

Abstract:

Acute severe asthma exacerbations present unique challenges in the pediatric emergency department. While most children presenting to the emergency department respond to standard asthma therapy including inhaled β_2 -agonists, ipratropium, and systemic corticosteroids, some children remain refractory to these treatments and require adjunct therapies. Here we provide a review of the most recent National Asthma Education and Prevention Program guidelines, Global Initiative for Asthma guidelines, as well as recent evidence guiding the management of severe asthma exacerbations in the pediatric emergency department.

Keywords:

Asthma; pediatric; children; status asthmaticus; severe asthma exacerbation; acute severe asthma

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1522-8401

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Improving Management of Severe Asthma: BiPAP and Beyond

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Asthma affects approximately 6.2 million children in the United States, or 8.4% of the population under 18 years of age, and there are approximately 600,000 emergency department (ED) visits for pediatric asthma in the United States annually.^{1,2} Despite preventative initiatives targeting asthma control, severe acute asthma exacerbations are the most common medical emergencies in children and remain an immediate threat to the health of children. In 2014, asthma attributed to 322 deaths in patients less than 25 years old.³ Near fatal asthma includes two distinct phenotypes. Some patients present with symptoms that are more insidious in onset, slowly worsening over days to weeks. While the other group of patients with near fatal asthma has a rapid onset of symptoms and may advance from symptom onset to respiratory failure within 2 hours of symptoms onset.⁴ Emergency medicine physicians are the primary healthcare providers for children presenting with severe acute asthma exacerbations, and therefore, must be knowledgeable and proficient with managing severe refractory status asthmaticus in children.

The National Asthma Education and Prevention Program (NAEPP) was begun in 1989 to address the growing epidemic of asthma. This NIH/NHLBI coordinated effort first developed guidelines for the diagnosis and management of asthma in 1991. These guidelines were last updated in 2007 in the NAEPP Expert Panel Report 3 (EPR3).⁵ This review will focus on current NAEPP guidelines for the treatment of severe asthma exacerbations, as well as updates to the literature since the EPR3. The

recommendations of the Global Initiative for Asthma (GINA), which released its most recent set of guidelines in 2017, will also be reviewed.⁶

STANDARD ASTHMA MANAGEMENT

According to the NAEPP EPR3, the three main treatment goals in any asthma exacerbation include correction of hypoxemia, rapid reversal of airflow obstruction, and reducing the likelihood of relapse.⁵ Standard therapy in acute asthma management is aimed at achieving these goals. The treatments in most mild to moderate acute asthma exacerbations include inhaled oxygen therapy, systemic corticosteroids, inhaled β_2 -agonists such as albuterol, and ipratropium.

Corticosteroids

Asthma is a disease of chronic inflammation, airway hyperresponsiveness, and airway obstruction.^{7,8} Corticosteroids facilitate asthma treatment by providing therapeutic synergy with β_2 -agonists to improve bronchodilatation by increasing β -receptors on the surface of bronchial smooth muscles. They also decrease airway inflammation.⁹ Even in severe asthma exacerbations, corticosteroids remain an important component of treatment. Evidence demonstrates that early systemic corticosteroids are imperative and even a modest delay can increase the likelihood of hospital admission.^{10,11} While timing of corticosteroid administration is very important, the route of administration is less so, as the oral and intravenous routes have been shown to be equivalent for the treatment of asthma.^{12,13} The NAEPP panel and GINA recommend oral administration as the preferred route because it is less invasive.^{5,6} While one may be tempted to give higher doses of steroids to mitigate inflammation, there is no data to support doses greater than 2 mg/kg even in the setting of severe exacerbation, and thus higher dosing is not recommended.⁵

Recommended dosing: oral route: 0.6 mg/kg dexamethasone (max 16 mg) or 1 mg/kg prednisone (max 80 mg); IV route: 2 mg/kg methylprednisolone (max dose 125 mg). If the patient is discharged home, a second dose of PO dexamethasone 0.6 mg/kg (max 16 mg) should be administered on day 2 as a single dose or a complete 5 day course of PO prednisone can be administered.^{14,15} If the patient is being admitted to the hospital, steroid administration should be continued as an inpatient.

Inhaled β_2 -agonists


Inhaled albuterol, a short-acting β_2 -agonist (SABA), is the first-line treatment for acute asthma exacerbations. SABAs work directly on bronchial

smooth muscle to relieve acute bronchoconstriction during an asthma exacerbation. SABAs bind directly to the G-protein coupled β_2 receptors on the surface of smooth muscle cells, promoting bronchorelaxation.¹⁸

Recommended dosing: nebulized route in children 12 years of age (or less than 35 kg): 0.15-0.3 mg/kg, up to 10 mg, every 1-4 hours as needed.⁵

Ipratropium Bromide

Ipratropium bromide is an acetylcholine receptor antagonist which binds muscarinic receptors on the airway smooth muscle cells decreasing bronchoconstriction.¹⁶ It is recommended by the NAEPP in severe asthma exacerbations and should be administered simultaneously with a short acting β -agonist as an inhaled therapy.⁵ When combined with β -agonists, ipratropium bromide improves lung function and reduces hospital admissions in patients with severe exacerbations.^{16,17}

Recommended dosing: nebulized route: 0.25-0.5 mg every 20 minutes x 3 doses and then every 6 hours as needed.⁵ 

THERAPY FOR SEVERE OR UNRESPONSIVE ACUTE ASTHMA EXACERBATIONS

Continuous Inhaled β_2 -agonists

The NAEPP guidelines recommend repeated β -agonist treatments for patients who do not respond to initial SABA therapy, followed by continuous inhaled or intravenous (IV) β -agonist therapy for patients with severe acute exacerbations.⁵ A 2003 systematic review and meta-analysis of mostly adult patients evaluated the use of continuous compared to intermittent SABAs, reporting an improvement in clinical asthma scores and a reduction in hospital admissions in patients with severe acute asthma who received continuous SABA.¹⁹

While continuous albuterol is effective in patients with severe asthma, there are some associated side effects. Recent literature has demonstrated that these side effects are rare even when continuous albuterol is delivered in the non-acute care setting.²⁰ Patients on continuous nebulized SABA should receive continuous vital sign monitoring, as there are several side effects associated with continuous SABA therapy including hypokalemia, dysrhythmias, tremors, and diastolic hypotension.²¹⁻²³ High doses of albuterol have also been associated with the development of lactic acidosis.^{24,25} The physiologic response to this

developing metabolic acidosis involves respiratory compensation and worsening tachypnea. For this reason, the decision to maintain a patient on continuous albuterol should include physical exam findings other than tachypnea. Patients should be spaced to intermittent albuterol as their acute exacerbation improves.

Recommended dosing: nebulized route in children up to 12 years of age: 0.15-0.3 mg/kg up to 10 mg every 1-4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization.⁵

Magnesium Sulfate

Magnesium sulfate is used in the treatment of asthma to enhance bronchorelaxation. Magnesium sulfate induces bronchodilation by enhancing calcium uptake into the sarcoplasmic reticulum of airway smooth muscle or by acting as a calcium antagonist, leading to relaxation of airway smooth muscle.²⁶ The NAEPP guidelines recommend using IV magnesium sulfate in children with severe acute asthma exacerbations not responding to initial standard therapy.⁵ Recent meta-analyses evaluating IV magnesium sulfate in children with acute asthma exacerbations found a significant decrease in hospital admission rates in children who received magnesium sulfate.^{27,28} One potential side effect of magnesium sulfate therapy is systemic vasodilation leading to hypotension.^{29,30} Concomitant administration of isotonic IV fluids may help ameliorate symptoms associated with hypotension.

Recommended dosing: IV route: 25-75 mg/kg/dose (max dose 2 grams) over 20 minutes.

Epinephrine and Terbutaline

Intramuscular administration of epinephrine and terbutaline are used for the emergency treatment of severe, life-threatening exacerbations characterized by severe obstruction or in cases where nebulizer therapy is not tolerated. Epinephrine administered intramuscularly (IM) has a rapid onset of action and can reverse severe bronchospasm within minutes by stimulating alpha and beta adrenergic receptors, causing relaxation of the airway smooth muscles via β_2 -adrenergic receptors and cyclic adenosine monophosphate mediated pathways.³¹ It is recommended when wheezing may be associated with an anaphylactic reaction or when administration of inhaled SABA is not possible.³² GINA guidelines also recommend the use of epinephrine for cases of asthma which may be associated with anaphylaxis.⁶ Terbutaline is a more selective β_2 -agonist that may be given in IV or subcutaneous form in the emergency setting. Terbutaline, like epinephrine, is reserved for patients with acute respiratory deterioration or who have failed to show any improve-

ment to standard initial therapy. The NAEPP guidelines note that there is limited data to support the use of IV terbutaline, as it is most commonly used in the ICU environment, and the GINA guidelines recommend its use when inhaled SABA cannot be given.^{5,6} A systematic review in adults and children found only one study that supported IV β_2 -agonist in children with severe acute asthma and thus found it difficult to perform adequate evaluation of the utility of this therapy. This single study demonstrated shorter recovery time and improvement in clinical asthma scores in patients who received IV β_2 -agonists.³³

Recommended dosing: Subcutaneous route: 0.01 mg/kg/dose (max 0.25 mg) every 20 minutes for three doses; IV route: 0.1 to 10 mcg/kg/min as a continuous infusion prepared in 0.9% normal saline or dextrose. Most patients are started at a dose of 1 mcg/kg/min with the dose titrated to effect. If starting at doses lower than 1 mcg/kg/min, a loading dose of 10 mcg/kg IV over 10 minutes can be given to more rapidly achieve effect.³⁴

High Flow Nasal Cannula

The use of heated, humidified, high flow nasal cannula (HFNC) oxygen therapy for respiratory distress has become increasingly popular over the last decade. While the majority of use of HFNC in most pediatric emergency departments is in the setting of bronchiolitis, it is an alternative option for patients with asthma before noninvasive and invasive mechanical ventilation is needed. This high flow system increases the FiO₂ delivered to patients by washing out dead space carbon dioxide, preventing room air entrainment, and providing positive end-expiratory pressure (PEEP) to atelectatic and mucous filled lower airways. The positive pressure also helps to improve pulmonary compliance and reduce work of breathing.³⁵ Recent small studies in patients with moderate to severe asthma exacerbations or status asthmaticus showed some improvement in asthma symptoms with HFNC over conventional oxygen delivery systems.^{36,37} In one study of patients with severe asthma, noninvasive ventilation was avoided in 47.6% of patients with use of HFNC. However, 40% of this group of patients subsequently failed HFNC treatment and required escalation to noninvasive ventilation.³⁸ Overall, the existing studies of HFNC for asthma are limited in sample size and generalizability. Further research is required before HFNC can be recommended for asthma treatment.

Noninvasive Ventilation

Noninvasive ventilation (NIV) refers to the methods of providing ventilator support without using an

invasive artificial airway. Positive pressure ventilation can be delivered using a variety of means, but orofacial masks are the commonly used in the pediatric population. The mode of support can be selected based on the patient's needs and include isolated volume or pressure-controlled ventilation, bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP). For optimal outcomes, awake patients need to be able to cooperate and tolerate the most appropriate therapy. Common indications for the use of NIV include significant increased work of breathing, hypercapnia, and hypoxemia. Contraindications to NIV include hypoventilation or conditions where adequate respiratory drive is not preserved, loss of intact gag reflex and inability to protect one's airway, respiratory arrest, and cardiac arrest.³⁹

Bilevel Positive Airway Pressure

BiPAP is the most common noninvasive positive pressure ventilation and involves both inspiratory and expiratory pressure support: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), which is equivalent to positive end-expiratory pressure (PEEP). BiPAP improves respiratory distress by decreasing the workload on fatigued respiratory muscles by providing a measured, pressure-supported inspiratory tidal volume and end-expiratory pressure support. The data on BiPAP in severe asthma exacerbations is limited. The NAEPP guidelines address the use of iPAP as noninvasive ventilation in asthma and consider this therapy to be an experimental approach for respiratory failure.⁵ The GINA guidelines acknowledge that data is limited and suggest that if NIV is used, these patients require close monitoring usually in an intensive care setting.⁶ A recent systematic review found limited high quality evidence to recommend for or against the use of NIV for acute asthma exacerbations.⁴⁰

Recommended dosing: Initial settings should aim for an adequate tidal volume of 5-7 mL/kg with an FiO₂ titrated to achieve a pulse oximetry of greater than 90%. Initial IPAP/EPAP settings of 10 cm H₂O/5 cm H₂O are usually adequate, but should be titrated to necessary effect. IPAP settings above 20-25 cm H₂O and EPAP settings above 10-15 cm H₂O are not recommended.³⁹ Some have recommended low dose ketamine infusion or dexmedetomidine infusion to assist patient tolerance of BiPAP.⁴¹

Heliox

Heliox is an inhaled gas composed of a mixture of helium and oxygen that has lower density relative to

oxygen alone. It is thought to improve work of breathing by reducing airway resistance, promoting laminar flow, and facilitating gas exchange and aerosol delivery in patients with asthma.⁴² Heliox itself does not have any bronchodilator or anti-inflammatory effects and should not replace standard asthma medications, but is used as a bridge therapy until targeted asthma therapy takes effect.⁴³ Four randomized, placebo-controlled studies evaluating heliox for acute severe asthma exacerbations have shown variable efficacy in the pediatric population; two reported improvements in clinical asthma scores,^{44,45} and two showed no improvements related to heliox therapy.^{46,47} The NAEPP guidelines recommend the administration of inhaled beta agonists with heliox in patients who have life-threatening asthma exacerbations.⁵ Their recommendation for use of heliox is based the randomized control trial conducted by Kim et al that demonstrated greater improvement in asthma symptoms and decrease lengths of hospital stay in patients who received continuous beta-agonist with heliox vs. oxygen.⁴⁵ The GINA guidelines also support the use of heliox in patients with severe asthma exacerbations who do not respond to conventional treatment.⁶ Their recommendations are based on a 2014 meta-analysis that reported decreased hospitalization rates and improved peak expiratory flow in patients with severe and very severe asthma treated with heliox.⁴⁸

Recommended dosing: Standard heliox cylinders contain a mixture of 79% helium and 21% oxygen, but concentrations can be adjusted to a concentration of 70% helium and 30% oxygen. However, as the concentration of oxygen increases, the benefits of laminar flow decrease. For these reasons, heliox therapy is not appropriate for patients with status asthmaticus and hypoxia requiring greater than 30% FiO₂.

Ketamine

Ketamine is an NMDA receptor antagonist with bronchodilatory properties. The NAEPP guidelines do not recommend the use of ketamine in severe acute asthma as they note trials in non-intubated patients have not demonstrated benefits. The GINA guidelines do not include recommendations regarding therapeutic ketamine use in asthma.^{5,6} The literature on ketamine use in asthma includes case reports involving anecdotal use of ketamine, but larger studies including one randomized controlled trial of ED patients have not demonstrated benefits.⁴⁹⁻⁵² Similarly a 2012 systematic review found insufficient evidence to support the use of ketamine in acute asthma.⁵³

Aminophylline

Aminophylline is a methylxanthine derivative phosphodiesterase inhibitor. When used in asthma, it causes bronchodilation and improves diaphragmatic contraction.⁵⁴ Documented benefit of aminophylline use in asthma is limited. One systematic review and meta-analysis of aminophylline use in children with severe asthma exacerbation showed that IV aminophylline in addition to inhaled β -2 agonists and glucocorticoids improved lung function, but did not have any effect on sustained reduction in symptoms, number of nebulized treatments required, or length of stay.⁵⁵ Aminophylline has a significant adverse side effect profile that includes tremors, nausea, vomiting and cardiac arrhythmias.^{54,55} Because of the limited benefit and high risk side effect profile, the NAEPP guidelines recommend against aminophylline use.⁵ GINA guidelines similarly recommend against the use of aminophylline especially in light of its known potentially fatal side effects.⁶

Inhaled Anesthetics

Inhaled anesthetics such as isoflurane and sevoflurane are potent bronchodilators. The mechanism of action of inhaled anesthetics is thought to be mediated through the B-adrenergic/cyclic adenosine monophosphate pathway or through inhibition of acetylcholine and histamine.⁵⁶ Inhaled anesthetics may offer a powerful therapeutic option for children in refractory status asthmaticus in the intensive care setting. There are several case reports of intubated asthmatic patients improving clinically with the use of inhaled anesthetics.⁵⁷⁻⁶⁰ One retrospective study using the Pediatric Health Information System, studied 1558 pediatric asthma patients who received mechanical ventilation at 40 hospitals and found no differences in mortality between those who received inhaled anesthetic agents and those that did not. They did, however, report increased length of stay, increased length of mechanical ventilation, and increased charges associated with receiving inhaled anesthetics.⁶¹ Further research needs to be conducted to determine the overall effectiveness of inhaled anesthetics in asthma, especially given the high associated costs; however it may be a treatment option in cases of severe refractory status asthmaticus.

SUMMARY

Severe asthma exacerbations continue to contribute to significant morbidity and mortality in children in the United States and continue to strain

emergency departments and healthcare system resources. Inhaled SABA, ipratropium bromide, and corticosteroids remain the mainstay of treatment, even in patients with acute severe and life threatening asthma exacerbations. There are several therapeutic options for patients who remain in distress despite conventional therapies, however many of these require additional research, especially in pediatrics. BiPAP, for example, is currently being used by some institutions as a means to avoid mechanical ventilation in patients with severe asthma, but further high quality research is necessary before its use can be fully and objectively evaluated. Further research in this population is required so that we may provide the best quality care for patients with severe and life-threatening asthma exacerbations. ☒

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