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 β2-agonists, anticholinergics, and corticosteroids. Early initiation of inhaled β-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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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.[1] Each year, over one third of children with asthma require urgent care, emergency room visits, or hospitalization.[2] 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.[3]

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.[4,5] It is a common cause of admission to pediatric intensive care units.[6] In some cases, it can be life-threatening.[7,8] 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.[9]

Risk factors

Risk factors for severe asthma exacerbation include poor compliance with asthma treatment,[10] inadequate severity assessment of acute exacerbation, improper therapy including excessive use of β_2-agonists and undertreatment,[11] concomitant use of β_2-blockers, failure to prescribe or use inhaled corticosteroids as a maintenance therapy, food allergy, specific comorbid factors,[12] and past history of severe exacerbations.[13,14] It should be noticed that children with asthma at any level, even those classified as mild intermittent ones may have acute severe exacerbation.[15,16] Becker et al[17] 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.[18] 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.[19] In fatal asthma, these processes are found not only in large but also in small airways.[20] 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.[21] 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 β2-agonists.[22] 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.[23] 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.[24]

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.[9]

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.[23,25]

Laboratory findings

Arterial blood gas analysis

Hypoxia is a universal finding during early stage of severe attacks (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.[4] 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%
PaO_2 (kPa)	Normal	≥8	<8	Respiratory failure
PCO_2 (kPa)	<6	<6	≥6	Respiratory failure
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; PaO_2: partial pressure of oxygen in arterial blood; SaO_2: saturation of 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.[8] The classification of the severity of asthma exacerbation in the emergency care setting is shown in Table 1.

Treatment

General management

Childen 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.[26] 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

β2-agonists

Rapid-acting β2-agonists are crucial in severe asthma exacerbation, which are always the first choice to

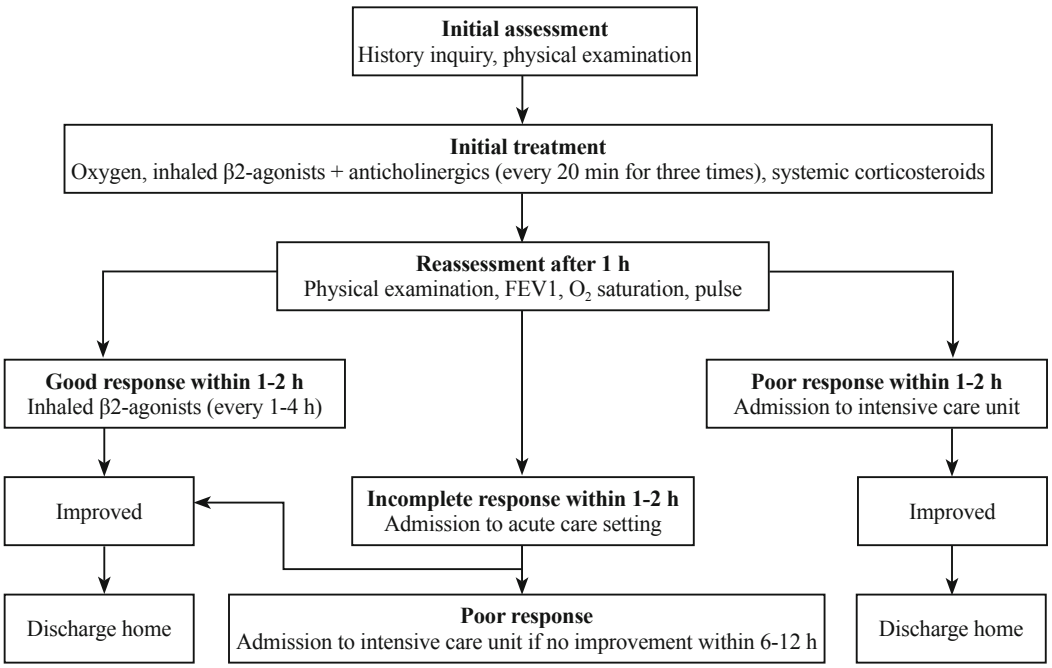

Fig. Management of asthma exacerbations: emergency department and hospital-based care. FEV1: forced expiratory volume in one second.

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 β2-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 β2-agonists)	250 μg	250 μg	250-500 μg
Systemic corticosteroids	Oral prednisolone (1-2 mg/kg daily for up to 3 d)	Oral prednisolone (1-2 mg/kg daily for 3-10 d)	Oral prednisolone (1-2 mg/kg daily for 3-10 d)
	Intravenous methylprednisolone (0.5-2 mg/kg every 4-6 h)	Intravenous methylprednisolone (0.5-2 mg/kg every 4-6 h)	Intravenous methylprednisolone (0.5-2 mg/kg every 4-6 h)

quickly relieve acute bronchoconstriction.[27,28] They produce airway dilation through stimulation of β2-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.[29]

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.[30] Comparing levalbuterol with racemic albuterol in children showed inconsistent results. Some studies[31-33] showed that levalbuterol provided greater bronchodilation and significantly reduced hospital admissions compared with racemic albuterol, while the others[34-36] 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 β2-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, β2-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.[25] Earlier studies[37-40] 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.[41]

If nebulizer is not available, rapid-acting β2-agonists can be inhaled by pressurized metered-dose inhaler with a spacer.[42-44] It can be given from one single puff (100 μg salbutamol or the equivalent) every one minute to a total of 4-10 puffs each time.[45] The dose interval is the same as nebulization.[46,47]

There are arguments about whether routine use of intravenous β2-agonists in patients with severe asthma exacerbation is beneficial.[48] Intravenous use of β2-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 μg/kg. The injection should be given slowly over 10 minutes.[49] For very severe exacerbations, when continuous intravenous infusion is necessary, the recommended dosages are 1 to 2 μg/kg per minute, no more than 5 μg/kg per minute.[50] For children of 5 years old or younger, an intravenous bolus of 5 μg/kg salbutamol can be given over 5 minutes, followed by continuous infusion of 5 μg/kg per hour. The dosage should be adjusted according to clinical effects and side effects.[26] Severe adverse effects of intravenous β2-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 β2-adrenergic agonists do not work or are not available. Epinephrine acts rapidly both on α- and β2-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.[51]

Corticosteroids

Systemic corticosteroids as first-line agents for the treatment of severe asthma exacerbation[52] should be administered in most cases.[23] 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 β2-agonists.[53] They should be used in the early stage as their effects are usually seen within several hours.[53,54] 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.[45,50] 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.[9,51]

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.[55-57] However, data on ICS in children are inconsistent.[58] 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.[59] Currently we can not replace oral systemic corticosteroids with ICS, or suggest the use of high-dose ICS in ED for children.[9] The effect of high-dose ICS in the treatment of acute asthma is poorly

understood. ICS may inhibit vascular mucosal vessel leakage.[60] The dose of budesonide is 0.5-1 mg each time.[45] 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,[27] as accumulating evidence suggest that anticholinergic agents are useful adjuncts to inhaled β2-agonists when used in severe asthma exacerbation.[61,62] Anticholinergic agents should be used early for patients intolerable to β2-agonists, but not as a monotherapy for severe asthma exacerbations. The recommended dose of ipratropium is 250 μg to 500 μg in combination with β2-agonist.[63,64] The dose interval is similar to that of inhaled β2-agonist.[26,51]

Aminophylline

The effect of theophylline in the treatment of children with severe asthma remains controversial. Most studies[65-68] 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.[69-71]

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 β2-agonists and steroids in ICU, who can be closely monitored.[26,51] 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.[45,50]

Magnesium sulfate

Magnesium is recommended for the treatment of acute asthma exacerbations. For those who are not responsible to the initial treatment, intravenous injection of magnesium may decrease the possibility of intubation.[9,51] 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.[72] The recommended dose is 25-40 mg/kg per day (maximum 2 g/d) for 20 minutes.[45,50] 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.[73,74]

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,[75-77] but not to critical asthmatic patients.[78-80] Heliox may be effective to relieve severe asthma attacks.[81,82]

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.[83-85] Omalizumab in treatment of severe allergic asthma has reduced use of corticosteroids and symptoms.[86,87] It is not recommended as a routine treatment for children with severe asthma exacerbation in most guidelines all over the world.

TNF-α antagonists

Patients with severe refractory asthma treated with TNF-α antagonists have shown improvement of lung function and airway hyper-responsiveness.[88] Treatment with infliximab can reduce the episodes of moderate exacerbations,[89,90] but TNF-α antagonists are only used in patients with increased TNF axis.[91] Effects and safety of TNF-α 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 β2-agonist and systemic corticosteroids, mechanical ventilation is recommended.[92] Mechanical ventilation aims to prevent the progressive exhaustion of respiratory muscles, reduce oxygen consumption, increase lung volume, raise exhalant CO_2 and inhalant O_2, improve cardiopulmonary function, and clear airway secretions. Intubation is usually carried out via the orotracheal route.[51]

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) $PaCO_2 \geq 65$ mmHg.[93]

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.[94,95]

Great care should be taken to avoid higher airway pressure which may lead to barotraumas.[96] On account of the principle of controlled hypoventilation with lower-than-conventional respiratory rates and tidal volumes, permissive hypercapnia can be applied.[97] The patient can tolerate high levels of PCO_2 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.[98-100] It was reported that bilevel positive airway pressure (BiPAP) in conjunction with β2-agonist therapy in treating children with severe asthma exacerbation was safe and well tolerated. This intervention serves as an adjunct to conventional treatments.[101] 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.[102] 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.[103,104]

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.[105,106] It may diminish the bronchoconstrictor response to insertion of an endotracheal tube.[23] 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.[107,108]

Neuromuscular blockers such as pancuronium and vecuronium may be useful to prevent large fluctuation in airway pressure, reduce oxygen consumption, CO_2 production, and lactic acid accumulation.[109] These agents can lead to muscular weakness, hypersecretion of airway mucous, histamine release, tachycardia and hypotension.[110,111] 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,[112,113] antibiotics are not recommended as a routine therapy. If there are definite signs of bacterial infection, appropriate antimicrobial treatment is necessary.[114]

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 β2-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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References

1 Chen YZ. Prevention and treatment of childhood asthma in China. World J Pediatr 2005;1:85-87.

2 Masoli M, Fabian D, Holt S, Beasley R. Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-478.
3 Hu N, Huang ZJ, Jiang Y, Wu F. Mortality and death cause proportion of respiratory disease in China, 2004-2005. Zhonghua Yu Fang Yi Xue Za Zhi 2010;44:298-302.
4 Cohen NH, Eigen H, Shaughnessy TE. Status asthmaticus. Crit Care Clin 1997;13:459-476.
5 Papiris SA, Manali ED, Kolilekas L, Triantafillidou C, Tsangaris I. Acute severe asthma: new approaches to assessment and treatment. Drugs 2009;69:2363-2391.
6 Carroll CL, Smith SR, Collins MS, Bhandari A, Schramm CM, Zucker AR. Endotracheal intubation and pediatric severe asthma exacerbation: site of original care affects treatment. Pediatr Crit Care Med 2007;8:91-95.
7 D'Orio V, Ghuysen A, Lambermont B. Acute exacerbation of asthma: a disease that still remains life-threatening. Rev Med Liege 2009;64:377-381.
8 Buysse CM, de Jongste JC, de Hoog M. Life-threatening asthma in children: treatment with sodium bicarbonate reduces PCO_2. Chest 2005;127:866-870.
9 National Asthma Education and Prevention Program. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol 2007;120:S94-138.
10 Chiang BL, Hsieh CT, Wang LC, Lee JH, Yu HH, Lin YT, et al. Clinical course and outcome of children with status asthmaticus treated in a pediatric intensive care unit: a 15-year review. J Microbiol Immunol Infect 2009;42:488-493.
11 Malmström K, Kaila M, Kajosaari M, Syvänen P, Juntunen-Backman K. Fatal asthma in Finnish children and adolescents 1976-1998. Pediatr Pulmonol 2007;42:210-215.
12 Subrata LS, Bizzintino J, Mamessier E, Bosco A, McKenna KL, Wikström ME, et al. Interactions between innate antiviral and atopic immunoinflammatory pathways precipitate and sustain asthma exacerbations in children. J Immunol 2009;183:2793-2800.
13 Federico MJ, Wamboldt FS, Carter R, Mansell A, Wamboldt MZ. History of serious asthma exacerbations should be included in guidelines of asthma severity. J Allergy Clin Immunol 2007;119:50-56.
14 ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005;26:812-818.
15 Romagnoli M, Caramori G, Braccioni F, Ravenna F, Barreiro E, Siafakas NM, et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. Clin Exp Allergy 2007;37:552-557.
16 Carroll CL, Schramm CM, Zucker AR. Severe exacerbations in children with mild asthma: characterizing a pediatric phenotype. J Asthma 2008;45:513-517.
17 Becker JM, Rogers J, Rossini G, Mirchandani H, D'Alonzo GE Jr. Asthma deaths during sports: report of a 7-year experience. J Allergy Clin Immunol 2004;113:264-267.
18 Frieri M. Asthma concepts in the new millennium: update in asthma pathophysiology. Allergy Asthma Proc 2005;26:83-88.
19 Constantino, Gde T, Mello Jr JF. Remodeling of the lower and upper airways. Braz J Otorhinolaryngol 2009;75:151-156.
20 Louis R. Severe asthma: how can we differentiate phenotypes? Swiss Med Wkly 2009;139:274-277.
21 Fahy JV. Eosinophilic and neutrophilic inflammation in asthma: insights from clinical studies. Proc Am Thorac Soc 2009;6:256-259.
22 Rodriguez-Roisin R. Acute severe asthma: pathophysiology and pathobiology of gas exchange abnormalities. Eur Respir J 1997;10:1359-1371.
23 Werner HA. Severe asthma exacerbation in children: a review. Chest 2001;119:1913-1929.
24 Restrepo RD, Peters J. Near-fatal asthma: recognition and management. Curr Opin Pulm Med 2008;14:13-23.
25 NIH, 2007. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf (accessed July 13, 2010).
26 Global Initiative for Asthma, 2009. Global strategy for the diagnosis and management of asthma in children 5 years and younger. http://www.ginasthma.org/guidelines-global-strategy-for-the-diagnosis.html (accessed May 23, 2010).
27 Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, et al. European Pediatric Asthma Group. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy 2008;63:5-34.
28 Lazarus SC. Emergency treatment of asthma. N Engl J Med 2010;363:755-764
29 Kercsmar CM. Current trends in management of pediatric asthma. Respir Care 2003;48:194-205.
30 Nelson HS, Bensch G, Pleskow WW, DiSantostefano R, DeGraw S, Reasner DS, et al. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. J Allergy Clin Immunol 1998;102:943-952.
31 Carl JC, Myers TR, Kirchner HL, Kercsmar CM. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. J Pediatr 2003;143:731-736.
32 Delmotte P, Sanderson MJ. Effects of albuterol isomers on the contraction and Ca2+ signaling of small airways in mouse lung slices. Am J Respir Cell Mol Biol 2008;38:524-531.
33 Nowak R. Single-isomer levalbuterol: a review of the acute data. Curr Allergy Asthma Rep 2003;3:172-178.
34 Andrews T, McGintee E, Mittal MK, Tyler L, Chew A, Zhang X, et al. High-dose continuous nebulized levalbuterol for pediatric status asthmaticus: a randomized trial. J Pediatr 2009;155:205-210.
35 Qureshi F, Zaritsky A, Welch C, Meadows T. Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. Ann Emerg Med 2005;46:29-36.
36 Hardasmalani MD, DeBari V, Bithoney WG, Gold N. Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. Pediatr Emerg Care 2005;21:415-419.
37 Ibsen LM, Bratton SL. Current therapies for severe asthma exacerbations in children. New Horiz 1999;7:312-325.
38 Montgomery VL, Eid NS. Low-dose β-agonist continuous nebulization therapy for status asthmaticus in children. J Asthma 1994;31:201-207.
39 Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. Crit Care Med 1993;21:1479-1486.
40 Ackerman AD. Continuous nebulization of inhaled β-agonists for status asthmaticus in children: a cost-effective therapeutic advance? Crit Care Med 1993;21:1422-1424.
41 Rodrigo GJ, Rodrigo C. Continuous *vs* intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. Chest 2002;122:160-165.
42 Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. J Pediatr 2004;145:172-177.

43 Deerojanawong J, Manuyakorn W, Prapphal N, Harnruthakorn C, Sritippayawan S, Samransamruajkit R. Randomized controlled trial of salbutamol aerosol therapy via metered dose inhaler-spacer *vs.* jet nebulizer in young children with wheezing. Pediatr Pulmonol 2005;39:466-472.
44 Delgado A, Chou KJ, Silver EJ, Crain EF. Nebulizers *vs* metered-dose inhalers with spacers for bronchodilator therapy to treat wheezing in children aged 2 to 24 months in a pediatric emergency department. Arch Pediatr Adolesc Med 2003;157:76-80.
45 Subspecialty Group of Respiratory Diseases Society of Pediatrics; Chinese Medical Association; Chinese Journal of Pediatrics Editorial Board. Guideline for the diagnosis and optimal management of asthma in children. Zhonghua Er Ke Za Zhi 2008;46:745-753.
46 Cates CC, Bara A, Crilly JA, Rowe BH. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev 2003;(3):CD000052.
47 Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. American College of Chest Physicians; American College of Asthma, Allergy, and Immunology. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005;12:335-371.
48 Global Initiative for Asthma, 2009. Global Strategy for Asthma Management and Prevention. http://www.ginasthma.org/guidelines-gina-report-global-strategy-for-asthma.html (accessed February 1, 2010).
49 Browne GJ, Trieu L, Van Asperen P. Randomized, double-blind, placebo-controlled trial of intravenous salbutamol and nebulized ipratropium bromide in early management of severe acute asthma in children presenting to an emergency department. Crit Care Med 2002;30:448-453.
50 Subspecialty Group of Respiratory Diseases, Pediatric Society, Chinese Medical Association and Editorial Board, Chinese Journal of Pediatrics, Chinese Medical Association. Diagnosis and treatment of critical status of asthma in children. Zhonghua Er Ke Za Zhi 2004;42:106-107.
51 British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. Thorax 2008;63:iv1-121.
52 Biarent D. Therapeutic strategies in near fatal asthma in children. Pediatr Pulmonol Suppl 2001;23:90-93.
53 Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. N Engl J Med 2000;343:689-694.
54 Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev 2001;(1):CD002178.
55 Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. Chest 2004;125:1081-1102.
56 Razi CH, Turktas I, Bakirtas A. Comparison of single 2000-microg dose treatment *vs.* sequential repeated-dose 500-microg treatments with nebulized budesonide in acute asthma exacerbations. Ann Allergy Asthma Immunol 2008;100:370-376.
57 Nuhoglu Y, Bahçeciler NN, Barlan IB, Mujdat Başaran M. The effectiveness of high-dose inhaled budesonide therapy in the treatment of acute asthma exacerbations in children. Ann Allergy Asthma Immunol 2001;86:318-322.
58 Rowe BH, Edmonds ML, Spooner CH, Diner B, Camargo CA Jr. Corticosteroid therapy for acute asthma. Respir Med 2004;98:275-284.
59 Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database Syst Rev 2003;(3):CD002308.
60 Volovitz B. Inhaled budesonide in the management of acute worsenings and exacerbations of asthma: a review of the evidence. Respir Med 2007;101:685-695.
61 Rodrigo GJ, Rodrigo C. First-line therapy for adult patients with acute asthma receiving a multiple-dose protocol of ipratropium bromide plus albuterol in the emergency department. Am J Respir Crit Care Med 2000;161:1862-1868.
62 Gelb AF, Karpel J, Wise RA, Cassino C, Johnson P, Conoscenti CS. Bronchodilator efficacy of the fixed combination of ipratropium and albuterol compared to albuterol alone in moderate-to-severe persistent asthma. Pulm Pharmacol Ther 2008;21:630-636.
63 Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax 2005;60:740-746.
64 Kohistani TA. Acute severe asthma; salbutamol plus ipratropium bromide nebulization versus salbutamol nebulization alone. Professional Med J 2007;14:586-590.
65 Mitra A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Cochrane Database Syst Rev 2005;(2):CD001276.
66 Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Cochrane Database Syst Rev 2000;(4):CD002742.
67 Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. Am Rev Respir Dis 1985;132:283-286.
68 Rodrigo C, Rodrigo G. Treatment of acute asthma. Lack of therapeutic benefit and increase of the toxicity from aminophylline given in addition to high doses of salbutamol delivered by metered-dose inhaler with a spacer. Chest 1994;106:1071-1076.
69 Wheeler DS, Jacobs BR, Kenreigh C, Bean J. Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. Pediatr Crit Care Med 2005;6:142-147.
70 Mitra A, Bassler D, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over 2 years using inhaled bronchodilators. Cochrane Database Syst Rev 2001;(4):CD001276.
71 Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. Arch Dis Child 1998;79:405-410.
72 Noppen M. Magnesium treatment for asthma: where do we stand? Chest 2002;122:396-398.
73 Bichara MD, Goldman RD. Magnesium for treatment of asthma in children. Can Fam Physician 2009;55:887-889.
74 Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. Arch Dis Child 2005;90:74-77.
75 Manthous CA, Hall JB, Melmed A, Caputo MA, Walter J, Klocksieben JM, et al. Heliox improves pulsus paradoxus and peak expiratory flow in nonintubated patients with severe asthma. Am J Respir Crit Care Med 1995;151:310-314.
76 Gupta VK, Cheifetz IM. Heliox administration in the pediatric intensive care unit: an evidence-based review. Pediatr Crit Care Med 2005;6:204-211.

77 Kim IK, Phrampus E, Venkataraman S, Pitetti R, Saville A, Corcoran T, et al. Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: a randomized, controlled trial. Pediatrics 2005;116:1127-1133.
78 Rodrigo GJ, Rodrigo C, Pollack CV, Rowe B. Use of helium-oxygen mixtures in the treatment of acute asthma: a systematic review. Chest 2003;123:891-896.
79 Rodrigo GJ, Pollack CV, Rodrigo C, Rowe BH. Heliox for non-intubated acute asthma patients. Cochrane Database Syst Rev 2006;(18):CD002884.
80 Ho J, Bender BG, Gavin LA, O'Connor SL, Wamboldt MZ, Wamboldt FS. Relations among asthma knowledge, treatment adherence, and outcome. J Allergy Clin Immunol 2003;111:498-502.
81 Sridharan G, Tassaux D, Chevrolet JC. Heliox in acute severe asthma. Rev Med Suisse 2007;3:2849-2850, 2852-2854.
82 Manthous CA. Heliox for status asthmaticus? Chest 2003;123:676-677.
83 Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254-261.
84 D'Amato G, Salzillo A, Piccolo A, D'Amato M, Liccardi G. A review of anti-IgE monoclonal antibody (omalizumab) as add on therapy for severe allergic (IgE-mediated) asthma. Ther Clin Risk Manag 2007;3:613-619.
85 Jones J, Shepherd J, Hartwell D, Harris P, Cooper K, Takeda A, et al. Omalizumab for the treatment of severe persistent allergic asthma. Health Technol Assess 2009;13:31-39.
86 Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF. Efficacy and safety of a recombinant anti immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy 2004;34:632-638.
87 Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of antiimmunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy 2004;59:701-708.
88 Berry M, Brightling C, Pavord I, Wardlaw A. TNF-alpha in asthma. Curr Opin Pharmacol 2007;7:279-282.
89 Erin EM, Leaker BR, Nicholson GC, Tan AJ, Green LM, Neighbour H, et al. The effects of a monoclonal antibody directed against tumor necrosis factor-alpha in asthma. Am J Respir Crit Care Med 2006;174:753-762.
90 Matera MG, Calzetta L, Cazzola M. TNF-alpha inhibitors in asthma and COPD: we must not throw the baby out with the bath water. Pulm Pharmacol Ther 2010;23:121-128.
91 Gjurow D, Grzelewski T, Sobocińska A, Stelmach I. Tumor necrosis factor inhibitors in pediatric asthma. Recent Pat Inflamm Allergy Drug Discov 2009;3:143-148.
92 Marik PE, Varon J, Fromm R Jr. The management of acute severe asthma. J Emerg Med 2002;23:257-268.
93 Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 1997. Expert panel report 2: guidelines for the diagnosis and management of asthma. http://www.ncbi.nlm.nih.gov/books/NBK2358/ (accessed June 23, 2010).
94 Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989;140:5-10.
95 Stather DR, Stewart TE. Clinical review: mechanical ventilation in severe asthma. Crit Care 2005;9:581-587.
96 Georgopoulos D, Kondili E, Prinianakis G. How to set the ventilator in asthma. Monaldi Arch Chest Dis 2000;55:74-83.
97 Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 1984;129:385-387.
98 Gupta D, Nath A, Agarwal R, Behera D. A prospective randomized controlled trial on the efficacy of noninvasive ventilation in severe acute asthma. Respir Care 2010;55:536-543.
99 Thill PJ, McGuire JK, Baden HP, Green TP. Noninvasive positive-pressure ventilation in children with lower airway obstruction. Pediatr Crit Care Med 2004;5:337-342.
100 Carroll CL, Schramm CM. Noninvasive positive pressure ventilation for the treatment of severe asthma exacerbation in children. Ann Allergy Asthma Immunol 2006;96:454-459.
101 Beers SL, Abramo TJ, Bracken A, Wiebe RA. Bilevel positive airway pressure in the treatment of severe asthma exacerbation in pediatrics. Am J Emerg Med 2007;25:6-9.
102 Brandao DC, Lima VM, Filho VG, Silva TS, Campos TF, Dean E, et al. Reversal of bronchial obstruction with bi-level positive airway pressure and nebulization in patients with acute asthma. J Asthma 2009;46:356-361.
103 Scala R. Noninvasive ventilation in severe acute asthma? Still far from the truth. Respir Care 2010;55:630-637.
104 Ram FS, Wellington S, Rowe B, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database Syst Rev 2005;(20):CD004360.
105 Nehama J, Pass R, Bechtler-Karsch A, Steinberg C. Continuous ketamine infusion for the treatment of refractory asthma in a mechanically ventilated infant: case report and review of the pediatric literature. Pediatr Emerg Care 1996;12:294-297.
106 Youssef-Ahmed MZ, Silver P, Nimkoff L, Sagy M. Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm. Intensive Care Med 1996;22:972-976.
107 Allen JY, Macias CG. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. Ann Emerg Med 2005;46:43-50.
108 Howton JC, Rose J, Duffy S, Zoltanski T, Levitt MA. Randomized,double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. Ann Emerg Med 1996;27:170-175.
109 Phipps P, Garrard CS. The pulmonary physician in critical care 12: acute severe asthma in the intensive care unit. Thorax 2003;58:81-88.
110 Griffin D, Fairman N, Coursin D, Rawsthorne L, Grossman JE. Acute myopathy during treatment of status asthmaticus with corticosteroids and steroidal muscle relaxants. Chest 1992;102:510-514.
111 Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. Am J Respir Crit Care Med 1996;153:1686-1690.
112 Sly PD, Kusel M, Holt PG. Do early-life viral infections cause asthma? J Allergy Clin Immunol 2010;125:1202-1205.
113 Vallet C, Pons-Catalano C, Mandelcwajg A, Wang A, Raymond J, Lebon P, et al. Human bocavirus: a cause of severe asthma exacerbation in children. J Pediatr 2009;155:286-288.
114 Blasi F, Cosentini R, Tarsia P, Allegra L. Potential role of antibiotics in the treatment of asthma. Curr Drug Targets Inflamm Allergy 2004;3:237-242.

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