

## Severe Acute Asthma Exacerbation in Children: A Stepwise Approach for Escalating Therapy in a Pediatric Intensive Care Unit

I. Federico Fernandez Nievas, MD and Kanwaljeet J. S. Anand, MBBS, DPhil, FRCPC

Departments of Pediatrics, Anesthesiology, Anatomy & Neurobiology, Division of Critical Care Medicine, University of Tennessee Health Science Center, and Le Bonheur Children's Hospital, Memphis, Tennessee

**OBJECTIVES** An increasing prevalence of pediatric asthma has led to increasing burdens of critical illness in children with severe acute asthma exacerbations, often leading to respiratory distress, progressive hypoxia, and respiratory failure. We review the definitions, epidemiology, pathophysiology, and clinical manifestations of severe acute asthma, with a view to developing an evidence-based, stepwise approach for escalating therapy in these patients.

**METHODS** Subject headings related to asthma, status asthmaticus, critical asthma, and drug therapy were used in a MEDLINE search (1980-2012), supplemented by a manual search of personal files, references cited in the reviewed articles, and treatment algorithms developed within Le Bonheur Children's Hospital.

**RESULTS** Patients with asthma require continuous monitoring of their cardiorespiratory status via non-invasive or invasive devices, with serial clinical examinations, objective scoring of asthma severity (using an objective pediatric asthma score), and appropriate diagnostic tests. All patients are treated with  $\beta$ -agonists, ipratropium, and steroids (intravenous preferable over oral preparations). Patients with worsening clinical status should be progressively treated with continuous  $\beta$ -agonists, intravenous magnesium, helium-oxygen mixtures, intravenous terbutaline and/or aminophylline, coupled with high-flow oxygen and non-invasive ventilation to limit the work of breathing, hypoxemia, and possibly hypercarbia. Sedation with low-dose ketamine (with or without benzodiazepines) infusions may allow better toleration of non-invasive ventilation and may also prepare the patient for tracheal intubation and mechanical ventilation, if indicated by a worsening clinical status.

**CONCLUSIONS** Severe asthma can be a devastating illness in children, but most patients can be managed by using serial objective assessments and the stepwise clinical approach outlined herein. Following multidisciplinary education and training, this approach was successfully implemented in a tertiary-care, metropolitan children's hospital.

**INDEX TERMS** asthma, child, critical care, infant, respiratory failure, status asthmaticus

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### INTRODUCTION

Asthma is one of the most common chronic diseases in childhood, with increasing prevalence in the past 3 decades. The severity of asthma can range from mild to severe; however, despite the degree of severity all patients are at risk for

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developing an acute severe asthma exacerbation. This review is focused on the treatment of acute asthma exacerbation in the pediatric intensive care setting with the application of a stepwise approach according to the severity and progression

of the exacerbation, calculated with a pediatric asthma score<sup>1</sup> that has been implemented in our institution, Le Bonheur Children's Hospital, Pediatric Intensive Care.

### DEFINITION

Severe acute asthma is defined as a condition in which children with acute asthma exacerbation and respiratory distress do not respond to bronchodilators and who either have not received corticosteroids as an outpatient or continue to experience respiratory distress despite outpatient treatment. The severity of these episodes varies

from mild to severe and each episode has the potential to progress to respiratory failure.<sup>2</sup> Severe acute asthma is currently the most common medical emergency in children and is responsible for nearly half a million admissions to the pediatric intensive care unit (PICU) each year.<sup>1,3,4</sup>

Different terms have been described for severe acute asthma exacerbation, which include *status asthmaticus*, *near-fatal asthma*, *sudden asphyxic asthma*, and *acute fatal asthma*. Status asthmaticus refers to an acute asthma exacerbation in which bronchial obstruction is severe and continues to worsen or not improve despite the institution of adequate standard therapy, leading to respiratory failure. Near-fatal asthma was described as an asthma exacerbation of sudden onset that rapidly progresses to hypercapnia and hypoxemia, leading to respiratory arrest. The near-fatal attribute of the exacerbation was due to the severe asphyxia rather than cardiac arrhythmias.<sup>5,6</sup> Sudden asphyxic asthma was characterized in a group of young patients presenting with rapid decompensation in less than 3 hours after onset of symptoms, severe hypercapnia, silent chest, and high incidence of respiratory arrest.<sup>7</sup> Acute fatal asthma was reported when respiratory failure and death occurred within minutes of the exacerbation onset.<sup>8</sup>

## EPIDEMIOLOGY

Recently, the National Center of Health Statistics reported that the asthma prevalence for the year 2009 in the United States was 8.2%, affecting 24.6 million people of all ages.<sup>9</sup> When discriminated by age, 17.5 million adults and 7.1 million children (0-17 years) were affected. The asthma exacerbation prevalence, defined as the proportion of the affected population with at least 1 attack in the previous year, was 4.2% of a total of 12.8 million people, of which 4.0 million were children.

Asthma prevalence increased from 2001 to 2009 at an annual rate of 1.2%. However, asthma exacerbation prevalence did not increase significantly during 1997-2009 (3.9%-4.3%). This trend could be explained by the distribution of national asthma guidelines focusing on preventive treatment as well as more effective clinical management.<sup>4,9-11</sup>

Age group, sex, race, ethnicity and socioeconomic factors play a major role in asthma

prevalence, health care use, and mortality.<sup>12-14</sup> Among patients aged 0 to 17 years, males have higher prevalence than females: 11.3% and 7.9%, respectively. Also, children have higher current asthma prevalence: 9.6% as compared to 7.7% in adults. Compared with the white population, the prevalence is higher among African Americans and lower for Asians.<sup>15</sup> Compared with non-Hispanic whites and non-Hispanic blacks, the current asthma prevalence is higher among Puerto Ricans and lower among Mexican ethnic groups.<sup>16,17</sup> The population with a family income below the federal poverty level has higher asthma prevalence than the population with incomes near or above the poverty threshold.<sup>9</sup> In the 2009 American Community Survey, 14.3% of the United States population had incomes below their respective poverty thresholds, providing a population at risk for the environmental factors associated with increased prevalence of asthma.<sup>12</sup>

Children aged 5 to 17 years missed 10.5 million school days owing to asthma, and activity limitations were reported in 5.5% as well. There were 1.75 million total emergency department (ED) visits, including 0.64 million for children aged 0 to 17 years. Total asthma-related hospitalizations were 456,000, of which 157,000 were children. During 2007, there were 3447 deaths due to asthma, and 185 were for children aged 0 to 17 years. Asthma deaths for children and adults younger than 35 years for that year was 3.4 per million.<sup>9,19</sup>

## PATHOPHYSIOLOGY

Asthma involves inflammation and edema of the bronchial mucosa, increased mucus production with airway plugging, and bronchospasm.<sup>20,21</sup> These factors produce increased airway resistance, leading to increased work of breathing. As the degree of airway obstruction progresses, expiration becomes active and inspiration starts before termination of the previous expiration, resulting in air trapping and hyperinflation. Areas of obstruction and premature airway closure cause ventilation/perfusion mismatch,<sup>22</sup> leading to hypoxemia.<sup>23</sup>

During a severe asthma exacerbation, the marked changes in lung volume and pleural pressures have a significant impact on cardiopulmonary interactions. Dynamic hyperinflation with progressive increased lung volumes stretches the

pulmonary vasculature, increasing pulmonary vascular resistance and right ventricular afterload. Pulmonary vasoconstriction, secondary to hypoxia and acidosis, further contributes to the increase in right ventricular afterload.<sup>24</sup> The high negative pulmonary pressures generated during inspiration in spontaneously breathing patients causes an increased left ventricular afterload<sup>25</sup> and decreased cardiac output with exaggerated decrease in systolic blood pressure during inspiration.<sup>26</sup> A decrease in systolic blood pressure by more than 10 mm Hg during inspiration is termed *pulsus paradoxus*.<sup>27</sup> The negative intrapleural pressure generated favors transcapillary fluid edema to the alveolar space.<sup>28</sup>

There appear to be 2 subsets of children who die from severe acute asthma, perhaps representing some differences in their pathophysiology.<sup>29</sup> Some children with fatal asthma have a long history of poorly controlled severe asthma, often with a previous history of respiratory failure (type 1, or slow onset-late arrival). This pattern of fatal asthma, responsible for most asthma-related deaths, is generally considered preventable, with death occurring owing to acute respiratory failure and asphyxia, or from complications associated with mechanical ventilation.<sup>6,30-35</sup> Pathologic examination in these cases demonstrates extensive bronchial mucus plugging, edema, and eosinophilic infiltrations of the airways.

Alternatively, some children present with a history of mild asthma, or even without a prior history of asthma. These patients experience a sudden onset of bronchospasm and rapidly progress to cardiac arrest and death (type 2, or fast-onset, asthma).<sup>7,34,36,37</sup> If recognized and managed early, these children respond faster to  $\beta$ -agonists and mechanical ventilatory support than children with type 1 fatal asthma.<sup>38</sup> Pathologic examination of these cases shows empty airways devoid of mucus plugging with a greater proportion of neutrophils and eosinophils.<sup>37,39</sup>

Robertson et al<sup>40</sup> reviewed 51 pediatric deaths from asthma in Australia between 1986 and 1999, and found that nearly one-third of these children were judged to have mild asthma with no prior hospitalizations. In the final acute exacerbation, 63% of these children experienced a sudden onset and collapse within minutes of the beginning of symptoms, and 75% died before reaching a hospital. Only 25% of these children had an acute progression of chronic, poorly controlled asthma

that resulted in eventual death. These authors concluded that 39% of these deaths would have been preventable with earlier recognition and intervention.

During a 6-year period at The Hospital for Sick Children in Toronto, 89 children were admitted to the PICU for severe acute asthma. Three children died in the PICU from hypoxic ischemic encephalopathy following out-of-hospital cardiac arrest.<sup>41</sup> Kravis and Kolski<sup>42</sup> reported a case series of 13 deaths secondary to asthma. Only 1 child died after admission to the hospital. Similarly, nearly 50% of asthmatic children in another study died before reaching the hospital, with the time from the onset of symptoms to death being less than 1 hour in 21%, and less than 2 hours in 50% of these cases, respectively.<sup>43,44</sup> Thus, these case series underscore the need for early recognition of children at risk for type 2 fast-onset, sudden asphyxial asthma.

## CLINICAL MANIFESTATIONS

Children with severe acute asthma commonly present with tachypnea, increased work of breathing, use of accessory muscles, nasal flaring, diaphoresis, and anxiety. They may also present obtunded, in respiratory failure, or cardiopulmonary arrest.

Wheezing is a common clinical finding in patients with acute asthma exacerbation, which is generated by turbulent airflow in the intrathoracic obstructed airways. The degree of wheezing correlates poorly with the severity of disease,<sup>45</sup> because wheezes are heard only in the presence of airflow. The presence of silent chest due to limited airflow is an ominous sign of impending respiratory failure. Wheezing is predominantly expiratory owing to the dynamic compression of the airways, but also can be biphasic and usually is symmetrical; an asymmetrical distribution should alert a clinician for the presence of atelectasis, pneumothorax, or foreign body.

Evaluating disease severity and response to therapy objectively are most important. A number of authors<sup>46-48</sup> have developed clinical asthma scores. Clinical scores have been shown to correlate with the need for hospitalization and prolonged bronchodilator therapy, and with the severity of an exacerbation.<sup>49</sup> However, they are not as effective at predicting disease progression and prolonged hospitalization.<sup>50,51</sup>

The implementation of an inpatient clinical pathway correlated with the pediatric asthma score in hospitalized asthmatic children could lead to a decrease in length of stay and a reduction in total cost with overall improving quality of care.<sup>1</sup> Because early recognition is important for improving outcomes, various authors<sup>13,52-54</sup> have attempted to define the risk factors for fatal asthma. These may include, among other factors:

1. History of previous asthma exacerbation with:
  - a. Severe, rapid progression of symptoms
  - b. Respiratory failure requiring endotracheal intubation or ventilatory support
  - c. Seizures or loss of consciousness
  - d. PICU admission
2. Denial or failure to perceive the severity of illness
3. Non-compliance with controller medications or asthma care plan
4. Lack of social supports or safety network (e.g., dysfunctional family, poverty)
5. Associated psychiatric disorder, for example, depression
6. African American and Hispanic children

### CHEST RADIOGRAPHY

Chest radiography is not routinely indicated in a child with previous history of asthma.<sup>55,56</sup> Potential indications for chest radiography may include clinical suspicion for pneumothorax, atelectasis, foreign body aspiration, or after endotracheal intubation.

### ARTERIAL BLOOD GAS

Arterial blood gas measurement provides objective information on gas exchange. Early in the course of asthma, hypoxemia and hypocapnia are found due to ventilation/perfusion mismatch and hyperventilation.<sup>57</sup> As the airflow obstruction progresses, PaCO<sub>2</sub> measurement returns to normal values, though in a tachypneic and hyperventilating child, a normal PaCO<sub>2</sub> value should be interpreted as a sign of early muscle fatigue.<sup>58</sup> Sicker patients often have a mixed respiratory and metabolic acidosis.<sup>59</sup> Lactic acidosis reflects a combination of excess production from respiratory muscles, tissue hypoxia (due to hypoxemia and decreased cardiac output), and dehydration (due to decreased intake and increased insensible

losses).<sup>60</sup> The decision to intubate a child with severe acute asthma should be based on the child's clinical status and not simply the arterial blood gas values.<sup>61</sup>

## TREATMENT

### Monitoring

Patients admitted to the PICU require intravenous access, as well as continuous monitoring of their cardiorespiratory status, including non-invasive blood pressure and oxygen saturations (SpO<sub>2</sub>). Those with respiratory failure requiring mechanical ventilation should undergo the placement of central venous, arterial, and urinary bladder catheters. These are often the sickest patients in the PICU and require expert nursing care, monitoring of fluid intake and output, and skin care to prevent decubitus ulcers, as well as frequent clinical examination.

The Pediatric Asthma Score (PAS)<sup>1</sup> has been adopted by Le Bonheur Children's Hospital for the assessment of patients with asthma exacerbation (Table 1). During patient assessment a respiratory therapist will document the PAS every 2 hours while the patient is receiving continuous albuterol treatment. Advancement in therapy to the next level will be performed when there is worsening of the PAS, using the stepwise approach (Figure).

### Oxygen

Children with severe acute asthma possibly will have ventilation/perfusion mismatch<sup>23</sup> as an effect of mucus plugging and atelectasis, causing hypoxemia. Treatment with  $\beta$ -agonists may aggravate hypoxemia by increasing cardiac output and eliminating the compensatory hypoxic pulmonary vasoconstriction.<sup>61,62</sup> Oxygen should be used as carrier gas for intermittent or continuous nebulization<sup>63</sup> and to keep oxygen saturation above 92%. There is no evidence that oxygen suppresses respiratory drive in children with severe asthma.<sup>64</sup>

### Fluids

Patients with severe acute asthma are often dehydrated because of poor oral intake and increased insensible fluid losses. Appropriate fluid resuscitation and maintenance fluids are indicated. The key is to avoid overhydration because of the increased risk of transpulmonary edema

**Table 1.** Pediatric Intensive Care Unit Pediatric Asthma Score<sup>1</sup>

Examination component	1	2	3
Respiratory rate			
1-4 y	≤34	35-39	≥40
4-6 y	≤30	31-35	≥36
6-12 y	≤26	27-30	≥31
>12 y	≤23	24-27	≥28
O <sub>2</sub> requirement	>95% on room air	90%-95% on room air	<90% on room air or any oxygen
Retractions	None or intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Work of breathing (count to 10)	Speaks in sentences, coos and babbles	Speaks in partial sentences, short cry	Speaks in single words/short phrases, grunting
Auscultation	Normal breath sounds to end-expiratory wheezes only	Expiratory wheezing	Inspiratory and expiratory wheezing to diminished breath sounds

in children with severe asthma associated with large fluctuations in intrathoracic pressures. The use of half normal saline or isotonic solution in dextrose is preferred in the pediatric population.

### Steroids


Corticosteroids are the first line of treatment for severe acute asthma, because of the inflammatory process.<sup>65</sup> Steroids control airway inflammation through a number of mechanisms,<sup>66</sup> such as reducing the number and activation of lymphocytes, eosinophils, mast cells, and macrophages; suppressing the production of cytokines, tumor necrosis factor- $\alpha$ , granulocyte-macrophage colony-stimulating factor, adhesion molecules, and inducible enzymes, including nitric oxide synthase and cyclooxygenase-2.<sup>67</sup> Mucous production is decreased, and inflammatory cell infiltration and activation are reduced.<sup>68,69</sup> In children with severe acute asthma, systemic corticosteroids are indicated and in the intensive care unit (ICU) setting the intravenous route is preferred.<sup>70</sup> Methylprednisolone is a widely used agent because of its limited mineralocorticoid effect.<sup>71</sup> The previous National Asthma Education and Prevention Program (NAEPP), still in use by some centers, recommended an initial methylprednisolone loading dose of 2 mg/kg followed by 0.5 to 1 mg/kg every 6 hours.<sup>72</sup> Nevertheless, the new dose recommendation for asthma exacerbations by the current NAEPP (2007) review is 1 to 2 mg/kg/day (maximum 60

mg/day) in 2 divided doses for children younger than 12 years, and 40 to 80 mg/day for children older than 12 years and adults given either oral or intravenous prednisolone or methylprednisolone, respectively.<sup>71-75</sup> The effect starts within 1 to 3 hours and peaks at 4 to 8 hours.<sup>76</sup> Duration of treatment depends on the severity of the asthma exacerbation. Adverse drug reactions related to the use of high-dose steroids have been described and include hyperglycemia, hypertension, and acute psychosis.<sup>77</sup> Allergic reactions have been described with the use of methylprednisolone.<sup>78</sup> The incidence of muscle weakness and myopathy is increased, especially when aminosteroid neuromuscular-blocking agents are used in combination with steroids in mechanically ventilated patients.<sup>79</sup>

### $\beta$ -Agonists

$\beta$ -Agonists are sympathomimetic agents that cause bronchodilatation due to bronchial smooth muscle relaxation by activating  $\beta$ 2-adrenergic receptors, which increase intracellular cyclic adenosine monophosphate (cAMP) concentrations within smooth muscles. The  $\beta$ 2-adrenoceptor coupling to adenylate cyclase is affected via a trimetric Gs protein with  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits.<sup>80</sup> The mechanism involved in airway smooth muscle cell relaxation is cAMP release, which catalyzes the activation of protein kinase A (PKA). PKA, in turn, phosphorylates regulatory and cytoskeletal proteins involved in the control





Step	Therapy	Comments
1	Albuterol, Ipratropium, Steroids	These medications should be ordered for all patients admitted to the PICU.
2	Continuous Albuterol	0.5-1 mg/kg/hr. If < 20 kg give 10-20 mg/hr; 20-30 kg give 10-30 mg/hr, > 30 kg give 15-45 mg/hr
3	IV Magnesium	25 to 50 mg/kg/dose (max 2 g) infused over 20 to 30 min. Follow by continuous infusion of 15-25 mg/kg/hr. Mg level $\approx$ 4 mg/dL. Monitor for hypotension.
4	Heliox	Provide O <sub>2</sub> using non-rebreathing mask. May combine O <sub>2</sub> by nasal cannula if necessary to keep SaO <sub>2</sub> > 92%.
5	IV Terbutaline	Loading dose of 10 mcg/kg over 10 min followed by 0.4 mcg/kg/min. Increase by 0.4 mcg/kg/min every 15 min. Range 0.1 to 10 mcg/kg/min (average dose is 4 mcg/kg/min)
6	IV Theophylline	Loading dose of 5 mg/kg over 20 min followed by continuous infusion of 0.5-1 mg/kg/hr. Check serum theophylline concentration 30 min after the end of the loading dose. Target theophylline concentration is 10-20 mg/L
7	Non-Invasive Ventilation	Consider BiPAP to unload WOB. IPAP:10 EPAP:5
8	IV Ketamine	1 mg/kg/hr for sedation. Bronchodilatory properties. Increase airway secretions.
9	Intubation	Ketamine + Midazolam + Rocuronium
10	Ventilation	Try to avoid neuromuscular blockade. Permissive hypercapnia. PC/PRVC/PSV. Monitor peak to plateau pressure difference.

**Figure.** Severe acute asthma stepwise approach for escalating therapy.

BiPAP, bilevel positive airway pressure; EPAP, Expiratory Positive Airway Pressure; IPAP, Inspiratory Positive Airway Pressure; Mg, Magnesium; O<sub>2</sub>, oxygen; PC, Pressure Controlled Ventilation; PRVC, Pressure Regulated Volume Control; PSV, Pressure Support Ventilation; SaO<sub>2</sub>, saturation level of oxygen; WOB, work of breathing

of muscle tone. cAMP inhibits the release of calcium ion from intracellular stores and reduces the membrane calcium entry and its intracellular sequestration, leading to airway smooth muscle relaxation.<sup>80,81</sup> Alternative, cAMP independent pathways involving the activation of membrane maxi-potassium channels through Gi to the MAP kinase system have also been described.<sup>82</sup>

The most reported adverse drug reactions with  $\beta$ -agonists are tachycardia, tremors, and nausea. Cardiovascular effects include diastolic hypotension,<sup>83</sup> arrhythmias, and prolonged QTc interval with hypokalemia.<sup>84</sup> Hypokalemia is the result of intracellular potassium shifting from an increased number of sodium-potassium pumps.<sup>85</sup>

### Albuterol

Albuterol is a 50:50 racemic mixture of R-albuterol and S-albuterol. The R-enantiomer is pharmacologically active, whereas the S-enantiomer is considered inactive and has a longer elimination

half-life. Levalbuterol is the pure R-enantiomer as a preservative-free solution. In comparison trials the use of equivalent doses of levalbuterol was not superior to albuterol.<sup>85,86</sup> Albuterol remains the drug of choice for treatment of severe acute asthma in the ICU owing to its lower cost and similar efficacy.

Continuous  $\beta_2$ -agonist nebulization is considered to be superior<sup>87</sup> or at least equivalent<sup>88</sup> to intermittent treatment<sup>89</sup> for severe asthma and was not associated with severe cardiotoxicity.<sup>90-93</sup> Transient increase in creatinine phosphokinase without evidence of cardiotoxicity during continuous albuterol nebulization has been reported.<sup>94</sup> Continuous nebulization offers more comfort to patients and is more cost-effective.<sup>95</sup> From the amount of drug that can be delivered per hour of nebulized treatment, approximately 25% of the dose will reach the lungs.<sup>96</sup> The usual dose for continuous albuterol nebulization ranges from 0.15 to 0.5 mg/kg/h. Larger doses of continuous albuterol nebulization for near-fatal asthma have

been used,<sup>97</sup> although we generally do not exceed maximum rates of 30 mg/h. In our institution we use conventional continuous-output nebulizer devices with oxygen.

### **Terbutaline**

Intravenous  $\beta_2$ -agonist should be considered in patients who are not improving with continuous albuterol nebulization,<sup>98</sup> probably owing to decreased respiratory flow and tidal volume resulting in a reduction of drug delivery to the small airways. Terbutaline is considered the drug of choice in the United States, although intravenous albuterol and other  $\beta_2$ -agonists are also available elsewhere.

Subcutaneous terbutaline is preferred because there are fewer adverse drug reactions when compared to epinephrine.<sup>99</sup> Subcutaneous terbutaline sulfate has been recommended for hospitalized children or adolescents older than 12 years with asthma exacerbation, at a dose of 0.25 mg every 20 minutes for a total of 3 doses,<sup>55</sup> as well as for children 12 years of age or younger at a dose of 0.01 mg/kg (maximum dose, 0.25 mg) every 20 minutes for a total of 3 doses, repeated every 2 to 6 hours as needed.<sup>55</sup> To accelerate the therapeutic effect, an intravenous loading dose of 2 to 10 mcg/kg infused for 10 minutes is recommended, followed by a continuous infusion of 0.1 to 10 mcg/kg/min.<sup>83</sup> Because of differences in drug metabolism and clinical effect among patients, dose adjustment should be assessed at regular intervals. Usually the starting dose is 0.4 mcg/kg/min; it is titrated to achieve the desired clinical effect with increments of 0.2 to 0.4 mcg/kg/min every 15 to 30 minutes depending on the patient's clinical response and on adverse drug reactions.<sup>100</sup> Monitoring the patient for the side effects of tachycardia, arrhythmias, diastolic hypotension, hypokalemia, or (rarely) myocardial ischemia is more important in patients receiving continuous infusions of  $\beta$ -adrenergic agonists.

### **Ipratropium**

Ipratropium bromide is a quaternary ammonium atropine derivative that does not cross the blood-brain barrier, precluding the manifestation of central anticholinergic effects. Ipratropium can produce bronchodilatation by inhibition of cholinergic-mediated bronchospasm, occurring without the inhibition of mucociliary clearance.<sup>101</sup> The parasympatholytic effect is produced by

blocking acetylcholine interaction with the muscarinic receptors on bronchial smooth muscle cells and reducing intracellular cyclic guanosine monophosphate concentrations that impair bronchoconstriction. Nebulized anticholinergic agents are considered an important adjunct in the treatment of moderate to severe asthma exacerbation in the ED setting.<sup>102-104</sup> After 1 dose of steroids, the use of ipratropium with the second and third albuterol doses was associated with clinical improvement and decreased hospital admission rates,<sup>105</sup> compared with albuterol and corticosteroids alone.<sup>106,107</sup> Nebulized ipratropium, in 0.25 to 0.50 mg doses, can be used every 20 minutes during the first hour, followed by the same dose range every 6 hours.<sup>108-110</sup> Systemic effects are usually minimal; nevertheless, mydriasis and blurred vision have been reported.<sup>111,112</sup> Although there is no significant apparent benefit with the addition of multiple doses of ipratropium to an albuterol and steroid regimen in hospitalized pediatric patients,<sup>113,114</sup> there is a need for specific data in the PICU population. With the high safety profile and documented beneficial effects in the ED setting,<sup>115</sup> we recommend its use every 6 hours in the critically ill patient owing to its potential advantages, despite not being recommended by the current National Heart, Lung, and Blood Institute asthma guidelines, until further data are obtained.<sup>55</sup>

### **Magnesium Sulfate**

Magnesium is a calcium antagonist that causes smooth muscle relaxation as a result of the inhibition of calcium uptake.<sup>116</sup> With respect to asthmatic patients, mechanisms such as the inhibitory action on smooth muscle contraction,<sup>117</sup> histamine release from mast cells,<sup>118</sup> acetylcholine release from nerve terminals,<sup>119</sup> and sedative action<sup>65,120</sup> may contribute to its therapeutic effects.

From current data, magnesium sulfate is likely to improve bronchospasm and consequent clinical symptoms and reduce hospitalization in children with moderate to severe acute asthma when added to classic therapy.<sup>121</sup> Some studies<sup>122-124</sup> have shown clinical improvement in patients with severe asthma receiving intravenous magnesium infusion.

The usual dose of magnesium sulfate in children with severe acute asthma is 25 to 50 mg/kg/dose (maximum 2 g), infused for 20 to 30 minutes.<sup>125-127</sup> A larger loading dose of magne-

sium sulfate has been recommended<sup>128</sup> to achieve serum magnesium concentrations between 3 to 5 mg/dL. For the treatment of acute asthma exacerbation refractory to conventional therapies, an initial bolus dose of 50 mg/kg (maximum dose, 2 g) infused for 20 to 30 minutes is recommended, followed by continuous infusion dependent on the patient's weight. Children weighing less than 30 kg may receive an infusion of 25 mg/kg/h and children weighing more than 30 kg may receive 20 mg/kg/h, although infusion rates must not exceed 2 g/h in any patient.<sup>129</sup> Titration to the desired clinical effect should be based on serum magnesium concentrations and tolerability. Adverse drug reactions, such as nausea, flushing, somnolence, vision changes, muscle weakness, and hypotension, were reported with magnesium concentrations above 9 mg/dL.<sup>130</sup> Severe adverse reactions such as respiratory depression and arrhythmias occurred with concentrations above 12 mg/dL.<sup>36</sup>

### **Methylxanthines**

Methylxanthines are formed by the methylation of xanthines, such as theophylline. The combination of theophylline and ethylenediamine generates a water-soluble salt, aminophylline. The proposed mechanism for bronchodilatation involves the non-selective inhibition of phosphodiesterase isoenzymes,<sup>131</sup> in particular, the inhibition of phosphodiesterase-IV, which reduces the intracellular degradation of cAMP.<sup>132</sup> Other mechanisms include increased respiratory drive and diaphragmatic contractility,<sup>133</sup> stimulation of endogenous catecholamine release,<sup>134</sup> prostaglandin antagonism,<sup>135</sup> and inhibition of afferent neuronal activity.<sup>136</sup> In addition, theophylline is known to have anti-inflammatory and immunomodulatory effects, although the contributions of these mechanisms to its therapeutic effects in children with asthma have not been studied.<sup>137,138</sup>

The therapeutic range for theophylline is narrow, 10 to 20 mcg/mL, and overlaps with toxicity concentrations, which occurs above 15 mcg/mL.<sup>139</sup> We recommend titration of dosing to a peak concentration of 10 to 15 mcg/mL. However, at a concentration above 5 mcg/mL bronchodilatory and anti-inflammatory effects were detected.<sup>140</sup> The theophylline dose is 80% of the aminophylline dose. A loading intravenous dose, 5mg/kg of theophylline or 6 mg/kg of aminophylline, given during 20 minutes is needed to

achieve a therapeutic concentration.<sup>97</sup> Assuming an average volume of distribution, 1 mg/kg of theophylline or 1.25 mg/kg of aminophylline increases serum concentration by 2 mcg/mL. After the loading dose, a continuous infusion should be started. The drug clearance is decreased in neonates and infants, and, therefore, infusion rates are based on patient age. Recommended doses for infants younger than 6 months are 0.5 mg/kg/h; for infants 6 months to 1 year, 0.85 to 1 mg/kg/h; for children 1 to 9 years, 1 mg/kg/h; and for children older than 9 years, 0.75 mg/kg/h.<sup>141</sup> These recommended doses are for patients with normal cardiac and liver functions. Serum drug concentrations should be obtained 30 to 60 minutes after the loading dose is finished, and again at 12 hours after the beginning of the continuous infusion, to check for steady-state concentrations, and then every 12 to 24 hours or when toxicity is suspected. Theophylline clearance possibly will be decreased in patients with acute pulmonary edema, congestive heart failure, cor pulmonale, fever, hepatic disease, hypothyroidism, sepsis with multiorgan failure, neonates, infants younger than 3 months with decreased renal function, children younger than 1 year, and patients after cessation of smoking or substantial second-hand smoke exposure. Many drugs decrease theophylline clearance. The most common are erythromycin, cimetidine, and oral contraceptives. Azithromycin has no effect on theophylline clearance because of the absence of interactions with cytochrome P450.<sup>142</sup>

Theophylline should be used for children with severe acute asthma exacerbation with impending respiratory failure, or those on mechanical ventilation who are already getting other bronchodilator or anti-inflammatory therapies.<sup>143,144</sup>

### **Helium-Oxygen Mixture (Heliox)**

Helium is a low-density gas that, when used in a mixture with oxygen, reduces turbulent airflow, enhancing laminar flow and in consequence reducing airflow resistance.<sup>145</sup> Limited evidence exists for the efficacy of helium-oxygen mixtures (i.e., heliox), typically 70%:30% or 79%:21%, in children with severe acute asthma. It has been demonstrated that heliox promotes a greater delivery and percentage of particle retention from nebulized albuterol.<sup>146</sup> Furthermore, a superior clinical improvement was associated with heliox use than with oxygen-driven continuous



**Table 2.** Albuterol Dosage (0.5% Albuterol, 5 mg/mL) and Mixing Proportions for Continuous Albuterol

Q1		Q2		4 h* (mL)		8 h† (mL)	
mL/h	mg	mL	mg	ALB	NS	ALB	NS
6	30	12	60	24	76	48	152
5	25	10	50	20	80	40	160
4	20	8	40	16	84	32	168
3	15	6	30	12	88	24	176
2	10	4	20	8	92	16	184

ALB, Albuterol; NS, Normal Saline (0.9%)

\* ALB + NS = 100 mL total

† ALB + NS = 200 mL total

albuterol in children with moderate to severe asthma.<sup>147</sup> Nevertheless, other studies<sup>148,149</sup> failed to show a decrease in length of hospital stay or a significant clinical improvement. Heliox reduces peak airway pressures when used in patients who require mechanical ventilation, presumably by allowing hyperinflated alveoli to decompress during expiration and reducing the functional residual capacity of patients with asthma.<sup>150</sup>

The existing evidence does not provide support for the routine use of helium-oxygen mixtures to all ED patients with acute asthma. However, new evidence suggests certain beneficial effects in patients with more severe airway obstruction.<sup>151</sup> Given the relatively small patient numbers and few studies, there is still a role for heliox trials in refractory severe acute asthma.<sup>152,153</sup>

### Ketamine

Ketamine, a non-competitive N-methyl-D-aspartate receptor antagonist, is used routinely as an anesthetic, analgesic, and sedative owing to its wide therapeutic index and favorable hemodynamic effects.<sup>154,155</sup> The bronchodilatory effects of ketamine were noted with its early use,<sup>156</sup> although a randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma showed no beneficial effects in adult patients.<sup>157</sup> Despite the current lack of high-level evidence, some studies have reported beneficial clinical effects from ketamine use in children presenting to the ED with acute asthma.<sup>158,159</sup> In critically ill children with asthma, a loading dose of ketamine (2 mg/kg) followed by continuous infusions (20-60 mcg/kg/min) significantly improved the PaO<sub>2</sub>/FiO<sub>2</sub> ratio in all patients, the dynamic compliance and PaCO<sub>2</sub>, and peak inspiratory pressures in mechanically ventilated patients.<sup>160</sup> The mean duration of ketamine infusion in this study was 40 ± 31

hours and no significant side effects were noted. Ketamine infusions have been used in patients with near-fatal asthma, in combination with other bronchodilator therapies.<sup>161</sup>

### Bilevel Positive Airway Pressure

Noninvasive positive pressure ventilation (NPPV) in addition to conventional therapy showed clinical improvement and correction of gas exchange abnormalities in children and adults with asthma.<sup>162-164</sup> NPPV was well tolerated in children, including patients as young as 1 year.<sup>164,165</sup> Utilization of NPPV in younger patients can be challenging. However, under strict monitoring, the use of a small dose of benzodiazepines or propofol with or without a low-dose ketamine infusion or dexmedetomidine may facilitate the tolerance for NPPV. Typically recommended settings include an inspiratory positive airway pressure of 10 cm H<sub>2</sub>O, an expiratory positive airway pressure of 5 cm H<sub>2</sub>O, with or without a low back-up ventilation rate. In patients with severe asthma, a low level of continuous positive airway pressure may reduce the premature airway closure point, reducing intrinsic end expiratory pressure and subsequently the inspiratory workload.<sup>166,167</sup> In addition, the use of NPPV may well improve the delivery of aerosolized albuterol to poorly ventilated areas.<sup>168</sup>

In conclusion, acute asthma exacerbation treatment in the pediatric population continues to require our proficiency to promptly intervene with a systematic and aggressive methodology. A stepwise approach for the management of acute asthma exacerbation is shown in the Figure. The use of this progressive treatment guideline is suggested for patients admitted to the PICU who are not responding to steroids and β<sub>2</sub>-agonists and need further therapy, based on their clinical status and asthma score.

At Le Bonheur Children's Hospital ICU, we use different doses of continuous albuterol per hour, based on the patient's age and weight, keeping the dose per kilogram roughly the same in each group. The guidelines and clinical pathway for treatment with and weaning from continuous albuterol are described in the Figure and Appendix. Table 2 provides practical guidelines for the dosage and mixing concentrations of the albuterol solutions used at Le Bonheur Children's Hospital.

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**ABBREVIATIONS** cAMP, cyclic adenosine monophosphate; ED, emergency department;  $FiO_2$ , fraction of inspired oxygen; Heliox, helium-oxygen mixtures; ICU, intensive care unit; NAEPP, National Asthma Education and Prevention Program; NPPV, noninvasive positive pressure ventilation;  $PaCO_2$ , partial pressure of carbon dioxide in the arterial blood;  $PaO_2$ , partial pressure of oxygen in arterial blood; PAS, Pediatric Asthma Score; PICU, pediatric intensive care unit; PKA, protein kinase A;  $SpO_2$ , oxygen saturation.

**CORRESPONDENCE** I. Federico Fernandez Nievas, MD, University of Tennessee Health Science Center, Department of Pediatrics, Division of Critical Care Medicine, 50 N Dunlap St, CFRC, 3rd Floor, Memphis, TN 38103, email: ifernand@uthsc.edu

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**APPENDIX**

The Pediatric Asthma Score<sup>1</sup> (PAS) has been adopted by Le Bonheur Children's Hospital for the assessment of patients with asthma exacerbation (Table 1). A respiratory therapist documents the PAS every 2 hours while the patient is receiving continuous albuterol treatment. Weaning can be done every 2 hours by lowering the dose by 5 mg/h for PAS scores  $\leq 8$ . Advancement can be made to the next level only when there is worsening of the PAS. Patients should remain on continuous albuterol therapy until terbutaline is discontinued. Atrovent 0.25 to 0.5 mg will be administered every 6 hours.<sup>115</sup> Peak flow measurements will be instituted along with the PAS assessment for children older than 5 years.

**Guidelines for Patients <20 kg:**

- Begin continuous albuterol treatment at 15 mg/h or per physician order. Duration = 8 hours.
- Mix subsequent continuous solutions for a duration of 4 hours.
- Continue at 15 mg/h or at present strength of solution for PAS assessment scores  $>8$ .
- Begin and continue to wean albuterol by 5 mg/h for PAS assessment scores  $\leq 8$ .

**Guidelines for Patients 20-30 kg:**

- Begin continuous albuterol treatment at 25 mg/h or per physician order. Duration = 8 hours.
- Mix subsequent continuous solutions for a duration of 4 hours.
- Continue at 25 mg/h or at present strength of solution for PAS assessment scores  $>8$ .
- Begin and continue to wean albuterol by 5 mg/h for PAS assessment scores  $\leq 8$ .

**Guidelines for Patients >30 kg:**

- Begin continuous albuterol treatment at 30 mg/h or per physician order. Duration = 8 hours.
- Mix subsequent continuous solutions for a duration of 4 hours.
- Begin and continue to wean albuterol by 5 mg/h for PAS assessment scores  $\leq 8$ .
- Continue at 30 mg/h or present milligram per hour delivery for PAS assessment scores  $>8$ .