



## Critical Issues in the Treatment of Pediatric Status Asthmaticus

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### Introduction

Asthma is the most common chronic disease of childhood, and consequently the most frequent cause of hospitalization among children in the United States [1]. Recently, the National Center of Health Statistics reported that in 2009 there was an 8.2% prevalence of asthma in the United States thereby affecting 7.1 million children (0-17 years) [1]. Amongst that population, 56.3% (4.0 million) were reported to have an exacerbation [1]. Derivatively, asthma exacerbation can be the source of nearly half a million admissions to pediatric intensive care units each year [2]. For this reason, it is important that all healthcare workers, especially those in the critical care setting, become familiar and stay up to date on current issues involving the treatment, management, and alternative therapies for acute severe asthma exacerbations (i.e., status asthmaticus).

### Definition

Asthma exacerbations are typically classified as mild, moderate, or severe. An acute severe asthma exacerbation is loosely defined, but relies on presenting signs, symptoms, response to therapy, or a peak flow rate <40 percent of the predicted value for age, sex and height. There are several scoring systems currently employed to help assess asthma severity in children. One such scoring system is known as the Pulmonary Index Score (PIS). The PIS involves determining respiratory rate, presence of wheezing, inspiratory/expiratory ratio, accessory muscle use and oxygen saturation. The severity of each factor is assessed and a total score of 12 or greater defines an acute severe asthma exacerbation [3]. The Modified Pulmonary Index Score (MPIS) is similar to the PIS, with the exception that it scores the child's heart rate as well [4].

The National Asthma Education and Prevention Program (NAEPP) developed their own criteria in 2007 for categorizing the severity of asthma exacerbations [5]. It includes symptoms such as breathlessness, coughing, and wheezing, while also including signs of an exacerbation. Signs that are mentioned in this criteria include agitation, increased respiratory rate, increased pulse rate, and decreased lung function as measured by FEV<sub>1</sub>, peak expiratory flow (PEF), Pao<sub>2</sub>, Paco<sub>2</sub> and arterial oxygen saturation (Sao<sub>2</sub>) [5].

Generally, status asthmaticus refers to an acute asthma exacerbation in which bronchial obstruction is severe and does not improve despite the institution of adequate standard therapy (i.e., administration of oxygen, inhaled  $\beta$ -agonists, and systemic corticosteroids), leading to respiratory failure [6]. These children are often admitted to the intensive care unit and started on aggressive pharmacotherapy.

### Critical concepts of management

This section will highlight recent data, appropriate interventions, pharmacologic treatment, and adjunct therapies used to treat a child presenting with status asthmaticus in the intensive care unit. Management of anxiety inherent in this hospitalized person and the child's family are important to address but not considered in this brief overview.

Currently, many institutions use a stepwise approach and an escalation of therapy in the treatment of an acute severe asthma exacerbation. When escalating therapy, it is very important to continuously assess disease severity and response to therapy. A number of institutions have developed and implemented clinical asthma scores, which have been shown to correlate with the need for hospitalization and prolonged bronchodilator therapy [6]. An inpatient clinical protocol correlated with an objective pediatric asthma score may lead to a decrease in length of stay and a reduction in the total cost of hospitalization in children [6].

When admitted to the intensive care unit, all patients should be started on albuterol, ipratropium, and corticosteroids. While the above initial management is widely accepted and practiced, there is less consensus on subsequent management and thus is a topic of our discussion. Currently, there no published guidelines in the detailed treatment and management of status asthmaticus using adjunct therapy in children. Adjunct therapies commonly include continuous albuterol, intravenous (IV) terbutaline, nebulized/IV magnesium, IV ketamine, heliox, non-invasive positive pressure ventilation (NPPV), and intubation/mechanical ventilation [7-9]. When considering the next step, it is extremely important to be well versed on the numerous therapies used for treating status asthmaticus in pediatrics. The following are primary treatments in addition to adjunct therapies currently discussed in today's literature.

### Short acting $\beta$ 2-agonists (SABA)

SABA's are sympathomimetic agents that cause bronchodilatation due to bronchial smooth muscle relaxation. All children with asthma should be treated with a SABA during an exacerbation. Albuterol, a commonly used SABA, can be delivered through wet nebulization, or a metered dose inhaler (MDI). For moderate to severe asthma exacerbations, NAEPP guidelines recommend 4-8 puffs every 20 min for three doses, then every 1-4 h as needed through MDI [5]. When using nebulized albuterol, it is recommended to use a dose of 0.15 mg/kg every 20 min for three doses then 0.15-0.30 mg/kg every 1-4 h as needed or 0.5 mg/kg/h by continuous nebulization [5]. The mode of delivery that works best remains a topic for discussion.

Randomized trials comparing the two methods of delivery have shown that MDIs (with or without a spacer) demonstrated equal or

greater efficacy, less tachycardia and tremor, and shorter ED times [10]. This recent data likely will not matter in the ICU setting because by the time the patient has been transferred to the ICU, the patient will have exhausted first line therapies.

For status asthmaticus, continuous  $\beta_2$ -agonist nebulization is considered to be superior to the intermittent therapy described above [6]. In patients who fail to respond to continuous albuterol inhalation, IV administration of a  $\beta_2$ -agonist (terbutaline) should be considered. One retrospective study demonstrated that early administration of IV terbutaline in severe pediatric asthma decreased the incidence of acute respiratory failure [11]. Given this data, in the ICU setting, treatment with an IV  $\beta_2$ -agonist is an appropriate escalation of therapy when a patient fails to respond with continuous inhaled albuterol.

### **Ipratropium bromide**

Ipratropium is an inhaled anti-cholinergic agent, and is used in the adjunct treatment for acute asthma. It blocks cholinergic receptors and decreases parasympathetic tone, resulting in bronchodilatation. Ipratropium has been shown to be ineffective when used alone; however, when used with a SABA, ipratropium can improve lung function and reduce hospitalization rates in children with moderate-to-severe exacerbations [10]. It is important to point out that ipratropium has only been shown to be effective in the emergency room setting. Many studies of children with severe asthma requiring hospitalization have failed to show any benefit to the addition of ipratropium to their treatment regimens [12]. Thus it appears that using ipratropium in the intensive care setting may not be beneficial or cost effective but is still often used due to its high safety profile and reported beneficial effects in the ED setting.

### **Magnesium sulfate**

Magnesium sulfate is one of several adjunct therapies that health care professionals may consider when treating a child not responsive to first line treatments. It acts primarily as a smooth muscle relaxer. Magnesium sulfate may be given intravenously or through nebulization. In one randomized placebo-controlled trial, adding nebulized magnesium to combined nebulized bronchodilator and systemic steroid therapy failed to significantly shorten the time of discharge for pediatric patients with severe asthma [13]. While many studies have not shown a beneficial effect with the use of nebulized magnesium sulfate, intravenous  $MgSO_4$  has been noted to improve pulmonary function and reduce hospitalization rates in children presenting with severe asthma exacerbations who fail to improve clinically following initial therapies [10]. Given this critical data, IV magnesium sulfate is an appropriate consideration to use as an adjunct therapy.

### **Ketamine**

Ketamine is a fairly new adjunct therapy that clinicians are considering when treating a patient with refractory status asthmaticus. Ketamine is a drug mainly used for the induction and maintenance of anesthesia, but has recently been used in the treatment of severe asthma exacerbation due to its profound bronchodilatory properties. A systematic review to evaluate the efficacy of ketamine for severe acute exacerbations in children not responsive to standard therapy found only one randomized controlled trial that fulfilled their inclusion criteria [14].

This study randomized 68 children to receive either ketamine 0.2 mg/kg IV bolus over one to 2 min, followed by a 0.5 mg/kg per h continuous infusion for 2 h or an equivalent volume of normal saline placebo [15]. The results of the study demonstrated no significant difference in respiratory rate, oxygen saturation, hospital admission rate and need for mechanical ventilation between ketamine and the placebo group. In conclusion, ketamine may not avoid the need for endotracheal intubation due to respiratory failure, but it remains the first line anesthetic for intubation due to its ability to dilate and relax the bronchioles.

### **Heliox**

With airway narrowing, as seen during severe exacerbations, there is a change of airflow from laminar to turbulent, thus decreasing delivery of oxygen and inhaled medications distally. Heliox is an inert gas that is seven times less dense than air, and when mixed with oxygen, it may have sufficiently low density to convert airflow back to a laminar state [10]. Because of these properties, heliox increases the deposition of inhaled particles to the distal airways in patients with severe asthma, increasing the availability and efficacy of inhaled beta-agonists.

Recent studies, comprised of adults and children, have indicated that heliox is more effective than oxygen [16]. The use of heliox presented a 17.2% increase in mean change from baseline PEF compared with oxygen [16]. This benefit was greater in patients with acute severe asthma, increasing to approximately 25%. Regarding pediatric studies, the pooled analysis showed a significant decrease in acute asthma severity during treatment with heliox. Although research with heliox is on going, it seems that it may be a very powerful adjunct in the treatment of status asthmaticus.

### **Non-invasive Positive Pressure Ventilation (NPPV)**

National Asthma Education and Prevention Program (NAEPP) guidelines recommend non-invasive ventilation as an experimental approach for treatment of respiratory failure due to severe asthma exacerbation [5]. Positive pressure ventilation is considered to open distal airways and allow increased exposure of beta-adrenergic receptors. It facilitates the delivery and increases the efficacy of inhaled beta-agonists. One retrospective review of children admitted to the intensive care unit with status asthmaticus who received NPPV demonstrated a statistically significant improvement in respiratory rate and Modified Pulmonary Index Score [17]. Although the evidence for using NPPV is lacking, the data presented here concludes that initiating NPPV may be an appropriate escalation of therapy in status asthmaticus.

### **Mechanical Ventilatory Support**

Currently, there are no evidence-based guidelines in deciding when to institute mechanical ventilation in a child presenting with status asthmaticus. The decision often lies in the hands of the physician and is based on clinical judgment. The NAEPP does suggest considering mechanical ventilation in any patient with an arterial carbon dioxide ( $pCO_2$ ) level greater than 42 mmHg or in any patient with apnea or coma [5]. A recent multicenter study reported an average  $pCO_2$  of 52 mmHg prior to intubation, ranging from 38-68 mmHg [18]. Only 48% of those patients had blood gases drawn prior to intubation [18]. 91% of patients had a normal mental status, while only 4% were classified as obtunded before intubation [18].

There is evidence that factors such as provider practice and local geography may play a larger role than patient characteristics in the decision to intubate a child with status asthmaticus [18]. Ultimately, mechanical ventilation remains the last resort when escalating therapy and practices regarding intubation vary widely. Although there are no strict guidelines on indications for mechanical ventilation, signs of hypercarbic and hypoxic respiratory failure are the most important factors to consider.

## Conclusion

Status asthmaticus is an acute severe exacerbation of asthma that does not respond to standard therapy with the administration of oxygen, inhaled  $\beta_2$ -agonists, and systemic corticosteroids. As a healthcare worker in the critical care setting, it is extremely important to recognize the signs and symptoms and classify the severity of asthma exacerbations. It is also essential to be familiar with the appropriate interventions and adjunct therapies that can be considered in the treatment of status asthmaticus. This discussion on status asthmaticus has reviewed and highlighted current critical topics regarding the treatment and management of status asthmaticus in the intensive care setting.

## Author's Contribution

B Thiel, designed and conducted the study, analyzed the data, and wrote the manuscript. R. Kraima, helped design and conduct the study, analyze the data, and write the manuscript. S. Klok, has collected and verified the original study data. R. Schrier, helped design and conduct the study. M. Godfried, helped design and conduct the study, analyze the data, and write the manuscript, reviewed the analysis of the data and approved the final manuscript. All authors read and approved the final manuscript.

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