Acute severe asthma

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Asthma is the most common medical emergency in children and is associated with significant morbidity and mortality worldwide¹. The prevalence of asthma in children varies significantly, with the highest rates in the United Kingdom, Australia and New Zealand, and the lowest rates in Eastern Europe, China, and Indonesia^{2,3}. In the United States (US), asthma affects 6 million children annually and is the leading cause of hospital as well as paediatric intensive care unit (PICU) admission for children less than 18 years of age. The number of asthma related deaths in all age groups in the US is around 5000 per year, 150-200 of those occurring in children less than 15 years of age. Most asthma-related deaths in children occur as a result of respiratory failure or cardiopulmonary arrest that occurs prior to obtaining medical care²⁻⁵.

Several factors are considered as predictors of fatal asthma. Clinical risk factors include a past history of PICU admission, respiratory failure or rapid, sudden, severe deterioration. Psychosocial and ethnic risk factors include poor compliance with outpatient medical treatment, failure to perceive the severity of asthma attack, inner-city residence, denial of disease severity, and non-white race⁶⁻⁸. However, despite the aforementioned risk factors, nearly half of fatal asthma exacerbations occur in children with mild asthma^{7,9}. This entity is characterized by rapid, sudden, severe airway obstruction that progresses to hypoxaemic respiratory arrest over a short period, usually before presentation to medical care.

Pathophysiology

Understanding the pathophysiologic changes that affect the cardio-respiratory system is important for the management of acute severe asthma. Asthma is an inflammatory disease characterized by air-flow obstruction due to hyper-responsiveness, mucosal oedema and mucous plugging of the small airways.

Airway inflammation is characterized by the submucosal cellular infiltrate of eosinophils, mast cells and CD4 lymphocytes. The cascade of inflammation begins with degranulation of mast cells, usually in response to exposure to the allergen^{5,9,10}.

Severe airways obstruction affects lung mechanics, resulting in a dramatic increase in the work of breathing as the patients use their accessory muscles to overcome the resistance to air flow. Expiration becomes active rather than passive. The patient is unable to expire the entire volume of inspired gas, causing dynamic hyperinflation and gas trapping (Figure 1). Airway obstruction leads to dynamic hyperinflation caused by inspiration commencing before the termination of the previous expiration. If the airway obstruction is not relieved, the enormous increase in work of breathing will eventually result in fatigue and a rapid decompensation¹.

Figure 1: Lung mechanics in asthmatic patients compared with normal

The bronchial obstruction in acute severe asthma is not distributed evenly throughout the lung. Some areas of the lung are completely obstructed while others are not obstructed at all. In other words, the lung is extremely in-homogeneous during acute severe asthma¹¹.

Schematically, the asthmatic lung can be described as consisting of four parallel compartments (Figure 2). Compartment A refers to the portion of the lung without bronchial obstruction; in compartment B the

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airways are entirely obstructed during the whole respiratory cycle (mucous plugging); in compartment C obstruction appears only during expiration whilst in compartment D partial obstruction of the airways is present throughout the respiratory cycle.

Figure 2: Effect of varying amounts of airway obstruction on end-expiratory alveolar volumes and pressures

Clinical features

The clinical findings commonly seen in acute severe asthma include tachycardia, tachypnoea, hyperinflation, wheeze, accessory muscle use, pulsus paradoxus and diaphoresis. Absence of wheezing may not be a sign of resolution, as the more severe the obstruction, the quieter the chest sounds^{5,9}. The inability to talk in sentences, marked intercostal and subcostal indrawing and accessory muscle use indicate severe airways obstruction. The extremes of

respiratory muscle fatigue are heralded by increasing agitation followed by apathy and somnolence, which precede apnoea.

The initial blood-gases show a reduction in PaCO₂ associated with hyperventilation. Any increase in PaCO₂ >40mmHg indicates that respiratory muscle fatigue is developing. Significant hypoxaemia is uncommon even in severe asthma, and its presence indicates lung collapse or pneumothorax^{5,9,12}. There is a variety of acid-base abnormalities seen in acute severe asthma. The most common is an initial respiratory alkalosis caused by hyperventilation. As the airway obstruction worsens, either a metabolic acidosis or a mixed respiratory and metabolic acidosis is a common finding. Lactic acidosis also develops in association with severe airways obstruction. This is caused by a combination of lactate production by the respiratory muscles and tissue hypoxia^{1,13,14}.

Clinical Management

Clinical management of acute severe asthma is based on Poiseuille law. According to that, in straight circular tubes with laminar flow the resistance is inversely proportional to the 4th power of the radius. Accordingly even a minute dilatation of the bronchi causes a dramatic reduction in the airway resistance¹⁵.

Poiseuille law

The pressure-flow characteristics for laminar flow were first described by the French physician Poiseuille. According to Poiseuille law in straight circular tubes with laminar flow, the resistance is given by

$$R = \frac{8nl}{\pi r^4}$$

R is the resistance,
r = radius,
n = viscosity,
l = length.

Note the critical importance of tube radius; if the radius is halved, the resistance increases by 16-fold! However, doubling the length only doubles resistance. Note also that the viscosity of the gas, but not its density, affects the resistance.

General Care

Children admitted with acute severe asthma require intravenous (IV) access, continuous cardio-respiratory monitoring, and continuous pulse oxymetry.

Fluids

They are often dehydrated as a result of decreased oral intake and increased insensible fluid losses due to hyperventilation. Providing appropriate fluid resuscitation and ongoing maintenance fluid is essential; however, over-hydration should be avoided because these children are at a higher risk for pulmonary oedema^{5,9}.

Oxygen

Nearly all patients with acute asthma have hypoxaemia as a result of ventilation-perfusion (V/Q) mismatching. Beta-2 agonists may worsen this mismatch by causing pulmonary vasodilation in areas of the lung that are poorly ventilated. Humidified oxygen should be provided as needed to maintain an oxygen saturation of ≥ 92 percent. All nebulized medications should also be delivered with oxygen, generally at a flow rate of 6 to 8L/min^{1,5,9}.

Corticosteroids

As the main physiologic derangement in asthma is airway inflammation, corticosteroids are the mainstay of management¹. Glucocorticosteroids suppress cytokine production, granulocyte-macrophage colony-stimulating factor and inducible nitric oxide synthase activation, which are components of the inflammatory processes of asthma^{17,18}. The currently available evidence does not support the use of inhaled corticosteroids in the treatment of acute severe asthma. Obstruction of the lower airways limits the distal delivery of inhaled corticosteroids, minimizing their effectiveness. However, several studies suggest an adjunctive role for inhaled corticosteroids in the management of acute severe asthma^{16,17}. There is evidence to suggest that enteral and parenteral corticosteroids are equally effective in the management of acute severe asthma. However, as the acutely ill child is less likely to tolerate oral medications, oral steroid administration is of limited value^{17,18}.

Methylprednisolone is the preferred agent used and is preferred because of its limited mineralocorticoid effects. The initial dose is 2 mg/kg, followed by 0.5-1mg/kg/dose administered IV every 6 hours. Other

agents that are used include dexamethasone and hydrocortisone^{5,9}. After administration of the first dose of systemic corticosteroids, it will take at least 1-3 hours for the initiation of the anti-inflammatory effect and the optimal effect may take as long as 4 to 6 hours. Therefore, early administration of systemic corticosteroids in the emergency department itself is very important in the management of acute severe asthma^{1,5,9}. Treatment duration depends upon the severity of illness but generally continues until the asthma exacerbation is resolved. Short courses of steroid treatment are generally well tolerated. Side effects include hyperglycaemia, hypertension, and occasionally, agitation related to steroid-induced psychosis.

Inhaled β_2 -agonists

β_2 -agonists cause direct bronchial smooth muscle relaxation. The safety and efficacy of inhaled β_2 agonist therapy has been tested in randomized controlled trials in both paediatric and adult asthmatics^{1,5,9}. In the treatment of acute severe asthma, inhaled β_2 -agonists will support ventilation and oxygenation until the anti-inflammatory effects of corticosteroids take effect¹. They can be administered by intermittent nebulisation every 20 minutes or continuous nebulisation. The most frequently studied drugs have been salbutamol (albuterol) and terbutaline^{5,9}. Side effects of continuous salbutamol nebulization are common but relatively minor. Cardiovascular-related effects include sinus tachycardia, palpitations, hypertension, diastolic hypotension, and rarely, ventricular cardiac dysrhythmias. Excessive central nervous system (CNS) stimulation including hyperactivity, tremors, and nausea with vomiting, are not uncommon^{1,19}. Hypokalaemia and hyperglycaemia are the most common metabolic derangements¹⁹. Periodic serum potassium levels should be monitored during inhaled salbutamol treatment.

Intravenous β_2 -agonists

IV beta 2 agonists are beneficial in acute severe asthma with severe airflow limitation where distribution of inhaled medications may be significantly reduced^{5,9}. Usually a loading dose of salbutamol 5 μ g/kg is given over 5 minutes followed by an infusion of 1-2 μ g/kg/minute, adjusted according to response up to 5 μ g/kg/minute. Dosages up to 10 μ g/kg/minute can be given in an intensive care setting^{20,21}. ECG monitoring and regular checking of serum potassium levels are required during the IV salbutamol therapy. The side effects of

IV-administered salbutamol are similar to those of inhaled therapy.

Methylxanthines

The methylxanthine group of drugs has been part of the treatment armamentarium for asthma for 40 years, either as oral theophylline for chronic asthma or IV aminophylline for acute severe asthma^{5,9}. They promote relaxation of the bronchial smooth muscles. The exact mechanism of action remains controversial. Suggested mechanisms include increase of intracellular cyclic adenosine monophosphate (cAMP) levels by blocking phosphodiesterase-4, control of intracellular calcium flux, inhibition of endogenous catecholamine release, and prostaglandin antagonism²². Aminophylline therapy may be helpful in poor responders. In acute severe asthma not previously treated with theophylline, aminophylline is administered by continuous IV infusion following a loading dose of 5mg/kg (max. 500 mg) infused over 20 minutes. Dosages for the IV infusion are as follows:^{23,24}

- Child 1 month- 9 years: 1 mg/kg/hour
- Child 9–16 years : 800 µg/kg/hour
- Child 16–18 years: 500µg/kg/hour

Ideally, serum theophylline levels should be measured 1-2 hours after the loading dose. The infusion should be adjusted accordingly. The main concern about aminophylline is its narrow therapeutic index (margin between therapeutic and toxic dose). In most individuals a plasma theophylline concentration of 10–20mg/L is required for satisfactory bronchodilation. Serum levels >20mg/L are associated with adverse effects that include nausea, jitters or restlessness, tachycardia and overall irritability²²⁻²⁴. Serum levels >35mg/L have been associated with seizures and cardiac dysrhythmias. Careful attention to serum drug level measurements is therefore required to minimize the risk.

Anticholinergics

Ipratropium bromide is the most frequently used anticholinergic in the treatment of acute severe asthma. It promotes bronchodilation without inhibiting mucociliary clearance, as occurs with atropine^{5,9}. By blocking the muscarinic receptors on bronchial smooth muscle cells, intracellular cyclic guanosine monophosphate levels are reduced and muscle contraction is impaired^{5,9}. Ipratropium bromide can be delivered either by aerosol or metered dose inhaler (MDI). Initial dose range is 125-500µg (if nebulized) or four to eight puffs (if via

MDI) administered every 20 minutes for up to three doses. The subsequent recommended dosing interval is every 4-6 hours^{24,26}. Ipratropium has few adverse effects because it has poor systemic absorption. The most common side effects are dry mouth, bitter taste, flushing, tachycardia, and dizziness²⁴⁻²⁶. There is good evidence for synergism when these drugs are combined with beta agonists.

Magnesium sulphate

Magnesium acts as a calcium channel blocker, inhibits calcium-mediated smooth muscle contraction and facilitates bronchodilation¹. However, the value of magnesium in the treatment of acute severe asthma remains controversial. Some studies, completed in the emergency department setting, have shown beneficial effects while others have shown no benefit²⁷. The usual dose of magnesium is 25-50 mg/kg/dose over 30 minutes, administered every 4 hours. Magnesium can also be given by continuous infusion at a rate of 10-20 mg/kg/hr^{5,27,28}. Side effects include hypotension, CNS depression, muscle weakness and flushing. Severe complications, such as cardiac arrhythmias, including complete heart block, respiratory failure due to severe muscle weakness, and sudden cardiopulmonary arrest, may occur in the setting of very high serum magnesium levels (usually >10-12mg/dl). Ideally, serum magnesium levels should be monitored regularly during the treatment^{5,9}.

Helium-oxygen

Helium-oxygen (Heliox) remains unproven therapy in critically ill children with acute severe asthma¹. For children who are not improving with conventional therapy or children who are receiving high-pressure mechanical ventilatory support, Heliox may be a reasonable adjunct therapy^{5,9}. According to the Poiseuille law airway resistance is directly proportional to the viscosity of the gas¹⁵. As helium is a low-viscosity gas, when administered by inhalation in a mixture with oxygen, it reduces air flow resistance in small airways. These characteristics may also enhance particle deposition of aerosolized medications in distal lung segments. These make a mixture of helium and oxygen (80% helium/20% oxygen - Heliox) an attractive therapeutic option in the management of acute severe asthma²⁹. However, studies done on the efficacy of Heliox in acute severe asthma have yielded conflicting results³¹.

Non-invasive mechanical ventilation

If all other measures fail in the management of acute severe asthma one has to consider ventilatory

support. However, ventilation in asthma can cause severe damage to the lungs^{5,9,11}. Non-invasive positive-pressure ventilation (NIPPV) is an alternative to conventional mechanical ventilation in these patients³². A trial of NIPPV may be warranted prior to the institution of conventional mechanical ventilation.

Mechanical Ventilation

In contrast to the usual practice in other forms of respiratory failure, mechanical ventilation in acute severe asthma is often delayed and is used mostly as an ultimate means when all conventional medical treatments have failed^{1,5,9,33}. As described earlier, airway obstruction in acute severe asthma is not distributed uniformly throughout the lung. There may be a spectrum of alveoli from completely patent to completely obstructed (Figure 2). In such a system, most of the tidal volume delivered by positive pressure ventilation goes to compartment A, which represents patent alveoli with almost normal mechanical characteristics, and damages them¹¹ (Figure 3)

Figure 3: *Expected distribution of the tidal volume during positive pressure mechanical ventilation in the context of inhomogeneous obstruction*

A rising PaCO_2 , failure to maintain oxygen saturations $>92\%$, a worsening metabolic acidosis, and a decreasing level of consciousness are signs predicting respiratory arrest and indicate the need of intubation and ventilation³⁴⁻³⁷. Tracheal intubation of an asthmatic child requires preparation and anticipation of patient deterioration. It should be performed by the most skilled individual available. Hypotension should be anticipated because many patients have relative hypovolaemia that may be exacerbated by reduced preload as positive-pressure ventilation is initiated and by reduced vascular tone induced by anaesthetic agents used for tracheal intubation³⁴⁻³⁶. Histamine-producing agents, such as morphine or atracurium, must be avoided. Ketamine is an excellent medication for induction because of its relatively long half-life, bronchodilating properties

and relative preservation of haemodynamic stability³⁸. Aims of ventilation in acute severe asthma are maintaining adequate oxygenation and arterial pH of >7.2 while allowing hypercarbia. Ventilatory strategies should minimize dynamic hyperinflation and air trapping by slow ventilator rates with prolonged expiratory phase, minimal end-expiratory pressure, and short inspiratory time^{1,5,35,36}.

Chest physiotherapy

Chest physiotherapy may augment airway clearance. However, it should only be considered in children with clear segmental or lobar atelectasis as it can be irritating to the severe asthmatic and may actually worsen clinical symptoms^{5,9}.

Antibiotics

Most asthma exacerbations are associated with viral infections so that routine empiric antibiotics are not indicated. However, as lower respiratory tract bacterial infections do occur in acute severe asthma, appropriate antibiotics should be administered when clinically indicated⁵.

Sedation, analgesia, muscle relaxants and inhalational anaesthetics

Sedation of the non-intubated asthmatic is generally not indicated. Mechanically ventilated children require sedation and, often, muscle relaxants. Ketamine by continuous infusion is the first choice for sedation. When opiates are used, fentanyl is preferred because morphine causes histamine release which may exacerbate bronchospasm. Neuromuscular blocking agents are frequently required to facilitate mechanical ventilatory support. Vecuronium is a commonly used agent^{1,5,9,38}. Inhaled general anaesthetics have been used when all other measures fail and their bronchodilating properties have proven beneficial in the management of the intubated asthmatic³⁹. These agents should be administered in conjunction with anaesthesia services. Hypotension and cardiac dysrhythmias are associated with their use and are more likely to occur in hypoxaemic children.

Frequent monitoring and clinical assessment

Close monitoring and frequent assessment is the key for the successful management of acute severe asthma. It is essential that the physician recognizes which episodes of airway obstruction are life-threatening and which patients demand what level of care. These distinctions can be made readily by

assessing selected clinical parameters in combination with measures of gas exchange. Even though different grading systems have been proposed to evaluate the severity of acute asthma in children no firm consensus exists^{5,40}.

The general appearance, respiratory rate and pattern, degree of tachycardia, and oxygen saturation should be continually assessed. Markers of severe distress include lethargy or agitation, markedly fragmented speech, severe retractions with accessory muscle use, thoraco-abdominal dissociation, inability or unwillingness to lie down and progressive desaturation on continuous pulse oximetry^{5,9,40}.

Although the estimation of pulsus paradoxus is more difficult in children, it is possible to observe variations in the amplitude of the pulse waveform through oximetry and the quality of the child's radial pulse with respiration. Peak flow manoeuvres, a common technique for following airway obstruction in the outpatient settings, may cause an acute deterioration in respiratory function and should be avoided in distressed patients⁵.

It is important to bear in mind that the extent of wheeze does not necessarily reflect the extent of

bronchopulmonary obstruction, since some degree of airflow is required to produce a wheeze. Therefore, *decreasing* wheeze and breath sounds and a "quiet chest" in a child with increasing respiratory efforts may signal imminent respiratory failure. Conversely, increasing wheeze in a child with severe asthma may indicate improvement⁴⁰.

Pulse oximetry is a reliable and non-invasive measure of oxygenation and should be used in all patients to guide oxygen supplementation. However, oxygen saturation is not a good parameter of adequate ventilation in children who receive oxygen treatment. Thorough and repeated clinical assessments are required to discover imminent respiratory failure. Blood gas analyses may support the clinical judgement, as increasing levels of CO₂ is an ominous sign. During a moderate asthma attack, a capillary blood gas analysis may be sufficient, while in patients admitted to an intensive care unit, arterial blood gas analyses should be routine. Sequential measurements are important as respiratory alkalosis with hypocarbia is common during the early phases of an asthma attack, while normalisation and a subsequent increase in the pCO₂ may be important indicators of clinical deterioration^{5,9,40}.

Management algorithm for acute severe asthma^{5,9,24}

- Give high flow oxygen via face mask with reservoir and non re-breathe valves at 6-8L/min,
- Cardiac and oxygen saturation monitoring.
- Obtain IV access.
- Give bolus IV fluids if dehydrated: 0.9% saline 20ml/kg.
- Salbutamol nebulisation (0.15mg/kg, maximum 5mg) combined with ipratropium bromide (250µg/dose if <20kg; 500µg /dose if >20kg), every 20 minutes for three doses.
- Patients who have received three doses of intermittent therapy and require additional salbutamol therapy may be treated intermittently every 20-30 minutes or may be switched to continuous therapy.
- Continuous nebulisation dose = 0.3mg/kg/hr
- Administration of systemic steroids after the first inhalation therapy
 - Methylprednisolone (2mg/kg x 1, then 0.5-1mg/kg six hourly).
 - Hydrocortisone (4-8mg/kg x 1, then 2-4mg/kg six hourly).
- Ipratropium bromide nebulisation (Dose = 250-500µg every 4-6 hours)
- Reassess clinical condition every 20 minutes and if no improvement
- Magnesium sulphate 50mg/kg over 20-30 minutes
- Reassess clinical condition every 20 minutes.
- If no improvement
 - IV β₂ agonists or IV aminophylline
 - Salbutamol load 5µg/kg over 1 hour followed by a continuous infusion 1-10µg /kg/min.
 - Aminophylline load 5mg/kg over 20 minutes followed by a continuous infusion 0.5-1mg/kg/hour.
 - Need ECG and K⁺ monitoring if on IV β₂ agonists.
 - Consider non invasive positive pressure ventilation (BiPAP)
 - Mechanical ventilation

References

1. Bohn D, Kissoon N. Acute asthma. *Pediatr Crit Care Med* 2001; **2**:151–63.
2. Sears MR, Rea HH. Patients at risk for dying of asthma: New Zealand experience. *J Allergy Clin Immunol* 1987; **80**:477–81.
3. Centers for Disease Control and Prevention. Asthma mortality and hospitalization among children and young adults-United States, 1980-93. *Morb Mortal Wkly Rep* 1996; **45**(17): 350-3.
4. Bauer JH. Recent asthma updates in the USA & UK. *Arch Dis Child Ed Pract* 2008; **93**: 66-8.
5. Michael TB, Richard JB. Status asthmaticus. In: Nichols DG, editor. *Roger Textbook of Paediatric Intensive Care*, 4th ed.. Lippincott Williams & Wilkins; 2008.
6. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: Prevalence, health care utilization, and mortality. *Pediatrics* 2002; **110**: 315-22.
7. Strunk RC. Asthma deaths in childhood: Identification of patients at risk and intervention. *J Allergy Clin Immunol*. 1987; **80**: 472–7.
8. Keller K, Sran S, Laszlo D, et al. Acute asthma management in children: Factors identifying patients at risk for intensive care unit treatment. *J Asthma*. 1994; **31**:393–400.
9. Wheeler DS, Page K, Shanley P. Status asthmaticus. in: Wheeler DS, Wong HR, Shanley P, editors. *Paediatric Critical Care Medicine Basic Science and Clinical Evidence*. London: Springer-Verlag; 2007.
10. Chedevergne F, Le Bourgeois M, de Blic J, et al: The role of inflammation in childhood asthma. *Arch Dis Child* 2000; **82**(Suppl 2): 116–9.
11. Oddo M, Feihl F, Denise M, Perret C. Management of mechanical ventilation in acute severe asthma: practical aspects. *Intensive Care Med* 2006; **32**:501–10.
12. Rodriguez-Roisin R. Acute severe asthma: Pathophysiology and pathobiology of gas exchange abnormalities. *Eur Respir J* 1997; **10**:1359–71.
13. Mountain RD, Heffner JE, Brackett NC, et al. Acid-base disturbances in acute asthma. *Chest* 1990; **98**:651–5.
14. Appel D, Rubenstein R, Schrager K, et al. Lactic acidosis in severe asthma. *Am J Med* 1983; **75**:580–4.
15. West JB, editor. *Respiratory Physiology: The Essentials*: 8th ed. Baltimore: Lippincott Williams & Wilkins; 2008.
16. Phelan PD. Management of acute life-threatening asthma in children. *Med J Aust* 1985; **143**:455–7.
17. Becker JM, Arora A, Scarfone RJ, et al. Oral versus intravenous corticosteroids in children hospitalized with asthma. *J Allergy Clin Immunol* 1999; **103**:586.
18. Rachelefsky G. Treating exacerbations of asthma in children: The role of systemic corticosteroids. *Pediatrics*. 2003; **112**:382.
19. Katz, RW, Kelly, HW, Crowley, MR, et al. Safety of continuous nebulized Albuterol for bronchospasm in infants and children. *Pediatrics* 1993; **92**: 666.
20. Bohn, D, Kalloghlian, A, Jenkins, J, et al. Intravenous salbutamol in the treatment of status asthmaticus in children. *Crit Care Med* 1984; **12**:892-6.
21. Cheong B, Reynolds SR, Rajan G, et al. Intravenous beta agonist in severe acute asthma. *BMJ*. 1988; **297**:448–50.
22. Aubier M, Roussos C: Effect of theophylline on respiratory muscle function. *Chest*. 1985; **88** (Suppl 2): 91S-97S.
23. Goodman DC, Littenberg B, O'Connor GT, et al. Theophylline in acute childhood asthma: A meta-analysis of its efficacy. *Pediatr Pulmonol* 1996; **21**: 211–8.
24. British National Formulary (BNF) for Children. London: BMJ Publishing Group; 2009.
25. Lanes SF, Garrett JE, Wentworth CE, et al: The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: A

- pooled analysis of three trials. *Chest* 1998; **114**:365–72.
26. Schuh S, Johnson DW, Callahan S, et al. Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. *J Pediatr*. 1995; **126**: 639–45.
 27. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. *Emerg. Med. J.* 2007; **24**: 823-30.
 28. Okayama H, Okayama M, Aikawa T, et al. Treatment of status asthmaticus with intravenous magnesium sulfate. *J Asthma*. 1991; **28**: 11–17.
 29. Abd-Allah SA, Rogers MS, Terry M, et al. Helium-oxygen therapy for paediatric acute severe asthma requiring mechanical ventilation. *Pediatr Crit Care Med* 2003; **4**: 353-7.
 30. Marc G, Forel JM. Use of helium-oxygen in critically ill patients. *Critical Care* 2006; **10**: 241-3.
 31. Tobias JD. Heliox in children with airway obstruction. *Pediatr Emerg Care*. 1997; **13**:29–32.
 32. Thill PJ, McGuire JK, Baden HP, et al. Non-invasive positive-pressure ventilation in children with lower airway obstruction. *Pediatr Crit Care Med*. 2004; **5**:408-9.
 33. Levy BD, Kitch B, Fanta CH. Medical and ventilatory management of status asthmaticus. *Intensive Care Med* 1998; **24**:105–17.
 34. Werner, HA. Status asthmaticus in children. *Chest*. 2001; **119**:1913-29.
 35. Shekerdemian L, Bohn D: Cardiovascular effects of mechanical ventilation. *Arch Dis Child*. 1999; **80**:475–80.
 36. Edmunds AT, Godfrey S. Cardiovascular response during severe acute asthma and its treatment in children. *Thorax*. 1981; **36**: 534–40.
 37. Jain S, Hanania NA, Guntupalli KK. Ventilation of patients with asthma and obstructive lung disease. *Crit Care Clin*. 1998; **14**:685–705.
 38. Strube PJ, Hallam PL. Ketamine by continuous infusion in status asthmaticus. *Anaesthesia*. 1986; **41**:1017–9.
 39. O'Rourke PP, Crone RK. Halothane in status asthmaticus. *Crit Care Med*. 1982; **10**: 341–3.
 40. Oymar K, Halvorsen T. Emergency presentation and management of acute severe asthma in children. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2009; **17**:757-68