Acute Severe Asthma

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ABSTRACT

Asthma is chronic inflammatory disorder of the airways; this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper responsiveness to a variety of stimuli.1 The intermittent worsening or exacerbation of asthma represents acute or subacute episodes of airflow obstruction that may be mild to life threatening in severity. In this article we have tried to explain the definition, clinical features and assessment of the severity. An attempt is made to discuss both conventional and unconventional modes of treating this life threatening condition if not recognized early.

DEFINITION

Acute severe asthma is characterized by bronchospasm that is refractory to outpatient therapy. Status asthmaticus refers to severe bronchospasm that does not respond to aggressive therapies within 30 to 60 minutes.[2] Near fatal asthma is identified by respiratory arrest or evidence of respiratory failure ($PaCo_2$ > 50 mm Hg). Fatal asthma occurs when patients succumbs to asthma.[3]

ASSESSMENT

Two factors which contribute to the mortality of asthma are the failure of the physician to appreciate the severity of air flow obstruction in acute asthma and the delayed seeking of medical attention during an attack. It is necessary to assess asthma exacerbations on basis of objective measures of airflow obstruction.

History

It is essential that the patients who are at high risk for developing life threatening asthma are identified (Table 1).

Table 1: Indicators of development of severe airflow obstruction leading on to fatal asthma

- Prior endotracheal intubation
- Frequent or recent emergency department visits.
- Frequent or recent hospitalization for asthma
- Syncope or seizures during asthma exacerbation
- Environmental exposures.

Physical Examination

This is important in excluding other causes of dyspnea. Physical signs like tachycardia, tachypnea etc. (Table 2) indicate severe airflow obstruction but their absence also does not rule out severe airflow obstruction.

Arterial Blood Gas Analysis

Assessment of oxygenation can be done continuously, quickly and non-invasively in most patients using pulse oximetry. An arterial blood gas (ABG) analysis is indicated if any patient fails to respond to the first 30 to 60 minutes of intensive bronchodilator therapy. Degrees of hypoxemia and hypercapnia can be quantified and help in deciding when to plan mechanical ventilation. Asthmatic subjects who were followed up after recovery from a severe attack

Table 2 : Signs and correlation with severity of asthma

Signs	: Severe asthma : FEV_1 < 1.0 L
Pulse rate ≥ 120	: May be less in some cases of severe asthma
Respiratory rate ≥ 40	: Most of the times is >20, so non-discriminative.
Pulsus paradoxus ≥ 10	: Absent in 50% of patients with severe asthma
Accessory muscle use	: Presence indicates severe asthma; If absent, may have equally severe asthma in 50% of cases.
Pulse rate ≥ 120	: All three abnormal, 90% with severe
Respiratory rate ≥ 20	: asthma, but only 40% with FEV_1 <1.0 L
Pulsus paradoxus ≥ 20	: have all three abnormal

revealed that those who developed hypercapnia during an acute attack did not show an anticipated improvement in ventilatory response to PCO_2 in remission.[4] It has also been observed that patients who develop hypercapnia during one severe attack are most likely to develop it again in a subsequent attack.[5] Respiratory alkalosis is the most common acid base disturbance in asthma.[5] If the $PaCo_2$ rises above normal, this is superceded by a respiratory acidosis. A metabolic acidosis is unusual in acute severe asthma, as observed in the study of Mountain et al.[5]

Patients with severe hypoxemia also had an increased 'anion gap' presumably due to lactic acidosis and this accounted for the metabolic acidosis which occurred along with respiratory acidosis in patients with hypercapnia.

Table 3 : Differential Diagnosis of Asthma

Cardiac conditions
Valvular heart disease
Congestive heart failure
COPD exacerbation
Pulmonary infection
Pneumonia
Allergic bronchopulmonary aspergillosis
Loeffler's syndrome
Chronic eosinophilic pneumonia
Upper airway obstruction
Laryngeal edema
Laryngeal neoplasm
Foreign body
Paradoxical vocal cord dysfunction
Endobronchial disease
Neoplasm
Foreign body
Bronchial stenosis
Pulmonary embolism
Carcinoid tumour
Anaphylactic reaction
Miscellaneous
GERD
Non-cardiogenic pulmonary edema
Addison's disease

DIFFERENTIAL DIAGNOSIS

Other diagnosis to be considered in patients with breathlessness are listed in Table 3.

MANAGEMENT

The main goal in the emergency department is to safety reverse acute airflow obstruction, and the rapidity of revisal is predictive of the outcome of the attack.[6] Effective bronchodilation results in decreased need for hospitalization with significant cost savings (Table 4).

Close monitoring and repeated airflow measurements are essential for detecting any further deterioration during this initial period of treatment. Increase in PEFR or FEV_1 to 70% of baseline or greater indicates a favorable response while a PEFR or a FEV_1 of less than 70% of predicted, indicates presence of active inflammation and edema in the airways requiring further treatment. All patients with a PEFR less than 40% of predicted after 4 hours of bronchodilator therapy should be hospitalized (Table 5).

Oxygen

All patients should receive supplemental oxygen to maintain an arterial oxygen saturation greater than 90% (>95% in pregnant women and those with co-existent heart disease). Continual oxygen saturation monitoring is essential during the acute phase. However, it has been observed that patients with acute

Table 5 : Factors favouring hospitalization

Poor response to 4 hour of bronchodilator therapy

or

Incomplete response to 4 hour of bronchodilator therapy and or more of the following.

- Recent emergency department visit for asthma
- Recent hospitalization for asthma
- Multiple hospitalizations for asthma in the last year.
- Multiple emergency department visits for asthma in the last year.
- Past history of endotracheal intubation for asthma.
- Duration of current exacerbation > 1 week.
- Current use of oral corticosteroids.
- Home situations inadequate for follow-up.
- Psychiatric conditions that may interfere with medical compliance.

Table 4: Initial severity Assessment and Therapies in Emergency Department

	Mild to moderate	Severe
FEV_1 or PEFR	> 50%	Unable or <50%
Oxygen	Maintain SPO_2 > 90%	Maintain SPO_2 >90%
Inhaled $beta_2$ agonist nebulized albuterol or salbutamol	2.5 mg Q 20-30 min x 3 doses	5 mg q 20-30 mins x 3 doses continuous for 1 hour if severe
MDI with spacer Albuterol 90 µg/puff	6-12 puffs q 20 mins 20 mins upto 4 hrs (under supervision)	may be unable to do
Inhaled anticholinergics nebulized solution (Ipratropium)	If known previous improvement	0.5 mg q 20-30 mins x 3 doses
Systemic corticosteroids	40-60 mg prednisolone	40-60 mg prednisolone
IV (unable to take oral or absorption problem)	60-125 methyl prednisolone	60 - 125 mg methyl prednisolone
IV Magnesium sulphate	Not indicated	2 - 3 gram (iv) at rate 1 mg/min

severe asthma and hypercapnia are at risk of further elevation of $PaCO_2$ if uncontrolled oxygen is given. Oxygen minimizes the potential episodes hypoxemia due to acute administration of Beta adrenergic agonists,[7] decreases elevated pulmonary vascular pressure due to hypoxic vaso- constriction, decreases bronchospasm due to hypoxia and improves oxygen delivery to muscles.

Adrenergic Medications

A metered dose inhaler (MDI) plus spacer is used often in treatment of acute asthma (Table 4). This therapy requires more supervision and patient cooperation as compared to nebulization via mouth piece or mask.

Intravenous Use of Adrenergic Agonist

Asthma guidelines, with the exception of those in the United States recommend the use of intravenous Beta-agonists for very severe and unresponsive acute asthma.

Albuterol is given as a loading dose of 4 µg/kg for 2-to 5 minutes followed by an infusion of 0.1 to 0.2 µg/kg/min, with close cardiopulmonary monitoring.[8] Intravenous epinephrine can be given as 2 to 10 ml of a 1:10,000 solution over 5 minutes, repeated if necessary and an infusion of 1 to 20 µg/min started if there is improvement with initial therapy.[9] There is an observation that high dose nebulized albuterol has greater efficacy with fewer side effects compared to intravenous use.

Subcutaneous Adrenergic Agents

Epinephrine, subcutaneously (1:1,000 solution 0.2 to 0.5 ml q 20 to 30 minutes as needed for 3 doses) is to be given only to those asthmatics who are severely bronchospastic and not inhaling adequate albuterol. The increased side effects due to its α and is β effect limit its widespread use.

Terbutaline is a longer acting Beta 2 agonist (0.25 mg, subcutaneously every 20 minutes for 3 doses), with its propensity to cause skeletal muscle tremor and tachycardia is to be used only in those unable to adequately inhale bronchodilating drugs.

Corticosteroids

The safety and effectiveness of short courses of corticosteroids in the treatment of status asthmaticus has been shown in many studies.[10,11] Corticosteroids decrease synthesis of leukotrienes, prostaglandins and thromboxanes, inhibit cytokine release by macrophages and T cells; decrease expression of endothelial cell adhesion molecules to inhibit migration of inflammatory cells into the airways; increase neutral endopeptidase expression to enhance degradation of neuropeptides that regulate inflammation and decrease secretions from gland cells. Corticosteroids also inhibit airway smooth muscle tachyphylaxis to beta adrenergic agonists.[12]

Systemic corticosteroids are the principal therapy for status asthmaticus.[13] Prednisone and methylprednisone are the preferred agents. Compared with beclomethasone and dexamethasone, prednisone and methylprednisone do not contain metabisulfites and have shorter half-lives. Although hydrocortisone has the shortest half-life, it has more mineralocorticoid effect with resultant sodium retention and may cause idiosyncratic bronchospasm in some aspirin sensitive individuals.[14] Intravenous methylprednisolone dosing are 60 to 125 mg and for hydrocortisone 200 to 500 mg, each given every 6-8 hours until improvement, at which time frequency can be decreased. Oral steroids used are prednisone or its active form, prednisolone. Prednisone is commonly the agent of choice for oral therapy and is given in dose of 40 to 60 mg in the same regimen as the intravenous steroids. Studies have suggested that, intravenous steroids confer no additional benefits over oral steroids.[15,16]

Oral steroid therapy is preferred unless the patient is very ill, is unable to swallow, or is suspected of having impaired gastrointestinal transit or absorption. Oral prednisone is gradually tapered by 2.5 to 5 mg per day. As the oral prednisone is being tapered successfully, the recovering patient should be started on a corticosteroid aerosol.

Cholinergic Antagonists

The anticholinergic drugs available for inhalation therapy include atropine sulphate, atropine methylnitrate, glycopyrrolate and ipratropium bromide. These bronchodilators overcome the smooth muscle constrictor and secretory consequences of the parasympathetic nervous system, blocking reflex bronchoconstriction and reversing acute air flow obstruction.

These agents are not the primary therapy for acute asthma. Indication for use includes bronchospasm caused by beta-adrenergic antagonists and patients with severe cardiac disease unable to tolerate the systemic side effects of beta adrenergic agonists.[17]

Though some studies indicate that addition of anticholinergic drugs in the management of acute severe asthma is beneficial,[18,19] meta analyses of trials assessing the role of ipratropium in combination with beta agonists for acute disease found that ipratropium provides a modest improvement in PFTs and a reduction in hospitalizations.[20]

There is wide interpatient variability in response to anticholinergics, implying that cholinergic mechanisms play a varied role in acute attacks. The time to reach maximum effect from inhaled ipratropium is 30 to 120 minutes, with effect lasting for up to 6 hours (Table 4).

Methylxanthines

Theophylline is the main oral methylxanthine used to treat asthma whereas aminophylline (80% theophylline by weight) is used intravenously. The mechanism of theophylline's bronchodilatory effects is unclear. It also enhances diuresis, cardiac output, mucociliary clearance, ventilatory drive, and contractility of the diaphragm while inhibiting the release of inflammatory mediators and suppressing microvascular permeability. The role of methyl xanthenes is patients with acute severe asthma is controversial. Results of trials against[21,22,23] use of aminophylline in acute severe asthma and those that favour its use[24,25] when analysed, have not shown any difference between aminophylline and beta-adrenergic agonist therapy.

Though the toxicity of methylxanthines are the main drawback to its use in status asthmaticus, in hospitalized patients it is recommended that methylxanthine be routinely used in the treatment of status asthmaticus.[26] The rational appears to be that methylxanthines prolong the bronchodilator effects of beta-

Table 6 : Intravenous dosage of Aminophylline

Loading dose (based on actual body weight)	5-6 mg/kg over 20 min, peripheral IV
Maintenance infuse based on ideal body weight	
Children to age 18	1.0 mg/kg/hr
Adult smoker under 50	0.9 mg/kg/hr
Adult non-smokers under 50	0.5 mg/kg/hr
COPD	0.6 to 0.7 mg/kg/hr
Congestive heart failure	0.35 to 0.68 mg/kg/hr
Liver dysfunction	0.25 to 0.45 mg/kg/hr

adrenergic agonist, thereby minimizing nocturnal symptoms of asthma in a recovering patient. Other beneficial effects include its positive inotropic and diuretic effects, induction of catecholamine release from adrenal glands, vagolytic effects, pulmonary and systemic vasodilatation, central respiratory drive stimulation and enhanced diaphragmatic contractility.

Optimal serum theophylline levels are 5 to 15 µg/ml; guidelines of aminophylline loading are given in Table 6.

If theophylline levels need adjustment, then every mg/kg of aminophylline given will increase the serums level by approximately 2 µg/ml. A repeat theophylline level should be obtained 12 hours after maintenance therapy is instituted. Serum concentration more than 20 µg/ml are toxic. Methyl-xanthine toxicity should be suspected when nausea, vomiting, diarrhoea, tachycardia, cardiac, cardiac dysrhythmias or seizures are present. Seizures occur suddenly in the absence of other symptoms so serum levels should be monitored closely.[27] Drug interactions and serum theophylline levels are shown in Table 7.

Other therapies

Fluids

Antibiotics

Use of antibiotics should generally be reserved for patients with fever, purulent sputum and pneumonia.

Magnesium sulphate

Magnesium relaxes smooth muscles in vitro and bronchodilates asthmatic airways in vitro. Mechanisms for their direct relaxing effect on bronchial smooth muscle include calcium channel blocking properties, inhibition of cholinergic neuromuscular transmission, stabilization of mast cells and T lymphocytes, and stimulation of nitric oxide and prostacyclin. But the bronchodilatory effects are transient[28] and do not augment the response the beta adrenergic agonists and so is not routinely recommended for routine use. 2-3 grams magnesium at the rate of 1 mg/min while continuing aggressive inhalational therapy can be given. Side effects of magnesium infusions are dose related and include warmth, flushing, sweating, nausea and emesis, muscle weakness and loss of deep tendon reflexes, hypotension and respiratory depression.

Management of Respiratory Failure

The critically ill asthmatic is hypoxic. This is shown by elevated lactic acid levels, which reflect the tissue hypoxemia and anaerobic metabolism. Persistent elevations of arterial lactate levels are often associated with a poor prognosis. Increase in lactate levels can occur even after clinical improvement is noted. This is due to muscle over production decreased hepatic metabolism or muscular 'washout' after bronchodilatation.[29] However hyperlactatemic is not predictive of respiratory failure in critically ill asthmatics.

Table 7 : Drugs affecting serum theophylline levels.

Drugs increasing serum theophylline levels	Drugs decreasing serum theophylline levels
Ciprofloxacin	Carbamazepine
Erythromycin	Phenobarbital
Troleadomycin	Phenytoin
Macrolide antibiotics	Rifampicin
Allopurinol	Drugs inducing hepatic enzymes
Propranolol	
Influenza vaccine	

Non-invasive strategies

Treatment of acute severe asthma must be started immediately (Table 4). Frequent nebulization, beta adrenergic agonists, supplemental oxygen and high dose intravenous corticosteroids should be administered.

Heliox (a mixture of 60% to 80% helium and 20 to 40% oxygen) improves PEFR in non-intubated asthmatics and decreases peak airway pressures in ventilated asthmatics.[30] Helium is an inert gas with one-eighth the density of nitrogen. When helium is blended with oxygen, the resultant gas mixture has a three-fold reduction in density compared to air. Heliox reduces respiratory muscle work and improves gas exchange by improving ventilation perfusion relationships. It is not intrinsically therapeutic but can decrease the work of breathing long enough to avoid intubation by allowing bronchodilators and antiinflammatory agents to take effect. Administration is by face mask and constant oxygen saturation monitoring and frequent blood gas monitoring is recommended.

NIPPV is acute severe asthma

The use of positive pressure ventilation on asthma appears counter productive as these devices may worsen hyperinflation and air trapping, increase intrathoracic pressure, resulting in decreased venous return and contribute to barotrauma. Continuous positive air way pressure (CPAP) delivered via a face mask or nasal prongs is reported to be beneficial to asthmatics. Theoretically CPAP improves oxygenation by increasing functional residual capacity and lung compliance. CPAP may also supply some of the inflatory pressure required during inspiration, thus reducing the use and fatigue of the respiratory muscles. Bilevel positive airway pressure (BI PAP) devices provide CPAP but deliver higher pressure during inspiration than expiration. An uncontrolled study[31] explored the role of mask ventilation in acute respiratory failure due to status asthmaticus. Tolerance of NIPPV was good with rapid physiological improvement, nil complications and deaths. However, till a randomized study of NIPPV versus conventional ventilation is carried out, NIPPV may be considered on selected cases only.

Table 8 : Goals of mechanical ventilation

- Maintain oxygen saturation of hemoglobin > 90%
- Minimise dynamic hyperinflation
  - Decrease minute ventilation
  - Increase expiratory time
  - Accept hypercarbia
- Monitor closely for complications of mechanical ventilation

Mechanical Ventilation

The main principles of mechanical ventilation in status asthmaticus are to provide adequate oxygenation while minimizing the risk of barotrauma (Table 8).

Unconventional Management Method

Sometimes, despite conventional therapy with bronchodilators corticosteroids and mechanical ventilation, air flow obstruction is still severe to cause tissue hypoxemia. At this point, unconventional measures, mainly based on anecdotal experience may be tried (Table 9).

Table 9 : Unconventional Therapeutic Measures

Intravenous beta adrenergic agents
Intravenous magnesium sulphate
Heliox
General anesthetics
Bronchoscopy with therapeutic lavage.
Hypothermia
Extracorporeal life support.

REFERENCES

1. National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma, National Institute of Health, National Heart, Lung, and Blood Institute. NIH Publication 1997;97:4051.
2. Panacek EA, Pollack CV. Medical Management of severe acute asthma. In Kaliner MA, editor: Emergency Asthma, New York, 1999, Marcel Dekker, Inc.
3. Guishard K. Fatal Asthma. In Kaliner MA; editor Emergency Asthma, New York, 1999, Marcel Dekker, Inc.
4. Rebuck A.S., Read J. Patterns of ventilatory response of carbon dioxide during recovery from severe asthma. *Clin Sci* 1971;41:13-21.
5. Mountain RD, Sahn SA. Clinical features and outcome in patients with acute severe asthma presenting with hypercapnia. *Am Rev Respir Dis* 1988; 138:535-9.
6. Rodrigo G, Rodrigo C. Early prediction of poor response in acute asthma in patients in the emergency department. *Chest* 1998;114:1016-1021.
7. Wasserfallen JB, Schaller MD, Feihl F, Perret CH. Sudden asphyxic asthma: a distinct entity? *Am Rev Respir Dis* 1990;142:108-16.
8. Nowak RM. National and international guidelines for the emergency management of adult asthma. In Brenner BE, editor: Emergency Asthma, New York, 1999, Marcel Dekker, Inc.
9. Bishop GF, Hillman KM. Acute severe asthma. *Int Care World* 1993;10: 166.
10. Fanta CH, Rossing TH, McFadden ER. Glucocorticosteroids in acute asthma: A critical control trial. *Am J Med* 1983;74:845.
11. Hashell RJ, Wang BM, Hanser JE. A double blind, randomized trial of methyl prednisolone in status asthmaticus. *Arch Intern Med* 1983;143: 1324.
12. Kaliner M. Mechanism of glucocorticoid action in bronchial asthma. *J Allergy Clin Immunol* 1985;76:421.
13. British Thoracic Society Guidelines for the management of asthma in adults: II - Acute Severe Asthma. *Thorax* 1992;47 supplement.
14. Partridge MR. Gibson GJ. Adverse bronchial reaction to intravenous hydrocortisone in two aspirin sensitive asthmatic patients. *Br Med J* 1978; 1:1521.
15. Stein LM, Cole RR. Early administration of corticosteroid in the emergency room treatment of acute asthma. *Ann Intern Med* 1990;112:822-7.
16. Morell F, Orriols R, J de Garcia, Currol V, Pujol A. Control trial of intravenous corticosteroid in acute severe asthma. *Thorax* 1992;47: 588-91.
17. Bethel RA, Irvin CG. Anticholinergic drugs and asthma. *Semin Respir Dis* 1987;8: 366.
18. Rebuck AS, Chapman KR, Abboud R et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med* 1987;82:59.
19. Higgins RM, Stradling JR, Lane DJ. Should ipratropium bromide be added to beta agonist in treatment of acute severe asthma? *Chest* 1988;94:718.
20. Rodrigo G, Rodrigo C, Burschitin O. A meta analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med* 1999;107: 363-370.
21. Littenberg B. Aminophylline treatment in severe acute asthma - a meta analysis. *JAMA* 1988;259:1678-1684.
22. Beswick K, Davies J, Davey AJ. A comparison of intravenous aminophylline and salbutamol in the treatment of severe bronchospasm. *Practitioner* 1975;214:561.
23. Williams SJ, Parrish RW, Seation A. Comparison of intravenous aminophylline and salbutamol in severe asthma. *Br Med J* 1975;4:685.
24. Pierson WE, Bierman CW, Stamm ST, et al. Double blind trial of aminophylline in status asthmaticus. *Paediatrics* 1971;48:642.
25. Evans MV, Monie RDH, Gimmins J, et al. Aminophylline, salbutamol and combined intravenous infusions in acute severe asthma. *Br J Dis Chest* 1980;74:385.
26. U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of Health, Expert Panel Report: Guidelines for the diagnosis and Management of Asthma Publication No. 91-3042, August 1991.
27. Zwillich CW, Sutlon FD, Netf TA, et al. Theophylline induced seizures. *Ann Intern Med* 1975;82:784.
28. Stalcup SA, Mellin RB. Mechanical forces producing pulmonary edema in acute asthma. *N Engl J Med* 1977;297:592.
29. Rabbat A, Laaban JP, Boussairi A, et al. Hyperlactatemia during acute severe asthma. *Intensive Care Med* 1998;24:304-312.