benefit to using mucolytics in the treatment of patients with acute life threatening asthma although the use of mucoactive medications has not been studied in acute life threatening asthma.

There has been a great deal of interest in phenotypic classification of severe or difficult to treat asthma. Although childhood asthma is generally an allergic, eosinophilic inflammatory disease, many patients with severe and “brittle” asthma or steroid-resistant asthma have significant neutrophilic inflammation^{30–33}. Corticosteroids induce apoptosis of eosinophils but they prolong neutrophil survival and this may contribute to neutrophilic inflammation³⁴. It has also been thought that neutrophilic

inflammation may be due to chronic airway infection with organisms such as *Mycoplasma* or *Chlamydia*³⁵. Macrolide antibiotics used as immunomodulatory drugs can reduce neutrophilic inflammation and decrease asthma severity and the need for corticosteroids. Macrolides may also drive T helper lymphocyte type 2 (TH2) or allergic inflammation toward a TH1 phenotype³⁶. Macrolide antibiotics have not been prospectively studied in treating life-threatening asthma.

Persons with asthma often have airway remodeling with collagen and fibrin deposition in the basement membrane putting them at risk for low lung function even when “well”. Airway “remodeling” can also be seen in early and mild asthma and none of the asthma medications currently used have been proven to attenuate the remodeling or repair response³⁷.

In a large study sponsored by the National Heart Lung and Blood Institute (NHLBI) Severe Asthma Research Program, persons with severe asthma were found to be older with longer duration of disease although most commonly with onset after age 12, more frequent symptoms, sinusitis, and pneumonia, lower lung function, and they had greater bronchodilator reversibility. They also had less atopy by skin tests, but exhaled NO, IgE and blood eosinophils did not differentiate severity³⁸. In a similar but smaller study, 80 subjects with severe asthma were studied by cross sectional analysis. Subjects with early-onset severe asthma had more allergy sensitivity ($p < 0.007$) and more allergic symptoms than those with onset after 12 years of age. Late onset severe asthma had lower PFT and more lung eosinophils on lung biopsy ($p < 0.007$)³⁹.

PHARMACOTHERAPY

Oxygen therapy

Hypoxaemia is always present in life threatening asthma and is a major contributing factor to asthma death. Therefore, supplemental oxygen is always given to patients admitted to hospital for life threatening asthma. While oxygen therapy is essential, unregulated oxygen therapy, that is the provision of high amounts of oxygen beyond what is necessary to obtain physiologic oxygen saturation levels, has been shown to be unnecessary and potentially harmful. Giving 100% FiO₂ supplemental oxygen can further depress compromised ventilation and significantly increase the partial pressure of carbon dioxide (pCO₂)^{40,41}. Therefore, it is recommended that only sufficient oxygen be administered to maintain peripheral oxygen saturation (SpO₂) between 0.89 and 0.94. It should also be recognized that increasing pCO₂ can depress oxygenation. Increasing pCO₂ is a sign of hypoventilation and requires support of ventilation (rate and volume) as discussed in the mechanical ventilation section below.

Bronchodilator medications

Smooth muscle contraction (“bronchospasm”) is a defining characteristic of asthma, and short acting bronchodilators are a mainstay of therapy. These are often given in large doses by aerosol, systemically, or occasionally by both routes simultaneously. Clinical trials have shown that there is no advantage to the systemic administration (oral, intravenous, or intramuscular) administration of beta agonist bronchodilators as compared to aerosol administration⁴² nor is there any advantage to combining systemic with aerosol administration⁴³. Although intravenous or intramuscular beta agonists are included in asthma care guidelines as add on therapy for severe asthma that is “unresponsive” to aerosol beta agonist, randomized controlled trials show a modest clinical benefit at best, with the possibility of side effects^{43,44}.

Aerosolized beta agonists can be given by pressurized metered dose inhaler (pMDI), by intermittent jet nebulization, or by continuous jet nebulization. When the patient is capable of using a pMDI and valved holding chamber, this has been shown to be effective as a much larger nominal dose of medication given by jet nebulization and there are fewer systemic side effects, mostly likely due to decreased swallowing of drug and systemic absorption⁴⁵.

It is common practice to give large doses of inhaled bronchodilators by continuous nebulization to treat acute severe asthma but controlled clinical trials show that this is no more effective than intermittent lower doses of a beta agonist⁴⁶. Beta receptors are down regulated and rapidly saturated with the use of inhaled beta agonists. High dose beta agonists carry greater risk of side effects than a lower dose; these side effects include hypokalemia, cardiac tachydysrhythmia, hypoglycemia, tremor, discomfort, ventilation-perfusion mismatch, and possibly increased mucus secretion^{44,47,48}. It is possible that the overly aggressive use of beta agonists in acute asthma may increase the risk of morbidity.

There are several different short acting bronchodilators available although albuterol/salbutamol is the most commonly used. There is no significant clinical difference in clinical effectiveness, duration of action, or systemic side effects comparing the single isomer levalbuterol (Xopenex) to racemic albuterol⁴⁹.

Anticholinergic bronchodilator medications can also be administered as aerosols. A Cochrane review strongly suggests significant clinical benefit to the concomitant use of a beta agonist and inhaled anticholinergic for treating acute severe asthma⁵⁰ and some studies have indicated an added benefit with minimal risk in the most severely ill patients with asthma⁵¹.

Data do not support the use of methylxanthine therapy (i.e. theophylline, aminophylline) in life threatening asthma⁵². Although these medications are effective bronchodilators, they do not have additive effects if a short acting beta agonist is being used but their use does entail a significant risk of serious side effects.

Anti-inflammatory therapy

Anti-inflammatory therapy is extremely important for the treatment of severe asthma. Typically oral or intravenous corticosteroids (e.g. Methylprednisolone) have been given at a dose of 2 mg/kg as frequently every 6 hours during an acute asthma attack. Although corticosteroids are often administered intravenously, there are no data showing that this is more effective than oral steroids and there are no data which show that giving prednisone 2 mg/kg/day (80 mg maximum for older children and adults) is less effective than higher doses. Furthermore there are no data that show that giving steroids more frequently than every 12 hours confers additional benefit. Conversely, a significant number of patients who die suddenly from asthma have evidence of adrenal suppression⁵³ and this might be exacerbated by high dose corticosteroids. There is possibly an increased risk of secondary bacterial infections with high doses of steroids.

While it is common to discontinue ICS in patients with acute severe asthma, the concomitant use of ICS along with systemic steroids may provide additional benefit for some children⁵⁴. Using ICS while a patient is in hospital also reinforces the importance of using ICS regularly to treat chronic asthma; an important educational objective.

Magnesium

Magnesium is safe, and a meta-analysis has shown that when given systemically it confers some additional benefit in the

treatment of life threatening asthma⁵⁵. There is no established paediatric dose and few controlled studies in children.

Monteleukast

In children with acute asthma, intravenous montelukast was not significantly better than placebo in improving FEV1, symptoms, or overall hospital course⁵⁶ although a similar study in adults suggest a small acute improvement in pulmonary function with intravenous monteleukast seem over the first 2 hours of therapy⁵⁷. However there were no clear benefits in clinical outcome after this initial period.

Mucoactive medications

Patients with life threatening asthma often have secretory hyperresponsiveness or a markedly enhanced secretion of abnormal mucus⁵⁸. This is analogous to the smooth muscle ("bronchial") hyperresponsiveness characteristic of asthma. Currently there are no approved mucoactive medications for the therapy of life threatening asthma and few studies of mucoactive medications for acute asthma.

MECHANICAL VENTILATION

Acute severe asthma alters respiratory mechanics causing a heterogeneous increase in airway resistance which produces premature airway closure, dynamic hyperinflation and high intrinsic PEEP. These abnormalities increase the work of breathing and can lead to respiratory muscle fatigue and life-threatening respiratory failure.

Mechanical ventilation is often considered as a last resort in the treatment of patients with life threatening asthma. In the patient with hyperinflation and gas trapping, mechanical ventilation can worsen ventilation-perfusion mismatch and dynamic air trapping and this can aggravate barotrauma. Controlled hypoventilation with permissive hypercapnia may reduce morbidity and mortality compared to conventional normocapnoeic ventilation. It is recommended that low or no end expiratory pressure is used, and there be a sufficiently long exhalation time and slow breathing rate to allow clearance of gas from airways with long time constants. Effective tidal volume should be minimized to reduce the risk of volume trauma and auto-PEEP⁵⁹. Ventilator flow graphic monitoring can be helpful in evaluating the stiffness of the lungs and the response to the different ventilator settings used to recruit lung volume. Although these strategies can lead to hypoventilation, this permissive hypercapnia may reduce the risk of severe lung injury⁶⁰.

Heliox

Inhalation of a helium/oxygen combination (heliox) reduces the viscosity of the inhaled gas and decreases work of breathing. However, published evidence does not support the use of heliox in the treatment of patients with acute severe asthma⁶¹.

SUMMARY

Severe life threatening asthma in children is often preventable. Fortunately, many life threatening asthma attacks can be prevented by patient monitoring and assessment, careful patient education and appropriate use of asthma medications^{62,63}. A written action plan to guide patient self-management of exacerbations at home and frequent follow-up may be life saving, especially for patients who have moderate or severe

Table 2

Grades of evidence for interventions in acute severe asthma

Intervention	Level of evidence
Use inhaled β_2 -agonists as primary bronchodilators in acute asthma and administer as early as possible	A1
Use IV or IM β_2 -agonists for those patients in whom inhaled therapy cannot be reliably administered	B1
In asthma that is poorly responsive to an intermittent aerosol of β_2 -agonist, use continuous nebulization	A2
For severe asthma, add nebulized ipratropium bromide. Doses every 30 min should be used early. The dose frequency should be reduced as clinical improvement occurs	B1
Give steroids in all cases of acute asthma. Oral are as effective as IV or IM if patient is able to swallow. Use prednisone 2 mg/kg once daily to a maximum does of 80 mg.	A1
A single dose of IV magnesium sulfate can be given to patients with acute severe asthma. (suggest dose to be used in children)	C1
A single dose of intravenous montelukast should be considered if given very early	D1
Mucoactive medications should not be used.	D2
Heliox does not provide benefits when used to treat severe asthma	B2
Oxygen should be administered in sufficient amount to maintain peripheral oxygen saturation (SpO ₂) between 0.89 and 0.95	A1
Mechanical ventilation (noninvasive or after endotracheal intubation) should considered for patients with hypoventilation (PaCO ₂ > 60 torr) and respiratory distress	A1
While on mechanical ventilation use a low tidal volume (VT) of 4–6 mL/kg and long exhalation times to minimize barotraumas and dynamic hyperinflation	B1

persistent asthma and any patient who has a history of severe exacerbations⁶⁴.

When treating acute severe and life threatening asthma in children there are few data supporting the aggressive use of pharmacotherapy. Overuse of bronchodilators and corticosteroids may carry risk to the patient [Table 2]. Similarly, if mechanical ventilation is required to treat respiratory failure, “gentle” or low volume ventilation with permissive hypercapnia appears to be as effective as and less traumatic than attempts to ventilate in order to normalize blood gas values.

GRADES OF RECOMMENDATION

Recommendations were based on a modification of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scoring system. The strength of the recommendation is given a level of 1 when the benefits clearly outweigh the risks and burdens (or vice versa) for nearly all patients. A level of 2 is weaker and given when risks and benefits are more closely balanced or are more uncertain. The quality of the evidence is given a grade of A, B, C, or D for high, moderate, low, and very low, respectively.

SUMMARIES AND QUESTIONS

Risk factors for near fatal asthma

Summary of key points: With greater emphasis on preventive care, decreasing tobacco smoke exposure, and greater use of inhaled corticosteroids, the incidence of near-fatal asthma has been decreasing for a decade. Many of the risk factors for severe or near fatal asthma are associated with poor adherence to medical therapy. The appropriate use of asthma medications and a written action plan has been shown to decrease the risk of near-fatal attacks.

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TRUE-FALSE QUESTIONS

- [1] Allergic rhinitis is a risk factor for severe asthma.
- [2] Morbid obesity is a risk factor for near-fatal asthma attacks.
- [3] Severe asthmatics often have a decreased sensation of dyspnea.
- [4] The incidence of near-fatal asthma has increased every year for the past 12 years.

- [5] Children under the age of 12 are at greatest risk for near-fatal asthma.

PHYSIOLOGY AND PHENOTYPES

Summary of key points:

Asthma is not a uniform disease with severity, presentation, and response to therapy being influenced by genetic, environmental, and social/psychological variables.

TRUE-FALSE QUESTIONS

- [1] Very severe asthma is associated with neutrophilic inflammation in the airway.
- [2] The degree of elevation in FeNO (fraction of exhaled nitric oxide) correlates with asthma severity.
- [3] ADAM33 is thought to be an asthma susceptibility gene.
- [4] Severe airway mucus obstruction is a common complication of very severe and fatal asthma.
- [5] The presence of airway remodeling is indicative of long-standing and poorly controlled asthma.

DRUG THERAPY FOR ASTHMA

Summary of key points:

Although there have been a large number of medications that have been used to treat acute severe asthma, there are few pediatric data to support using any medications beyond oxygen, short acting beta agonists and anticholinergic bronchodilators, and corticosteroids.

TRUE-FALSE QUESTIONS

- [1] Heliox therapy in acute severe asthma can decrease the likelihood of endotracheal intubation and mechanical ventilation.
- [2] Levalbuterol (Xopenex) is recommended when using continuous nebulization as it causes less tremor and tachycardia than a similar dose of racemic salbutamol.
- [3] Patients with life threatening asthma respond best to the combination of systemic (intravenous) and aerosol beta agonists.
- [4] Supplemental oxygen should always be given to hypoxaemic patients with acute severe asthma; but only enough to maintain oxygen saturation between 0.89 and 0.94 (89% to 94%).

- [5] Although magnesium sulfate may be beneficial in treating acute severe asthma in adults, pediatric dosage and effectiveness have not been established.

MECHANICAL VENTILATION

Summary of key points:

Mechanical ventilation can be difficult in persons with severe asthma and should be undertaken with caution; however delay in securing adequate oxygenation by avoiding mechanical ventilation also carries a great risk. Permissive hypercapnea, low or no end expiratory pressure, and minimal tidal volume ventilation are effective lung protective strategies that minimize gas trapping and volume trauma.

TRUE-FALSE QUESTIONS

- [1] Auto-PEEP and dynamic hyperinflation is a potential complication of mechanical ventilation in persons with severe asthma
- [2] Controlled hypoventilation with permissive hypercapnia decreases the risk of barotrauma
- [3] Persons with severe asthma have low intrinsic PEEP
- [4] Effective tidal volume should be minimized in order to decrease the risk of volume trauma.