

# Management of severe asthma exacerbation in children

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**Background:** Asthma is a common disease in children and acute severe asthma exacerbation can be life-threatening. This article aims to review recent advances in understanding of risk factors, pathophysiology, diagnosis and treatment of severe asthma exacerbation in children.

**Data sources:** Articles concerning severe asthma exacerbation in children were retrieved from PubMed. Literatures were searched with MeSH words "asthma", "children", "severe asthma exacerbation" and relevant cross references.

**Results:** Severe asthma exacerbation in children requires aggressive treatments with  $\beta_2$ -agonists, anticholinergics, and corticosteroids. Early initiation of inhaled  $\beta$ -agonists and systemic use of steroids are recommended. Other agents such as magnesium and aminophylline have some therapeutic benefits. When intubation and mechanical ventilation are needed, low tidal volume, controlled hypoventilation with lower-than-traditional respiratory rates and permissive hypercapnia can be applied.

**Conclusions:** Researchers should continue to detect the risk factors, pathophysiology, diagnosis and treatment of severe asthma exacerbation in children. More studies especially randomized controlled trials are required to evaluate the efficacy and safety of standard and new therapies.

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**Key words:** asthma;  
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## Introduction

Asthma is a common chronic disease in childhood. In China, there are about 10 million children suffering from asthma. Data from the Asthma Insights and Reality in Asia-Pacific (ARIAP) revealed that the control of asthma was not satisfactory in big cities in China such as Shanghai, Beijing, and Guangzhou.<sup>[1]</sup> Each year, over one third of children with asthma require urgent care, emergency room visits, or hospitalization.<sup>[2]</sup> The crude death rate of patients with asthma was 2.45/100 000 during 2004-2005 in China. The standard death rate of asthmatic patients was 2.14/100 000. The mortality of patients with asthma was similar in both rural and urban areas.<sup>[3]</sup>

Acute severe asthma exacerbation is defined as a condition with progressive respiratory failure due to asthma, refractory to conventional medical therapies with inhaled bronchodilators and systemic use of corticosteroids.<sup>[4,5]</sup> It is a common cause of admission to pediatric intensive care units.<sup>[6]</sup> In some cases, it can be life-threatening.<sup>[7,8]</sup> In clinical practice, if a patient does not respond to initial doses of nebulized bronchodilators, he/she should be considered to have severe asthma exacerbation and be treated immediately.<sup>[9]</sup>

## Risk factors

Risk factors for severe asthma exacerbation include poor compliance with asthma treatment,<sup>[10]</sup> inadequate severity assessment of acute exacerbation, improper therapy including excessive use of  $\beta_2$ -agonists and undertreatment,<sup>[11]</sup> concomitant use of  $\beta_2$ -blockers, failure to prescribe or use inhaled corticosteroids as a maintenance therapy, food allergy, specific comorbid factors,<sup>[12]</sup> and past history of severe exacerbations.<sup>[13,14]</sup> It should be noticed that children with asthma at any level, even those classified as mild intermittent ones may have acute severe exacerbation.<sup>[15,16]</sup> Becker et al<sup>[17]</sup> reported that one third of children who died from acute severe asthma exacerbation only had mild asthma and were not classified with "high risk" by any available criteria.

## Pathophysiology

Asthma is characterized by reversible, diffuse lower-airway

obstruction, caused by bronchial smooth muscle spasm, airway epithelium damage, mucous hypersecretion and increased capillary permeability.<sup>[18]</sup> Persistent inflammation and profound remodeling exist in severe asthma. The main histological features of chronic inflammation and remodeling include macrophage and lymphocyte infiltration, fibroblast proliferation, angiogenesis, fibrosis, and tissue destruction.<sup>[19]</sup> In fatal asthma, these processes are found not only in large but also in small airways.<sup>[20]</sup> Neutrophils are prominent in airway secretions during acute severe asthma exacerbation, and they play an important role in the initiation and resolution of the attacks.<sup>[21]</sup> However, the mechanisms of neutrophilia in acute asthma exacerbation have not been clarified.

Hypoxemia, hypercapnia, lactic acidosis, and dynamic hyperinflation are relevant pathophysiological events. Smooth muscle bronchoconstriction, airway edema and inflammation result in airway occlusion. Mucus plugs form the pathologic basis of gas-exchange abnormalities and lead to the development of extensive intrapulmonary shunting. Inhomogeneous distribution of areas of premature airway closure and obstruction cause ventilation/perfusion mismatching, thus resulting in hypoxemia and acidosis. In patients with severe respiratory acidosis caused by hypercapnia, metabolic acidosis may coexist. It may be related to diaphragmatic fatigue or the excessive use of  $\beta_2$ -agonists.<sup>[22]</sup> Elevated negative intrapleural pressure causes increased ventricular afterload and favors transcapillary filtration of fluid into airspaces, which at last leads to ventilation/perfusion mismatching and a high risk for pulmonary edema.<sup>[23]</sup> Right-ventricular afterload may increase as a result of the pulmonary hypertension caused by lung hyperinflation. In advanced stages, the absence of pulsus paradoxus indicates ventilatory muscle fatigue and impending respiratory failure.<sup>[24]</sup>

## Clinical features

### Symptoms

The symptoms of severe asthma exacerbation consist of cough, wheezing, dyspnea and anxiety. Patients are diaphoretic at rest, unable to lie in supine and talk with sentences or phrases. Critical cases are featured with apparent cyanosis, obtundation and cardiopulmonary dysfunction. Drowsiness and confusion are ominous signs of imminent respiratory arrest.<sup>[9]</sup>

### Signs

Central cyanosis, use of accessory respiratory muscles and audible wheezing, are often presented in children with severe asthma exacerbation. In some cases, the airway may be too limited to produce wheezing, and the only diagnostic clue on auscultation may be globally reduced breath sound with prolonged expiration. Signs of tachycardia and pulsus paradoxus from the cardiovascular system indicate significant obstruction of airways and ventilatory muscle fatigue.<sup>[23,25]</sup>

## Laboratory findings

### Arterial blood gas analysis

Hypoxia is a universal finding during early stage of severe attacks ( $\text{PaO}_2 < 60$  mmHg, oxygen saturation  $< 95\%$ ). Most individuals may have hypocapnia and respiratory alkalosis caused by compensatory hyperventilation. As disease progresses, metabolic acidosis presents, either alone or as part of a mixed acidosis.<sup>[4]</sup> In acutely ill patients, the transition from hypocapnia to normocapnia tends to be associated with severe obstruction and may indicate the need for mechanical ventilation.

**Table 1.** Classification of asthma exacerbation severity in the emergency care settings

Clinical features	Mild	Moderate	Severe	Respiratory arrest imminent
Breathlessness	While walking	While at rest	While at rest	While at rest
Talks in	Sentences	Phrases	Words	Unable
Alertness	May be agitated	Agitated	Agitated	Drowsy
Respiratory rate	Increased	Increased	Obviously increased	Slow or irregular
Use of accessory muscles	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Pulse rate	Increased	Increased	Obviously increased	Slow or irregular
Wheezing	Moderate, only end expiratory	Loud, throughout exhalation	Loud, throughout inhalation and exhalation	Absence
PEF (predicted or personal best)	$> 80\%$	$60\% - 80\%$	$< 60\%$ or response lasts $< 2$ h	$< 33\%$
$\text{PaO}_2$ (kPa)	Normal	$\geq 8$	$< 8$	Respiratory failure
$\text{PCO}_2$ (kPa)	$< 6$	$< 6$	$\geq 6$	Respiratory failure
$\text{SaO}_2$ (on air)	$> 0.95$	$0.92 - 0.95$	$0.90 - 0.92$	$< 0.90$

Normal rates of breathing in awaking children:  $< 2$  mon:  $< 60$ /min; 2–12 mon:  $< 50$ /min; 1–5 y:  $< 40$ /min; 6–8 y:  $< 30$ /min. Normal pulse rates in awaking children: 2–12 mon:  $< 160$ /min; 1–2 y:  $< 120$ /min; 2–8 y:  $< 110$ /min. PEF: peak expiratory flow;  $\text{PaO}_2$ : partial pressure of oxygen in arterial blood;  $\text{SaO}_2$ : saturation of  $\text{O}_2$  in artery.

## Pulmonary function

Pulmonary function test helps to assess the degree of airflow obstruction. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio are used to evaluate the severity of asthma. Peak expiratory flow rate (PEFR) less than 50% of the predicted value indicates a severe airflow obstruction, and less than 33% of the predicted value suggests a high risk for the development of hypercapnia and hypoxemia.<sup>[8]</sup> The classification of the severity of asthma exacerbation in the emergency care setting is shown in Table 1.

## Treatment

### General management

Children with severe exacerbations of asthma must be treated in a comfortable and supportive environment. In general, mild exacerbations may be managed at home, whereas serious attacks may require Emergency

Department (ED) visits or hospital admissions. Those with most severe exacerbations should be admitted into the intensive care unit (ICU) for optimal monitoring and treatment.

Correction of hypoxemia by using supplemental oxygen is of paramount importance. Humidified high-flow oxygen via a nasal cannula or face masks should be given to maintain oxygen saturation above 94% in patients.<sup>[26]</sup> Initial concentration of supplemental oxygen is suggested to be 40%, with a constant flow rate of 4-5 L/min. Pulse oximetry, arterial blood gas and serum electrolytes measurements are necessary. Sedatives are contraindicated for those who are not intubated. A schematic procedure for treatment of asthma in EDs and hospitals is presented in the Fig.

### Pharmacologic agents

#### $\beta_2$ -agonists

Rapid-acting  $\beta_2$ -agonists are crucial in severe asthma exacerbation, which are always the first choice to

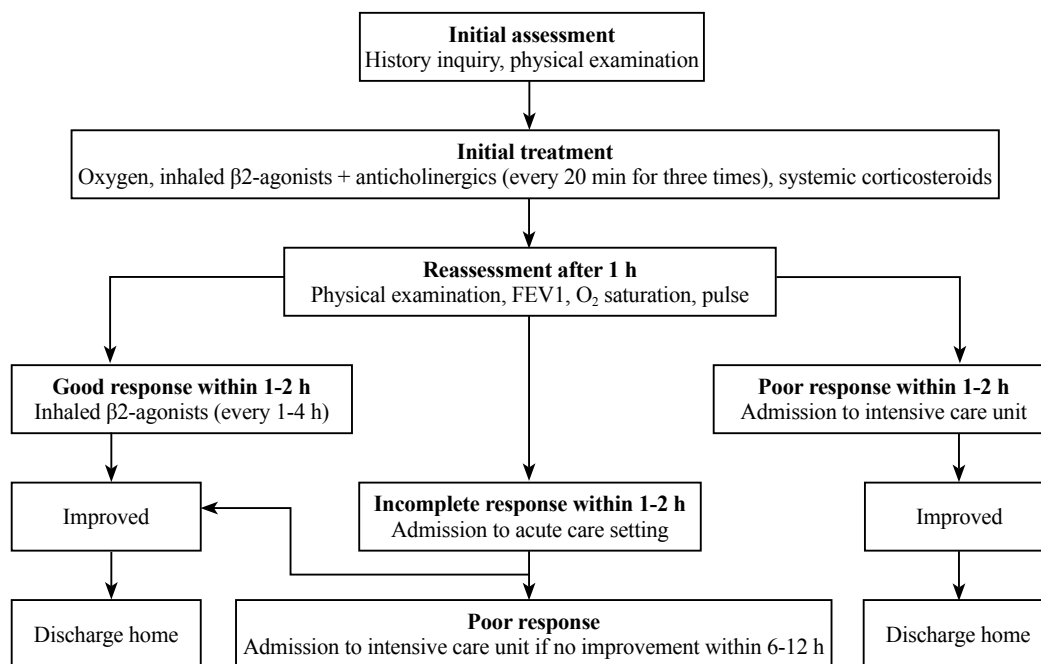


Fig. Management of asthma exacerbations: emergency department and hospital-based care. FEV1: forced expiratory volume in one second.

Table 2. Dosages of drugs for the treatment of asthma exacerbations in patients of different ages

Drugs	<2 y	2-5 y	>5 y
Short-acting $\beta_2$ -agonists	2.5 mg salbutamol by nebulizer every 20 min for the first hour, then every 1-4 h as needed	2.5 mg salbutamol by nebulizer every 20 min for the first hour, then every 1-4 h as needed	2.5-5 mg salbutamol by nebulizer every 20 min for the first hour, then every 1-4 h as needed
Ipratropium (in combination with $\beta_2$ -agonists)	250 $\mu$ g	250 $\mu$ g	250-500 $\mu$ g
Systemic corticosteroids	Oral prednisolone (1-2 mg/kg daily for up to 3 d) Intravenous methylprednisolone (0.5-2 mg/kg every 4-6 h)	Oral prednisolone (1-2 mg/kg daily for 3-10 d) Intravenous methylprednisolone (0.5-2 mg/kg every 4-6 h)	Oral prednisolone (1-2 mg/kg daily for 3-10 d) Intravenous methylprednisolone (0.5-2 mg/kg every 4-6 h)

quickly relieve acute bronchoconstriction.<sup>[27,28]</sup> They produce airway dilation through stimulation of  $\beta_2$ -adrenergic receptors and activation of G proteins with resultant formation of cyclic adenosine monophosphate (AMP). Rapid efficacy, flexibility of dose, and good clinical-effect-to-adverse-effect ratio are their advantages.<sup>[29]</sup>

The most frequently used agent is albuterol. Conventional or racemic albuterol is a 50/50 mixture of R-albuterol and S-albuterol. Levalbuterol is an isomer of racemic albuterol. It is the pure formulation of R-albuterol.<sup>[30]</sup> Comparing levalbuterol with racemic albuterol in children showed inconsistent results. Some studies<sup>[31-33]</sup> showed that levalbuterol provided greater bronchodilation and significantly reduced hospital admissions compared with racemic albuterol, while the others<sup>[34-36]</sup> showed similar efficacy and adverse effects. Further studies are needed before definitive recommendation of evalbuterol in severe cases.

Continuous or intermittent administration of nebulized short-acting  $\beta_2$ -agonists remains the first line and most effective therapy for reversing airflow obstruction. Oxygen with a flow rate of 6-8 L/min should be used as a driving force for nebulization in patients with severe hypoxemia. Within the first hour,  $\beta_2$ -agonists can be inhaled every 20 minutes for three times, followed by once every 1 to 4 hours according to the patient's condition. For intermittent nebulization, the recommended dosages are 2.5 mg to 5 mg of salbutamol according to the patient's age (Table 2). For continuous nebulization, salbutamol is used at a rate of 0.5 mg/kg per hour.<sup>[25]</sup> Earlier studies<sup>[37-40]</sup> suggested that continuous nebulization might be more effective in most severe cases, but could be more expensive. However, a systematic review of randomized controlled trials of acute asthma in adults failed to identify any significant differences in lung function or hospital admission rates between continuous and intermittent strategy.<sup>[41]</sup>

If nebulizer is not available, rapid-acting  $\beta_2$ -agonists can be inhaled by pressurized metered-dose inhaler with a spacer.<sup>[42-44]</sup> It can be given from one single puff (100  $\mu$ g salbutamol or the equivalent) every one minute to a total of 4-10 puffs each time.<sup>[45]</sup> The dose interval is the same as nebulization.<sup>[46,47]</sup>

There are arguments about whether routine use of intravenous  $\beta_2$ -agonists in patients with severe asthma exacerbation is beneficial.<sup>[48]</sup> Intravenous use of  $\beta_2$ -agonists can be considered in patients who appear to have no response to nebulization, but this case is not common. The recommended dosage for intravenous injection of salbutamol is 15  $\mu$ g/kg. The injection should be given slowly over 10 minutes.<sup>[49]</sup> For very severe exacerbations, when continuous intravenous infusion is necessary, the recommended dosages are 1 to 2  $\mu$ g/kg per minute, no

more than 5  $\mu$ g/kg per minute.<sup>[50]</sup> For children of 5 years old or younger, an intravenous bolus of 5  $\mu$ g/kg salbutamol can be given over 5 minutes, followed by continuous infusion of 5  $\mu$ g/kg per hour. The dosage should be adjusted according to clinical effects and side effects.<sup>[26]</sup> Severe adverse effects of intravenous  $\beta_2$ -agonist include arrhythmia, hypokalemia and so on. The utility and dosages must be strictly controlled. Electrocardiogram, serum electrolytes and blood gas measurement must be followed up.

### **Epinephrine**

A subcutaneous injection of epinephrine can be used when nebulized  $\beta_2$ -adrenergic agonists do not work or are not available. Epinephrine acts rapidly both on  $\alpha$ - and  $\beta_2$ -adrenergic receptors. Close clinical observation is necessary for preventing cardiovascular side effects. The recommended dose of subcutaneous injection of 1:1000 epinephrine is 0.01 mL/kg and the maximum dose is less than 0.3 mL each time for children.<sup>[51]</sup>

### **Corticosteroids**

Systemic corticosteroids as first-line agents for the treatment of severe asthma exacerbation<sup>[52]</sup> should be administered in most cases.<sup>[23]</sup> They accelerate resolution of exacerbations, prevent relapse and reduce mortality. Corticosteroids inhibit airway inflammation, decrease airway hyperresponsiveness, normalize ciliated cell to goblet cell ratio, and increase the effects of  $\beta_2$ -agonists.<sup>[53]</sup> They should be used in the early stage as their effects are usually seen within several hours.<sup>[53,54]</sup> The commonly used intravenous steroid agents include hydrocortisone and methylprednisolone, with recommended dosages of 4 to 8 mg/kg and 0.5 to 2.0 mg/kg respectively every 4 to 6 hours.<sup>[45,50]</sup> When the exacerbation is under control, they can be replaced by oral prednisone. The duration of corticosteroids therapy depends on the severity of exacerbations. If long-time treatment with corticosteroids is required, slow dosage taper is recommended.<sup>[9,51]</sup>

High-doses of corticosteroids for inhalation help to relieve severe asthma exacerbation. Increasing evidence indicates that inhalation of high-dose corticosteroids (ICS) is beneficial when it is initiated early.<sup>[55-57]</sup> However, data on ICS in children are inconsistent.<sup>[58]</sup> A meta-analysis showed that inhaled steroids reduced admission rates of patients with acute asthma. But it is unclear whether there are benefits of inhaled corticosteroids except those of systemic corticosteroids. No sufficient evidence shows that inhaled corticosteroids alone are as effective as systemic steroids.<sup>[59]</sup> Currently we can not replace oral systemic corticosteroids with ICS, or suggest the use of high-dose ICS in ED for children.<sup>[9]</sup> The effect of high-dose ICS in the treatment of acute asthma is poorly

understood. ICS may inhibit vascular mucosal vessel leakage.<sup>[60]</sup> The dose of budesonide is 0.5-1 mg each time.<sup>[45]</sup> But in critical situation, systemic corticosteroids should not be fully replaced by ICS.

### **Anticholinergics**

Anticholinergic agents reverse acute bronchospasm via inhibition of M-receptor. They are now an integral part of the treatment of severe asthma exacerbation in children,<sup>[27]</sup> as accumulating evidence suggest that anticholinergic agents are useful adjuncts to inhaled  $\beta_2$ -agonists when used in severe asthma exacerbation.<sup>[61,62]</sup> Anticholinergic agents should be used early for patients intolerable to  $\beta_2$ -agonists, but not as a monotherapy for severe asthma exacerbations. The recommended dose of ipratropium is 250  $\mu$ g to 500  $\mu$ g in combination with  $\beta_2$ -agonist.<sup>[63,64]</sup> The dose interval is similar to that of inhaled  $\beta_2$ -agonist.<sup>[26,51]</sup>

### **Aminophylline**

The effect of theophylline in the treatment of children with severe asthma remains controversial. Most studies<sup>[65-68]</sup> showed that theophylline had no efficacy but increased toxicity in children hospitalized for severe asthma. Recently, theophylline has been found to be of therapeutic value. Intravenous aminophylline can be used as an add-on therapy for children with severe asthma exacerbation.<sup>[69-71]</sup>

Adverse effects of aminophylline need to be monitored closely in addition to its serum levels. Guidelines recommend the use of aminophylline only in severe patients without response to  $\beta_2$ -agonists and steroids in ICU, who can be closely monitored.<sup>[26,51]</sup> The loading dose of aminophylline is suggested as 4-6 mg/kg (maximum 250 mg) infused over 20-30 minutes, followed by 0.6-1 mg/kg per hour for different age groups. If oral aminophylline has been given, a maintaining dose can be infused constantly. Intermittent infusion of 4-6 mg/kg aminophylline every 6-8 hours can be an alternative.<sup>[45,50]</sup>

### **Magnesium sulfate**

Magnesium is recommended for the treatment of acute asthma exacerbations. For those who are not responsive to the initial treatment, intravenous injection of magnesium may decrease the possibility of intubation.<sup>[9,51]</sup> Magnesium inhibits calcium uptake and relaxes smooth muscle. In severe acute asthma attacks, intravenous injection of magnesium improves pulmonary function in addition to conventional treatments.<sup>[72]</sup> The recommended dose is 25-40 mg/kg per day (maximum 2 g/d) for 20 minutes.<sup>[45,50]</sup> It can be used for 1-3 days. Adverse effects include epigastric or facial warmth, flushing, pain and numbness at the infusion site, dry mouth, malaise, and

hypotension. Overdose toxicity can be treated with 10% calcium gluconate.<sup>[73,74]</sup>

### **Heliox**

Heliox is a 70:30 mixture of helium to oxygen and is less viscous than ambient air. It can reduce breathing or propel therapeutic aerosols more efficiently. Heliox-driven nebulization can be used in patients with life-threatening attacks. It is most effective when used early in acute attacks. Heliox is used to relieve respiratory distress, decrease breathing, and improve gas exchange,<sup>[75-77]</sup> but not to critical asthmatic patients.<sup>[78-80]</sup> Heliox may be effective to relieve severe asthma attacks.<sup>[81,82]</sup>

### **Omalizumab**

Omalizumab, a humanized monoclonal antibody against IgE, is clinically efficacious. It is capable of improving quality of life of patients with severe persistent allergic asthma which is inadequately controlled by available asthma medications.<sup>[83-85]</sup> Omalizumab in treatment of severe allergic asthma has reduced use of corticosteroids and symptoms.<sup>[86,87]</sup> It is not recommended as a routine treatment for children with severe asthma exacerbation in most guidelines all over the world.

### **TNF- $\alpha$ antagonists**

Patients with severe refractory asthma treated with TNF- $\alpha$  antagonists have shown improvement of lung function and airway hyper-responsiveness.<sup>[88]</sup> Treatment with infliximab can reduce the episodes of moderate exacerbations,<sup>[89,90]</sup> but TNF- $\alpha$  antagonists are only used in patients with increased TNF axis.<sup>[91]</sup> Effects and safety of TNF- $\alpha$  antagonists in asthma patients need to be further clarified.

### **Intubation and mechanical ventilation**

If patient's condition continues to deteriorate after treatment with oxygen, inhaled  $\beta_2$ -agonist and systemic corticosteroids, mechanical ventilation is recommended.<sup>[92]</sup> Mechanical ventilation aims to prevent the progressive exhaustion of respiratory muscles, reduce oxygen consumption, increase lung volume, raise exhalant CO<sub>2</sub> and inhaled O<sub>2</sub>, improve cardiopulmonary function, and clear airway secretions. Intubation is usually carried out via the orotracheal route.<sup>[51]</sup>

Indications for intubation and mechanical ventilation are as follows: (1) apnea or respiratory arrest; (2) diminished or absent breathing sound or absent wheezing; (3) limitation of chest movement because of over-ventilation and airway muscle fatigue; (4) drowsiness or confusion, irritation or repression, even coma; (5) progressive central cyanosis despite supplemental oxygen; and (6) PaCO<sub>2</sub>  $\geq$  65 mmHg.<sup>[93]</sup>

Volume-control mode is recommended at the

beginning of ventilation as appearance of severe respiratory muscles fatigue in children with acute asthma exacerbation. Some patients may benefit from use of positive end-expiratory pressure.<sup>[94,95]</sup>

Great care should be taken to avoid higher airway pressure which may lead to barotraumas.<sup>[96]</sup> On account of the principle of controlled hypoventilation with lower-than-conventional respiratory rates and tidal volumes, permissive hypercapnia can be applied.<sup>[97]</sup> The patient can tolerate high levels of PCO<sub>2</sub> as long as oxygenation is maintained at an adequate level.

Noninvasive ventilation (NIV) has been used to improve gas exchange and to treat respiratory failure in a variety of conditions. It has been proved to be well tolerated and can improve subjective and objective measures of respiratory dysfunction in children with severe asthma exacerbation.<sup>[98-100]</sup> It was reported that bilevel positive airway pressure (BiPAP) in conjunction with  $\beta$ 2-agonist therapy in treating children with severe asthma exacerbation was safe and well tolerated. This intervention serves as an adjunct to conventional treatments.<sup>[101]</sup> Also nebulization coupled with NIV in patients with acute asthma was found to be effective to reduce bronchial obstruction and symptoms secondary to augmented peak expiratory flow compared with nebulization in spontaneous breathing. In reversing bronchial obstruction, this combination appears to be more efficacious when a low pressure delta is used in combination with a high positive pressure at the end of expiration.<sup>[102]</sup> These findings however should be confirmed by prospective investigations. Large, prospective, randomized controlled trials are needed to determine the role of NIV in children with severe asthma exacerbation.<sup>[103,104]</sup>

In children receiving mechanical ventilation, sedatives and neuromuscular blockade may be used to reduce agitation, decrease intrinsic airway pressure, increase lung compliance, reduce barotraumas, improve circling condition, and increase cardiac output. Ketamine, the dissociative anesthetic agent, may be very useful as an induction agent for intubation in children with severe asthma exacerbation who require mechanical ventilation.<sup>[105,106]</sup> It may diminish the bronchoconstrictor response to insertion of an endotracheal tube.<sup>[23]</sup> It is given usually with an intravenous bolus of 0.2 mg/kg followed by a continuous infusion of 0.5 to 2 mg/kg per hour.<sup>[107,108]</sup>

Neuromuscular blockers such as pancuronium and vecuronium may be useful to prevent large fluctuation in airway pressure, reduce oxygen consumption, CO<sub>2</sub> production, and lactic acid accumulation.<sup>[109]</sup> These agents can lead to muscular weakness, hypersecretion of airway mucous, histamine release, tachycardia and hypotension.<sup>[110,111]</sup> They should be used with great caution.

## Other therapies

The balance of fluid and electrolytes should be maintained. Acid-base disturbance should be corrected promptly especially in younger children. Most children with severe asthma are dehydrated on admission because of poor fluid intake, vomiting and increased insensible fluid loss from the respiratory tract. Since secretion of anti-diuretic hormone can be seen in children with severe asthma exacerbation, daily physiological supplements should be given with caution after dehydration is corrected. Excessive fluid replacement can lead to pulmonary edema. Changes in intrapleural pressure can cause increased ventricular afterload and increase the burden of the heart. If heart failure occurs, therapy with digitalis should be cautious and the dose of cardiotonic agent should be adjusted carefully as the patient may be more vulnerable to toxic effects under hypoxemia. Because asthma exacerbations are usually triggered by virus infection,<sup>[112,113]</sup> antibiotics are not recommended as a routine therapy. If there are definite signs of bacterial infection, appropriate antimicrobial treatment is necessary.<sup>[114]</sup>

## Conclusions

The burden of severe asthma exacerbation is high. Early recognition and timely intervention are crucial to decrease the mortality and morbidity of severe attacks. Inhaled  $\beta$ 2-agonists, corticosteroids and anticholinergic agents are first-line drugs for severe asthma exacerbation, and magnesium is effective for critically ill patients. Aminophylline is not suggested unless in ICU setting. If intubation and mechanical ventilation are necessary, low tidal volume, controlled hypoventilation with lower-than-conventional respiratory rates and permissive hypercapnia can be used. Noninvasive ventilation, heliox, sedatives and neuromuscular blockers should be used cautiously. Further investigation of risk factors, pathophysiology, early diagnosis and treatment of severe asthma exacerbation in children are needed.

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