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PEDIATRIC ASTHMA

Pediatric acute asthma exacerbations: Evaluation and management from emergency department to intensive care unit

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Abstract

Objective: The goal of this report is to review available modalities for assessing and managing acute asthma exacerbations in pediatric patients, including some that are not included in current expert panel guidelines. While it is not our purpose to provide a comprehensive review of the National Asthma Education and Prevention Program (NAEPP) guidelines, we review NAEPP-recommended treatments to provide the full range of treatments available for managing exacerbations with an emphasis on the continuum of care between the ER and ICU.

Data Sources: We searched PubMed using the following search terms in different combinations: asthma, children, pediatric, exacerbation, epidemiology, pathophysiology, guidelines, treatment, management, oxygen, albuterol, β₂-agonist, anticholinergic, theophylline, corticosteroid, magnesium, heliox, BiPAP, ventilation, mechanical ventilation, non-invasive mechanical ventilation and respiratory failure. We attempted to weigh the evidence using the hierarchy in which meta-analyses of randomized controlled trials (RCTs) provide the strongest evidence, followed by individual RCTs, followed by observational studies. We also reviewed the NAEPP and Global Initiative for Asthma expert panel guidelines.

Results and conclusions: Asthma is the most common chronic disease of childhood, and acute exacerbations are a significant burden to patients and to public health. Optimal assessment and management of exacerbations, including appropriate escalation of interventions, are essential to minimize morbidity and prevent mortality. While inhaled albuterol and systemic corticosteroids are the mainstay of exacerbation management, escalation may include interventions discussed in this review.

Epidemiology and public health burden of pediatric asthma exacerbations

Asthma is a complex genetic and environmental disease [1–3]. It is the most common chronic disease of childhood and the most frequent cause of childhood disability, affecting 7.1 million (9.6% of) children in the USA [1,4–6]. Acute asthma exacerbations largely preventable and an indicator of poorly managed disease.

Nearly 60% of children with asthma have one or more acute exacerbations each year [2,6]. Exacerbations are highest in young children, decrease with age, account for 640 000 childhood emergency department (ED) visits annually, and are the most frequent reason for childhood hospitalization [2,3,6]. In children and adults, asthma control questionnaires and FEV1 have been predictive of future exacerbations [7–9]. However, acute exacerbations are not entirely predictable and may occur in any patient with asthma. Moreover, any severe acute exacerbation may progress to life-threatening respiratory failure [10,11]. As such clinicians must closely monitor the severity of an exacerbation and escalate therapy appropriately.

Annual US costs for asthma are $56 billion [12]. ED visits account for 8% and hospitalizations for as much as 50% of overall direct costs and are the most expensive component of asthma care [12,13]. Exacerbations impair quality of life and disproportionately affect children who are African-American, have Medicaid insurance, are poor, or live in rural areas [6,14–22]. The USA has the highest rate of hospital admissions and mortality due to asthma amongst 17 high-income peer countries [23]. Clearly, exacerbations are a significant public health burden. ED clinicians need to be skilled in assessment and management of acute exacerbations and in assuring that affected children have appropriate follow-up for prevention of future episodes. Additionally, collaboration and coordination of care between the ED and ICU is essential to minimize morbidity and potential mortality due to severe exacerbations.

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National and international asthma guidelines

In response to recommendations of the National Asthma Education and Prevention Program (NAEPP) expert panels have been convened by the National Heart, Lung, and Blood Institute (NHLBI) to develop asthma guidelines [24]. The Global Initiative for Asthma (GINA) has issued and updated similar expert panel guidelines [25]. The NAEPP guidelines, most recently updated as Expert Panel Report 3, are a notable achievement in the care of patients with this chronic disease [26].

However, within the nearly 500 pages comprising these guidelines, only about 40 pages are directed toward assessment and management of acute exacerbations. This is, in part, the result of a limited repertoire of medications and other interventions available to ED clinicians for patients with acute exacerbations. However, since publication of Report 3, some recommended adjunct therapies have become more widely used (e.g. magnesium) and others (e.g. montelukast, ketamine) not included in the report might be considered for patients with severe exacerbations not responding to short-acting β₂-agonists (SABAs) and systemic corticosteroid. Finally, recommended assessment of acute exacerbations includes measurement of forced expiratory volume (FEV) and peak expiratory flow (PEF), yet spirometry is generally not available in the ED and PEF is unreliable as a measure of acute exacerbation severity [27,28].

We searched PubMed using the following search terms in different combinations: asthma, children, pediatric, exacerbation, epidemiology, pathophysiology, guidelines, treatment, management, oxygen, albuterol, β₂-agonist, anticholinergic, theophylline, corticosteroid, magnesium, heliox, BiPAP, ventilation, mechanical ventilation, non-invasive mechanical ventilation, and respiratory failure. We attempted to weigh the evidence using the hierarchy in which meta-analyses of randomized controlled trials (RCTs) provide the strongest evidence, followed by individual RCTs, followed by observational studies. We also reviewed the NAEPP and GINA expert panel guidelines.

The goal of this report is to review available modalities for assessing and managing exacerbations by clinicians caring for pediatric patients, including several treatments that go beyond the NAEPP guidelines. While it is not our purpose to provide a comprehensive review of the NAEPP guidelines, we review NAEPP-recommended treatments to provide the full range of treatments available for managing exacerbations.

Bedside assessment of acute asthma exacerbation severity

Exacerbations are highly variable in severity and response to treatment, and recommended management is based on accurate assessment of severity [29]. The pediatric patient with either a mild or severe exacerbation is readily identified. For example, patients presenting with agitation may be hypoxemic and those with somnolence may be hypercarbic, fatigue and approaching respiratory failure. Immediate, maximal intervention is clearly needed for such a patient, as well as consideration of alternative diagnoses (e.g., foreign body aspiration, pneumothorax).

However, assessing severity and response to treatment may be more challenging for patients with moderate-severity exacerbations. There are few objective measures available to evaluate exacerbations across the range of disease severity most frequently encountered, and physicians’ assessment of exacerbation severity has been noted to be variable and limited in accuracy [30-32]. Bedside asthma scores may facilitate communication between members of the clinical team. Yet proposed asthma severity scores are limited by the subjective nature of most variables comprising the scores, and most lack sufficient validation [33,34].

The NAEPP guidelines include a method for severity assessment based on breathlessness, speech, alertness, respiratory rate, accessory muscle use, wheezing, heart rate, pulsus paradoxus, PEF, SpO₂, and pCO₂ [24]. Qureshi et al. modified this system to develop a severity score that has been widely used [35]. While each physical signs or symptoms may represent clinically relevant domains of exacerbation severity, some are subjective or infrequently measured. For example, although pulsus paradoxus is one of the few severity measures for which measurement is not effort-dependent on the part of the patient, it is measured in only 1% of children or adults presenting with acute asthma [36-38]. On the other hand, visual examination for accessory muscle use is reasonably objective, can be readily assessed at the bedside, and correlates with FEV₁ [39]. In addition, we have found that scores with fewer and more objective components have comparable criterion validity as more complex scores [40].

Notwithstanding the limitations of beside severity scores, an accurate measure of exacerbation severity that can be used by clinicians at the bedside is essential. With these considerations in mind, our children’s hospital uses the Acute Asthma Intensity Research Score (AAIRS) for assessment of severity and as the basis for an asthma clinical practice guideline (CPG) [41]. The AAIRS validated well against the criterion standard %-predicted FEV₁ as a measure of pre-treatment severity and response to treatment.

Imaging and laboratory testing during exacerbations

Most exacerbations in pediatric patients are precipitated by viral respiratory infections [42-45]. As a result many children with exacerbations present to the ED with fever in addition to wheezing, shortness of breath or cough [44,46]. With this in mind, a comprehensive physical exam is essential, and ancillary testing such as blood work and chest X-rays are not routinely indicated unless other diagnoses need to be excluded. Most clinically significant radiographic findings can be predicted by localized rales, wheezes or decreased breath sounds that do not resolve with bronchodilator treatment [47,48].

For patients presenting with significant chest pain or hypoxemia, pneumothorax or pneumonia must be considered and a chest X-ray is warranted. Patients with severe episodes may warrant capnography to identify rising end-tidal CO₂ as a sign of ventilatory failure. The ubiquitous use of pulse oximetry has obviated the need to obtain arterial blood gas analysis for almost all patients. However, the pulse oximeter provides no information on ventilation or acid–base status, and a normal SpO₂ may provide clinicians with a false sense of
security. Capnometry, serial pulmonary exams and bedside severity scores are of value for patients with severe episodes who do not respond to initial inhaled β₂-agonist; arterial blood gas analysis may be indicated for patients who appear fatigued or progressing toward respiratory failure.

Lactic acidosis resulting from high doses of albuterol has been reported in adults and children, and is thought to be a result of excess β-receptor stimulation leading to glycogenolysis and production of pyruvate and lactate [49–51]. It may result in respiratory compensation with hyperventilation. This may be misinterpreted as worsening airway obstruction and result in inappropriate escalation of β₂-agonist treatment [51]. With this in mind we believe it is appropriate for clinicians to consider a venous blood gas for lactate measurement in patients who have received prolonged albuterol treatment, and to carefully apply the AAIRS or other comprehensive severity score as a measure of response to treatment.

Treatments recommended by NAEPP guidelines

NAEPP guidelines identify three principal goals for treating asthma exacerbations: (1) Correction of significant hypoxia; (2) Rapid reversal of airflow obstruction and (3) Reduction of the likelihood of relapse or future recurrence. Recommended treatments align with these goals.

Oxygen

Most patients with exacerbations have ventilation-perfusion mismatch rather than true shunt. As a result, mild hypoxemia (>90%) is common and most often corrects with minimal supplemental oxygen. More severe hypoxemia may occur with severe exacerbations and, if not readily corrected after administration of supplemental oxygen, warrants consideration of pneumothorax, pneumonia, methemoglobinemia and/or other pathologic processes. Finally, if more serious etiologies of hypoxia are ruled out, it is possible that intrapulmonary shunt has developed as a result of β₂-agonist induced pulmonary arteriolar dilation reversing the normal reflex hypoxic-vasoconstriction seen in ventilation-perfusion mismatch.

Short-acting inhaled β₂-agonists (SABA)

We have reported that pediatric EDs frequently use much greater doses and prolonged treatment with nebulized albuterol than are recommended by NAEPP guidelines for moderate and severe exacerbations [52]. In a small double-blind randomized trial we found that although albuterol at 25 mg/h might provide greater bronchodilation in comparison with 10 mg/h, the higher dose results in greater hypokalemia [53].

Hypokalemia is a result of skeletal muscle β-receptor activation from systemically-absorbed albuterol with intracellular potassium shift. Although serum potassium levels likely normalize quickly after cessation of albuterol, patients nonetheless experience skeletal muscle weakness and may appear more ill as a result. An additional concern for patients who have been using high and/or frequent doses of albuterol or long-acting β₂-agonists is β-receptor desensitization [54–56]. Moreover, cardiac arrhythmias due to hypokalemia aggravated by β-receptor desensitization with refractory bronchospasm and hypoxia cannot be excluded as the immediate cause of deaths during exacerbations [57,58]. Finally, very high-dose albuterol (75 or 150 mg/h) resulted in a 53% decrease of diastolic and 37% decrease of mean arterial blood pressure from baseline, changes that are clinically meaningful [59].

The delivery mode for inhaled albuterol also bears discussion. Wet nebulizers have been the traditional delivery mode for children in the ED. However, innovations in metered-dose inhalers (MDI) have resulted in output of much smaller particles and, when used with a valved holding chamber (VHC), much improved delivery to distal airways. Randomized trials comparing these two delivery modes have consistently demonstrated equal or greater efficacy, less tachycardia and tremor, shorter ED times, and lower cost with MDI-VHC [60–62]. NAEPP guidelines recommend 4–8 puffs every 20 min for three doses, then every 1–4 h as needed [24]. MDI-VHC use also affords the opportunity for parent and patient teaching of the proper technique.

The guidelines also recommend nebulized albuterol at a dose of 0.15 mg/kg (minimum 2.5 mg) every 20 min for three doses then 0.15–0.30 mg/kg up to 10 mg every 1–4 h as needed, or 0.5 mg/kg/h by continuous nebulization. Clinicians may prefer these nebulized options for patients unable to cooperate for MDI-VHC treatment due to young age or respiratory distress.

For patients with more than minimal ventilation, IV or SQ β-agonists have no therapeutic advantage over inhaled delivery and are associated with greater systemic side effects [63]. However, for the patient with a severe exacerbation who has minimal air entry that does not respond to initial treatment with inhaled albuterol and IV MgSO₄, this mode of delivery should be considered. Oral administration of albuterol or other β-agonists is not recommended due to slow onset of action and systemic side effects.

Ipratropium

Ipratropium bromide, an inhaled anticholinergic agent, is a useful adjunct treatment for acute asthma. Ipratropium exerts its effects by blocking cholinergic receptors, which diminish cholinergic bronchomotor tone and decreases mucosal edema and secretions. Though it has been shown to be ineffective when administered as a single agent, ipratropium given in conjunction with SABA can improve lung function and reduce hospitalization rates in children with moderate-to-severe exacerbations [35,63,64]. NAEPP guidelines recommend two or three doses of 250–500 μg via nebulization or 2–3 puffs of 17 μg/puff administered via MDI [24]. It is important to emphasize that ipratropium has only been shown to be effective in the ED setting. Studies of children with asthma requiring hospitalization have failed to show any benefit to the addition of ipratropium to their treatment regimens after the transition from the ED to the inpatient setting [65,66].

Systemic corticosteroid

Corticosteroids have been used to treat asthma for over 50 years and significant benefit has been demonstrated in numerous studies. In one Cochrane Review, short courses of steroids were shown to contribute to improvement in symptom score, reduced rates of relapse, fewer hospitalizations, and less need for β₂-agonist use [67]. In addition to bronchodilators, systemic corticosteroid is essential to successful therapy in acute asthma.
exacerbations by decreasing inflammation and mucous production as well as enhancing the efficacy of bronchodilators [68].

Current guidelines recommend treatment of moderate to severe asthma exacerbations with oral prednisone or dexamethasone. Oral prednisone or prednisolone (1–2 mg/kg/day) is taken for a 3–5 day course and dexamethasone (0.3–0.6 mg/kg) is given in either a one or two-dose regimen.

Potential side effects are consistently a concern with the use of oral corticosteroids as therapy. However, short bursts of prednisone 1–2 mg/kg daily for 5 days have been shown to have no effect on bone density, height, and adrenal function at 30 days post-therapy [69]. Other potential side effects such as hypertension, hyperglycemia and behavioral disturbances exist, but have not been well-reported.

Growing evidence supports the use of dexamethasone in preference to prednisone or prednisolone in the treatment of acute asthma exacerbations. This therapy has the same bioavailability when given orally and as an intramuscular injection, lasting up to 72 h after a single dose [70]. It has a half-life that is approximately double that of prednisone (12–36 h). Dexamethasone has been shown to increase oral steroid compliance and provide fewer side effects, such as vomiting, while remaining equally efficacious [71].

A recent meta-analysis determined that there was no increased risk of relapse for children receiving dexamethasone when compared to those receiving prednisone or prednisolone for treatment of asthma [68]. Other studies suggest that the use of 2-day dexamethasone therapy is superior to 5-day prednisone/prednisolone in cost-effectiveness, patient compliance and palatability [72]. Additionally, there seems to be a caregiver preference of dexamethasone administration over a course of prednisolone as it eliminates the need for filling a prescription and, therefore, simplifies the home treatment regimen [73]. There is limited data to compare the efficacy of different routes of Dexamethasone (IM vs. PO) and whether single-dose is equally efficacious to multiple doses [68].

Adjunctive treatments

Intravenous magnesium sulfate

Intravenous magnesium sulfate (MgSO₄) is one of several adjunctive therapies that clinicians may consider in children with an inadequate response to first-line treatments. Intravenous MgSO₄ has been shown to improve pulmonary function and reduce hospitalization rates in children presenting with severe asthma exacerbations who fail to improve clinically following initial therapies [74–77].

MgSO₄ acts primarily as a smooth muscle relaxer and thus relieves bronchoconstriction. On a cellular level, MgSO₄ decreases intracellular calcium by blocking its entry into the cell and its release from the endoplasmic reticulum, which results in bronchial smooth muscle relaxation. Furthermore, it diminishes inflammatory mediators by inhibiting mast cell degranulation and stabilizing T cells [75].

The recommended dose of MgSO₄ for the treatment of severe asthma is 25–75 mg/kg IV given over 20 min. It is generally safe and well tolerated at this dose, however, hypotension may result due to vascular smooth muscle relaxation. This is an uncommon effect and can be counteracted by the simultaneous infusion of a fluid bolus [78–80].

Heliox

Airflow is laminar during normal tidal breathing with resistance inversely proportional to the fifth power of airway radius. With airway narrowing during severe exacerbations, gas velocity increases and airflow becomes turbulent, with much greater airway resistance (thought to be inversely proportional to the fourth power of radius). This contributes to increased work of breathing, decreased airflow and decreased deposition of inhaled medication in distal airways. Because β₂-adrenergic receptors are present throughout the airways and alveoli, delivery of albuterol to these most distal receptors may be clinically important [81].

Helium is an inert gas that is seven-times less dense than air and, when mixed with oxygen (heliox), may have sufficiently low density to convert airflow back to a laminar state. Heliox appears to not provide benefit to patients with mild or moderate severity exacerbations [82,83]. However, a recent meta-analysis of available trials found that for patients with severe or very severe exacerbations in which heliox of 70:30 was most frequently used (mean 120 min), there were significant decreases in hospitalization (OR 0.49, 95% CI 0.31–0.79) amongst adult and pediatric studies and meaningful decreases in severity scores amongst pediatric studies [83]. Although heliox is more expensive than some other treatments we consider it a useful adjunct that may result in sufficient distal airway β₂-agonist delivery and ventilation to prevent progression toward respiratory failure.

Treatments beyond the guidelines

As noted, since publication of the most recent NAEPP guidelines, additional adjunctive treatments have been considered by pediatric ED clinicians. We present these treatments alphabetically because evidence is lacking to establish a hierarchy or preferred stepped-care algorithm.

BiPAP and other non-invasive ventilatory support

NAEPP guidelines recommend non-invasive ventilation as an “experimental approach for treatment of respiratory failure due to severe asthma exacerbation” [24]. Positive-pressure ventilation has potential to open distal airways and expose more β₂-adrenergic receptors and to offload increased work of breathing due to auto-PEEP. However, it may also increase air-trapping, auto-PEEP and ventilation-perfusion mismatch.

In patients with moderate-severity exacerbations who are not approaching respiratory failure we have reported that Bilevel Positive Airway Pressure (BiPAP) treatment substantially increases the likelihood of hospital and PICU admission with no apparent benefit in decreased length of stay or time to spacing of albuterol treatments to every 4 h or greater [84]. In addition, there is currently no means to assess auto-PEEP for patients receiving BiPAP treatment. BiPAP is an option for the child with a severe episode who is fatiguing or approaching respiratory failure, in an effort to avoid endotracheal intubation. It should not be used for children with mild- or moderate-severity exacerbations.
High-flow nasal cannula (HFNC) therapy provides heated, humidified supplemental oxygen by nasal cannula and provides positive airway pressure at similar levels to that provided by CPAP. Wing et al. retrospectively examined their institutional experience before and after HFNC became available for children with respiratory illness severe enough to require PICU admission, approximately half of whom had an acute asthma exacerbation [85]. There was an 83% reduction in the odds of endotracheal intubation in the PED for the overall population after implementation of an HFNC guideline, though there were not significant reductions in endotracheal intubations for patients with asthma. Further study of HFNC for patients with asthma exacerbations may be warranted.

Ketamine

Emergency Medicine physicians are familiar with ketamine as a dissociative sedative-analgesic for procedural sedation and as an induction agent for endotracheal intubation. Because of its profound sympathomimetic properties ketamine is also the preferred induction-sedative agent for endotracheal intubation of patients with respiratory failure due to asthma. However, this drug may have an additional role in avoiding respiratory failure and endotracheal intubation.

A systematic review to evaluate the efficacy of ketamine for severe acute exacerbations no responsive to standard therapy found only one RCT that met inclusion criteria [86]. This study randomized pediatric patients who continued to have severe exacerbations after standard therapy for 1 h to ketamine 0.2 mg/kg IV bolus followed by 0.5 mg/kg/h as a continuous infusion for two hours or to saline placebo [87]. There were no differences in oxygen saturation, respiratory rate or odds of hospitalization. However, the dose of ketamine employed in this study is below that typically used for procedural sedation. Data for greater doses of ketamine are limited, but in two pediatric patients with severe asthma who were approaching respiratory failure, ketamine provided prompt improvement sufficient to avoid endotracheal intubation [88]. The investigators used a bolus (2 mg/kg) followed by a continuous infusion (2–3 mg/kg/h), doses familiar to ED physicians using ketamine for procedural sedation. Ketamine has potential to aggravate bronchospasm, and this side effect is controlled by ipratropium.

Montelukast

Montelukast (Singulair®) is leukotriene inhibitor (LTI). Leukotrienes have long been recognized as inflammatory mediators of exacerbations in patients with atopic asthma [89,90]. Decreased urine and serum LT levels accompany clinical improvement of acute episodes and may identify patients who respond to acute treatment [91–93]. Trials of IV montelukast for exacerbations in adults demonstrated rapid and sustained (24 h) improvement of lung function [94–96]. Camargo et al. demonstrated significant and clinically important improvement of FEV₁ within 20 min of either 7 mg or 14 mg IV montelukast in adults with moderate to severe acute episodes, and in a subsequent study of 7 mg IV montelukast demonstrated similar beneficial improvement in FEV₁ (0.32 vs. 0.22 L) at 60 min in adults with FEV₁ ≤ 50% predicted after initial standard treatment [95,96]. Morris et al. did not find similar benefit in a pediatric study [97]. However, participants included for analyses had greater initial %FEV₁ values (52%) compared with the Camargo studies (45% and 37%). Greater benefit in patients with more severe airway obstruction may account for the different outcomes of these studies.

The intravenous preparation of montelukast is not available, and two RCTs of oral montelukast using doses of 5 or 10 mg did not demonstrate a difference in bedside acute severity score or FEV₁. However, further trials of oral montelukast at greater doses might be considered for pediatric patients with acute exacerbations, based on the following rationale. First, pharmacokinetic studies indicate that a 5.25-mg IV dose in children 6–14 years of age is equivalent to the 7 mg IV dose used in the adult studies above [98]. Second, the montelukast chewtab is rapidly absorbed and achieves peak serum levels within 2 h [99–101]. Finally, extensive study of IV and oral formulations at doses as high as 800 mg/day indicate that this drug is extremely safe with a similar frequency of adverse effects amongst treatment and placebo groups [94,102].

Nebulized magnesium

Although inhaled β₂-agonists have been the mainstay of therapy in patients with acute bronchospasm, the efficacy of intravenous MgSO₄ as an adjunctive agent has led to speculation that inhaled MgSO₄ may also provide some benefit. This topic has remained controversial as previous investigations into the benefits of inhaled MgSO₄ have produced mixed results. A multi-center RCT of nebulized MgSO₄ in comparison with nebulized saline placebo for severe asthma did not demonstrate a difference in bedside severity scores at 1-h, but did demonstrate a significant improvement in comparison with placebo in those with the most severe exacerbations [101]. A systematic review of six clinical trials appeared to show that some benefit, although small and of limited clinical use, may been seen when this therapy is combined with β₂ agonists. However, multiple clinical trials suggest that it provides very little benefit to the patient when used alone and does not lead to reduced hospital admission or time to discharge from the ED [78,103].

The reason for decreased benefit with nebulized administration of MgSO₄ is unknown, but may be secondary to the location of action within the smooth muscle, which may not necessarily be accessible from the mucosal surface [104]. Currently, this method of delivery of MgSO₄ sulfate is not part of recommended treatment guidelines. Further research in the use of nebulized MgSO₄ in acute asthma exacerbation would be necessary to determine if there is a true clinical benefit [78].

Theophylline

NAEPP guidelines recommend against use of theophylline for patients with acute asthma exacerbations. However, 59% of surveyed pediatric ICUs continue to use aminophylline, and for this reason it is briefly discussed [105]. Aminophylline, the IV form of theophylline, was a mainstay of acute exacerbation management for decades. However, the low therapeutic index and multitude of drug interactions with aminophylline and effectiveness of selective β₂-agonists prompted its removal from recommended treatments. In this regard, we have found that patients with exacerbations who...
received aminophylline in the PICU had longer time to symptom improvement [106]. We believe it is rarely appropriate to initiate aminophylline in the ED.

**Titration of supplemental oxygen**

As mentioned previously, hypoxemia during acute asthma exacerbations is most often a result of ventilation-perfusion mismatch rather than true shunt, and for this reason usually corrects with minimal supplemental oxygen. β2-agonists and oxygen may each result in pulmonary arteriolar vasodilation, increased perfusion of poorly ventilated areas and aggravation of ventilation-perfusion mismatch. In addition, adults with acute exacerbations randomized to receive 28% oxygen had decreased PaCO2, reflecting aggravation of ventilation-perfusion mismatch with 100% oxygen, had increased PaCO2. A trial of adults randomized to either oxygen titrated to maintain SpO2 at 93–95% or to high concentration oxygen had found similar results [107]. With this in mind, oxygen should be titrated to maintain SpO2 93–95% [25].

**Mechanical ventilatory support**

**Overview and indications**

No specific evidence-based guidelines exist from which to recommend the ideal timing of the application of mechanical ventilator support to the therapeutic regimen of patients with critical or life-threatening asthma. Previous recommendations for mechanical support have utilized hypercarbia, hypoxia, altered mental status, and perceived exhaustion as indications for support [26,108]. Although the recommendation for timing of intubation “is based on clinical judgment”, the guidelines cite specific guides such as carbon dioxide levels over 42 mmHg or any patient with apnea or coma.

Given the lack of specific recommendations in the guidelines, studies report a wide variability in practices regarding endotracheal intubation in the asthma cohort [109–112]. As a result of this variability, the incidence of mechanical ventilation support in the asthma cohort ranges from 6 to 26% for invasive ventilation and 0.3–6% for non-invasive ventilation [109].

A recent multicenter study using the Pediatric Critical Care Research Network (CPCCRN) database, the median reported partial pressure of carbon dioxide (pCO2) prior to intubation was 52 torr and ranged from 38 to 68 torr, however, only 48% of patients intubated had blood gas analysis prior to intubation [112]. In this same cohort, the mental status was reported as normal in 91% of patients and obtunded in only 4% of those intubated for asthma management [112]. Rising serum lactate might be used as an objective measure of perceived exhaustion, however, the association of lactic acidosis and β-agonist administration may complicate the ability of clinicians to reliably differentiate medication side effect from metabolic failure [49,50].

No recent data have improved the specificity for recommendations for escalation to mechanical ventilatory support and it remains in the hands of the individual clinician. Signs of hypercarbic and hypoxic respiratory failure and associated physiologic derangements such as altered mental status and anaerobic metabolism resulting in metabolic acidosis remain the indications for intervention.

**Methods and modes of support**

Invasive mechanical ventilation has long been the standard for respiratory failure resulting from status asthmaticus. However, non-invasive mechanical ventilatory support for status asthmaticus is not a new concept, and reports date back nearly two decades in adult patients [113,114]. In the pediatric population there is limited data regarding the efficacy of non-invasive support [115,116]. Although this modality appears safe overall, we have recently reported that the use of BiPAP in pediatric patients with no signs of respiratory failure is associated with greater likelihood of hospital and critical care unit admission with no benefit measured using the time needed to wean to Q 4-h albuterol and length of hospital stay [84,117].

These observational cohort studies allow limited comparative assessment of non-invasive versus invasive mechanical ventilatory support, yet it is reasonable to consider support in a step-wise fashion with the escalation from inhaled medication therapies to non-invasive mechanical support, culminating in invasive mechanical support for treatment failure for patients with respiratory failure.

For patients undergoing support with invasive mechanical ventilation, no specific mode of ventilation has been demonstrated to be superior [108]. The goal is to limit barotrauma and volutrauma while providing adequate gas exchange to support the patient. In either a volume targeted or pressure targeted mode the converse dependent variable will need close monitoring. For those who choose a volume targeted mode, initial tidal volume settings will need to attempt to maximize minute ventilation while limiting volutrauma. However, it is to be remembered that exceedingly high peak inspiratory pressures are likely due to airway resistance and not transmitted to the alveoli. This can be discerned by measuring the plateau pressure (Pplateau) at end expiration with goal <30 cm H2O. Conversely, pressure targeted mode will need to ensure an adequate minute ventilation is achieved when pressures are limited. Combining elements of pressure and volume mode ventilation, the benefits of high initial inspiratory flow combined with a set tidal volume target is realized in centers that utilize pressure-regulated–volume–control (PRVC). A recent study of multiple children’s hospitals demonstrated that pressure control mode (63%) was the most frequent initial setting; however, that final ventilator mode was more evenly distributed between pressure (34%), volume (20%), PRVC (10%), pressure support with PEEP (36%) [112].

**Pulmonary physiology in status asthmaticus and the effects on mechanical support**

Patients with status asthmaticus demonstrate predominantly increased airway resistance as the pathophysiologic mechanism of respiratory failure. Although it is possible for areas of atelectasis (and reduced static lung compliance) to develop, status asthmaticus demonstrates a dominance of changes to the dynamic compliance of the system. In this model, the resistance to air flow in affected airways increases work of breathing, leading to the increased distress and effort noted on clinical asthma scores. Gas-trapping is also termed dynamic hyperinflation and occurs as disease and support related variables conspire to limit full exhalation.
Under normal conditions, the end-expiratory alveolar pressure is approximately 5 cm H$_2$O, and the normally compliant system requires a change in pressure of only 3–5 cm H$_2$O to generate airflow. The diaphragm moves downward, creating a further decrease in already negative intra-pleural pressures, which in turn is transmitted to the alveolus, generating the negative pressure gradient “dragging” air into the airways. This process is easily reversed and exhalation occurs very quickly with 70–80% of the vital capacity exhaled in the first second.

However, in status asthmaticus exhalation is inhibited by airway resistance and there is a dramatic lengthening of the time needed for full exhalation. As a result gas remains “trapped” in the alveolus at the time of the next inhalation with the trapped volume rising with each subsequent breath leading to increased end alveolar and intrathoracic pressures that must be overcome to initiate the next inspiration (Figure 1) [118]. The presence of dynamic hyperinflation (gas-trapping) can be discerned by measuring the measured total end expiratory pressure ($\text{PEEP}_{\text{tot}}$) using an expiratory pause maneuver or by notation of the volume of end expiratory flow (Vee) [119]. If the $\text{PEEP}_{\text{tot}}$ is greater than the set PEEP or if the Vee is $>$ 0 L/min, then dynamic hyperinflation (auto-PEEP) is present.

As a result, the end-expiratory alveolar pressure is often increased 2–3-fold increasing the required change in pressure to reach the negative alveolar pressures necessary to generate airflow by the patient [120]. Mechanical ventilatory support, either non-invasive or invasive, is used to overcome the increased work of breathing of severe status asthmatics. The change in work of breathing associated with increased airway resistance is coupled with gas-trapping to create a scenario in which the patient must apply a greater change in intrapleural pressure to generate airflow. The non-invasive application of continuous positive airway pressure (CPAP) in this situation functionally normalizes this gradient and has been shown to reduce the work load in the spontaneously breathing asthma patient [121]. In addition to the reduced work load of generating a breath, the application of non-invasive inspiratory positive pressure support assists the patient in overcoming the overall increased resistance in the system. Hence, in the care of patients with severe episodes not responding to treatment or approaching respiratory failure, the addition of inspiratory positive airway pressure (IPAP) to the CPAP regimen is often used, resulting in the application of non-invasive bi-level positive airway pressure (BiPAP). For the patient on invasive mechanical ventilation who is spontaneously breathing, the set positive end expiratory pressure (PEEP) is increased to 1–2 cm H$_2$O below to reduce the work of breathing for the patient.

Complications of mechanical support

Complications of mechanical ventilatory support specific to status asthmatics are related to dynamic hyperinflation. As gas is trapped in alveoli at end expiration during dynamic hyperinflation, the alveolar pressure may increase leading to baro-volutrauma and pneumothorax and pneumomediastinum. Additionally, as intrathoracic pressure rises, transmural right atrial pressure decreases and venous return declines leading to a potentially life threatening situation. Early reports of high rates of complications associated with mechanical ventilation in asthma led to concerns about intubation by some centers for asthma. In an adult cohort, Zimmerman et al. reported complications in 45% of mechanically ventilated adults with asthma [122]. Although it is true that complications of mechanical ventilation in asthma may lead to pneumothorax and pneumomediastinum, recent data suggest these rates remain low with reported incidence of 1% and 3%, respectively, using data from the CPCCRN [109]. The low rates of complications are likely related to vigilance for developing gas-trapping as well as the recognition that normalization of carbon dioxide levels in the patient were not necessary. The concept of “permissive hypercapnea” adopted in the cohort of patients with the acute respiratory distress syndrome has helped diminish the focus on normalization of $p$CO$_2$ values. In general, improving $p$CO$_2$ levels is a sign of decreasing airway obstruction, but until such improvement maintaining a pH $>$ 7.2 is adequate unless there are specific contraindications to hypercarbia.

In the event of worsening gas-trapping as evidenced by increasing $\text{PEEP}_{\text{tot}}$ or Vee, attempts should be made to maximize time for exhalation in addition to pharmacologic relief of airway obstruction. For the patient treated with mechanical ventilation who is spontaneously breathing augmentation of the patient’s spontaneous breaths with pressure support should be titrated to achieve adequate tidal ventilation in lieu of setting a ventilator rate. For any set demand breath, the inspiratory time should be decreased to the lower end of normal for age, however, remembering that the varied time constants will require a minimum inspiratory time to achieve inflation and that the greater effect on time to exhalation is the number of

Figure 1. The graphic representation of progressive end-expiratory air-trapping in asthma represented over four breaths with progressive increase in total end expiratory pressure ($\text{PEEP}_{\text{tot}}$) and alveolar dilation.

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set breaths per minute. In the patient not spontaneously breathing on invasive mechanical ventilation, adjustment of the rate and inspiratory time should be titrated to limit PEEP$_{tot}$ and Vee while maximizing tidal ventilation as measured by $p$CO$_2$. In the event of the patient with declining cardiopulmonary function in whom rising intrathoracic pressures is suspected, some suggest disconnecting the endotracheal tube from the ventilator and allowing complete exhalation prior to resuming ventilation. Although there is no published literature to support its use or indicate its safety, manual exhalation support by leaning on the chest is often suggested to acutely reverse life threatening gas-trapping, while the ventilator is disconnected.

Pneumomediastinum is highly unlikely to create clinically relevant symptoms and no recommendations can be made other than individual case by case assessment for the need to intervene. Pneumothorax should be treated per usual practice using acute drainage by a qualified individual.

**Institutional CPGs**

Because pediatric acute asthma exacerbations are one of the most frequent reasons for ED visits in US hospitals and because these facilities have varying levels of resources, quality of care may be optimized by creating a CPG tailored to institutional capabilities and resources. Our children’s hospital uses an asthma CPG created by a multi-disciplinary group of nurses, respiratory therapists, pharmacists, and emergency medicine, pulmonary medicine and general pediatric clinicians. The CPG includes separate guidelines for inter-hospital transport, the ED, PICU and pediatric units.

**Disposition/NIH recommended follow-up**

**Provision of controller-medication prescriptions in the ER**

Controller therapy is recommended for children with persistent asthma [24]. Inhaled corticosteroids (ICS) are the most widely prescribed controller therapy and have been shown to improve asthma control with less need for rescue medications, fewer urgent-care visits, fewer hospitalizations and fewer asthma deaths [18]. Children treated for acute asthma in the ED are at high risk for future exacerbations, making it essential that this particular population receive appropriate controller therapy. Generally, the prescribing of preventative asthma medications occurs in the outpatient setting. Unfortunately, rates of outpatient follow up after ED visits for asthma exacerbations are low, and consequently few patients receive ICS after ED visits for asthma [18,123–125].

A proposed solution is to prescribe or dispense ICS in the acute care setting [126,127]. A cost-effective analysis suggests that initiating ICS at the time of ED discharge is more cost-effective than relying on an outpatient visit for ICS initiation and will reduce bounce-back ED visits and subsequent hospitalizations [18]. Additionally, a quality-improvement intervention to encourage ICS prescribing at the time of PED discharge resulted in a median ICS initiation rate of 79% versus only 11% prior to the intervention [128]. Finally, a survey of pediatricians found that 83% support initiation of controller medications in the ED [129].

**Influenza vaccine**

The 2015 Advisory Committee on Immunization Practices recommends annual influenza vaccine for all pediatric asthma patients over 6 months of age [130]. Children with asthma are at a substantially increased risk of influenza complications including pneumonia and death. The prevalence of asthma in US children is close to 10%; however, those with asthma represent over one-third of pediatric patients who are hospitalized for influenza complications. Despite considerable risk for influenza complications in pediatric asthma patients, vaccination among children with asthma remains low [131,132].

In an effort to boost influenza vaccination rates among at-risk populations, there has been a push for implementing influenza vaccination programs across all healthcare settings, including the ED [133]. NAEPP guidelines advise providers to consider influenza vaccines in all children with asthma starting at 6 months of age. However, providers are cautioned that immunization should not be given with the the expectation that it will decrease the frequency or severity of asthma exacerbations during the influenza season.

**Primary care follow-up**

Central to efforts to improve care of patients with asthma is establishing primary care provider (PCP) follow-up after an ED visit or hospital admission. Currently, follow-up with the patient’s PCP is recommended within 3–5 days. This follow-up visit or phone call is essential to evaluate adherence to the treatment regimen. Additionally, this is an excellent opportunity to consider starting or increasing current controller medication therapy. If not already established, an asthma action plan should be provided and/or reviewed as each visit.

Indications for referral to asthma specialist care should be considered in patients having difficult-to-control asthma, frequent exacerbations (more than two per year) or risk-factors for asthma-related death including previous intensive care unit admission, mechanical ventilation, and anaphylaxis to food. Additionally, referral should be considered in patients with evidence of side-effects to therapy (e.g. growth delay) or when the diagnosis of asthma is in question [24].

**Declaration of interest**

The authors have no conflicts of interest to disclose.

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