Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: http://www.tandfonline.com/loi/ijas20

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

Brittany Pardue Jones MD, Geoffrey M. Fleming MD, Jaime Kaye Otillio MD, Ishan Asokan MSc, BA & Donald H. Arnold MD, MPH

To cite this article: Brittany Pardue Jones MD, Geoffrey M. Fleming MD, Jaime Kaye Otillio MD, Ishan Asokan MSc, BA & Donald H. Arnold MD, MPH (2016) Pediatric acute asthma exacerbations: Evaluation and management from emergency department to intensive care unit, Journal of Asthma, 53:6, 607-617, DOI: 10.3109/02770903.2015.1067323

To link to this article: http://dx.doi.org/10.3109/02770903.2015.1067323

Published online: 26 Apr 2016.

Journal of ASTHMA

http://tandfonline.com/ijas
ISSN: 0277-0903 (print), 1532-4303 (electronic)

J Asthma, 2016; 53(6): 607–617
 DOI: 10.3109/02770903.2015.1067323

Taylor & Francis
Taylor & Francis Group

PEDIATRIC ASTHMA

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

Brittany Pardue Jones, MD[1,*], Geoffrey M. Fleming, MD[2,*], Jaime Kaye Otillio, MD[1,*], Ishan Asokan, MSc, BA[3], and Donald H. Arnold, MD, MPH[1,4]

[1]Department of Pediatrics, Division of Emergency Medicine, [2]Division of Critical Care Medicine, [3]School of Medicine, and [4]Center for Asthma Research, Vanderbilt University School of Medicine, Nashville, TN, USA

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, β_2-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.

Keywords

Mechanical ventilation, non-invasive ventilation, pediatric, respiratory failure, status asthmaticus

History

Received 21 April 2015
Revised 22 June 2015
Accepted 24 June 2015

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 FEV_1 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.

*Drs. Pardue Jones, Fleming and Otillio are co-first authors as they contributed equally to this work.

Correspondence: Donald H. Arnold, MD, MPH, Division of Emergency Medicine, Vanderbilt Children's Hospital, Room 1348A, Nashville, TN 37232-9001, USA. Tel: +1 6159364498. Fax: +1 6155071943. E-mail: don.arnold@vanderbilt.edu

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 β_2-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, β_2-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, fatiguing 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, SpO_2, and pCO_2 [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 FEV_1 [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 FEV_1 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 CO_2 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 SpO_2 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 β_2-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 β_2-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 β_2-agonist induced pulmonary arteriolar dilation reversing the normal reflex hypoxic-vasoconstriction seen in ventilation-perfusion mismatch.

Short-acting inhaled β_2-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 or frequent doses of albuterol or long-acting β_2-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-VCH 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 $MgSO_4$, 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 diminishes 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 β_2-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 ($MgSO_4$) is one of several adjunctive therapies that clinicians may consider in children with an inadequate response to first-line treatments. Intravenous $MgSO_4$ 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].

$MgSO_4$ acts primarily as a smooth muscle relaxer and thus relieves bronchoconstriction. On a cellular level, $MgSO_4$ decreases intracelluar 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 $MgSO_4$ 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 β_2-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 β_2-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 β_2-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 bronchorrhea, but this side effect is controlled by inhaled 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 FEV_1 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 FEV_1 (0.32 vs. 0.22 L) at 60 min in adults with $FEV_1 \leq 50\%$ 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 $\%FEV_1$ 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 FEV_1. 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 β_2-agonists have been the mainstay of therapy in patients with acute bronchospasm, the efficacy of intravenous $MgSO_4$ as an adjunctive agent has led to speculation that inhaled $MgSO_4$ may also provide some benefit. This topic has remained controversial as previous investigations into the benefits of inhaled $MgSO_4$ have produced mixed results. A multi-center RCT of nebulized $MgSO_4$ 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 β_2 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 $MgSO_4$ 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 $MgSO_4$ sulfate is not part of recommended treatment guidelines. Further research in the use of inhaled $MgSO_4$ 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 β_2-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. β_2-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 $PaCO_2$, reflecting aggravation of ventilation-perfusion mismatch with 100% oxygen, had increased $PaCO_2$. A trial of adults randomized to either oxygen titrated to maintain SpO_2 at 93–95% or to high concentration oxygen had found similar results [107]. With this in mind, oxygen should be titrated to maintain SpO_2 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 (pCO_2) 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 ($P_{plateau}$) at end expiration with goal <30 cm H20. 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_2O, and the normally compliant system requires a change in pressure of only 3–5 cm H_2O 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 ($PEEP_{tot}$) using an expiratory pause maneuver or by notation of the volume of end expiratory flow (Vee) [119]. If the $PEEP_{tot}$ 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 asthmaticus. The

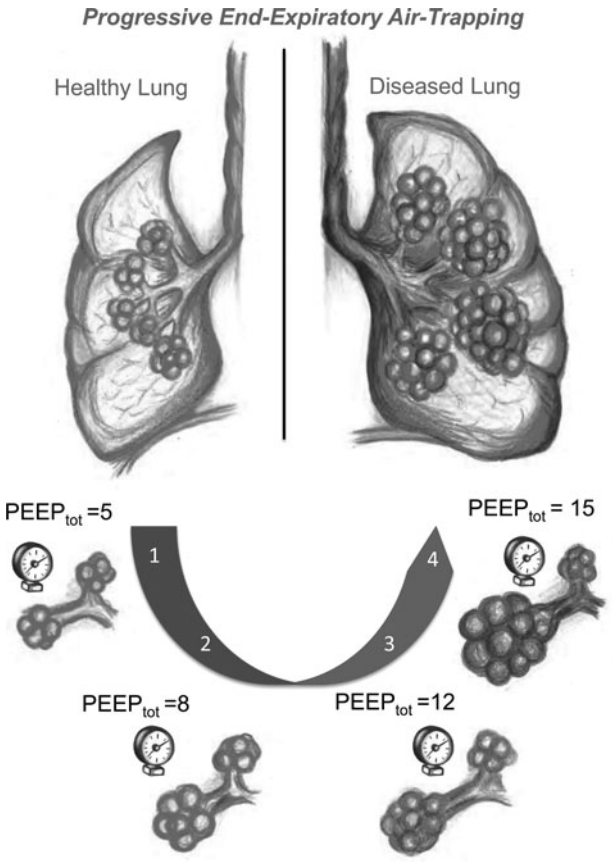

Figure 1. The graphic representation of progressive end-expiratory air-trapping in asthma represented over four breaths with progressive increase in total end expiratory pressure ($PEEP_{tot}$) and alveolar dilation.

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_2O below to reduce the work of breathing for the patient.

Complications of mechanical support

Complications of mechanical ventilatory support specific to status asthmaticus 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 pneumomediastium, 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 pCO_2 values. In general, improving pCO_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 $PEEP_{tot}$ 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

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 pCO_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.

References

1. Malveaux FJ. The state of childhood asthma: introduction. Pediatrics 2009;123:S129–S130.
2. Akinbami LJ, Moorman JE, Garbe PL, Sondik EJ. Status of childhood asthma in the United States, 1980–2007. Pediatrics 2009;123:S131–S145.
3. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, Liu X. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. NCHS Data Brief 2012;94:1–8.
4. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma–United States, 1980–1999. MMWR Surveill Summ 2002;51:1–13.
5. Newacheck PW, Halfon N. Prevalence, impact, and trends in childhood disability due to asthma. Arch Pediatr Adolesc Med 2000;154:287–293.

6. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. Natl Health Stat Rep 2011;32:1–14.
7. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, Weiss ST. FEV(1) is associated with risk of asthma attacks in a pediatric population. J Allergy Clin Immunol 2001;107:61–67.
8. Bateman ED, Buhl R, O'Byrne PM, Humbert M, Reddel HK, Sears MR, Jenkins C, et al. Development and validation of a novel risk score for asthma exacerbations: the risk score for exacerbations. J Allergy Clin Immunol 2014;135:1457–1464.
9. Robroeks CM, van Vliet D, Jobsis Q, Braekers R, Rijkers GT, Wodzig WK, Bast A. Prediction of asthma exacerbations in children: results of a one-year prospective study. Clin Exp Allergy 2012;42:792–798.
10. Restrepo RD, Peters J. Near-fatal asthma: recognition and management. Curr Opin Pulmon Med 2008;14:13–23.
11. McFadden Jr ER. Acute severe asthma. Am J Respir Crit Care Med 2003;168:740–759.
12. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. J Allergy Clin Immunol 2011;127:145–152.
13. Gergen PJ. Understanding the economic burden of asthma. J Allergy Clin Immunol 2001;107:S445–S448.
14. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in the parents of children with asthma. Qual Life Res 1996;5:27–34.
15. Centers for Disease Control and Prevention (CDC). Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001–2009. MMWR 2011;60:547–552.
16. Lieu TA, Lozano P, Finkelstein JA, Chi FW, Jensvold NG, Capra AM, Quesenberry CP, et al. Racial/ethnic variation in asthma status and management practices among children in managed medicaid. Pediatrics 2002;109:857–865.
17. Lozano P, Connell FA, Koepsell TD. Use of health services by African-American children with asthma on Medicaid. JAMA 1995;274:469–473.
18. Andrews AL, Teufel II RJ, Basco Jr WT. Low rates of controller medication initiation and outpatient follow-up after ED visits for asthma. J Pediatr 2012;160:325–330.
19. Fisher EB, Strunk RC, Sussman LK, Sykes RK, Walker MS. Community organization to reduce the need for acute care for asthma among African American children in low-income neighborhoods: the Neighborhood Asthma Coalition. Pediatrics 2004;114:116–123.
20. Fisher Jr EB, Sussman LK, Arfken C, Harrison D, Munro J, Sykes RK, Sylvia S, Strunk RC. Targeting high risk groups. Neighborhood organization for pediatric asthma management in the Neighborhood Asthma Coalition. Chest 1994;106:248S–259S.
21. Kit BK, Simon AE, Ogden CL, Akinbami LJ. Trends in preventive asthma medication use among children and adolescents, 1988–2008. Pediatrics 2012;129:62–69.
22. Perry TT, Vargas PA, McCracken A, Jones SM. Underdiagnosed and uncontrolled asthma: findings in rural schoolchildren from the Delta region of Arkansas. Ann Allergy Asthma Immunol 2008;101:375–381.
23. Woolf SH, Aron L. U.S. health in international perspective: shorter lives, poorer health. Panel on understanding cross-national health differences among high-income countries. Washington, DC: National Research Council and Institute of Medicine; 2013.
24. National Heart, Lung, and Blood Institute. Expert Panel Report 3: guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program. Bethesda, MD: National Institutes of Health; 2007.
25. Halfon N. Addressing health inequalities in the US: a life course health development approach. Soc Sci Med 1982 2012;74:671–673.
26. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol 2007;120:S94–S138.
27. Gorelick MH, Stevens MW, Schultz T, Scribano PV. Difficulty in obtaining peak expiratory flow measurements in children with acute asthma. Pediatr Emerg Care 2004;20:22–26.
28. Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Can peak expiratory flow predict airflow obstruction in children with asthma? Pediatrics 2000;105:354–358.
29. Lemanske Jr RF, Busse WW. Asthma: clinical expression and molecular mechanisms. J Allergy Clin Immunol 2010;125:S95–S102.
30. Spiteri MA, Cook DG, Clarke SW. Reliability of eliciting physical signs in examination of the chest. Lancet 1988;1:873–875.
31. Holleman Jr DR, Simel DL. Does the clinical examination predict airflow limitation? JAMA 1995;273:313–319.
32. Wolfenden LL, Diette GB, Krishnan JA, Skinner EA, Steinwachs DM, Wu AW. Lower physician estimate of underlying asthma severity leads to undertreatment. Arch Intern Med 2003;163:231–236.
33. Baxt WG. Prospective application of an asthma severity rule. Acad Emerg Med 2002;9:868–869.
34. van der WD. Promises and pitfalls in the evaluation of pediatric asthma scores. J Pediatr 2000;137:744–746.
35. Qureshi F, Pestian J, Davis P, Zaritsky A. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. N Engl J Med 1998;339:1030–1035.
36. Jardin F, Farcot JC, Boisante L, Prost JF, Gueret P, Bourdarias JP. Mechanism of paradoxic pulse in bronchial asthma. Circulation 1982;66:887–894.
37. Canny GJ, Reisman J, Healy R, Schwartz C, Petrou C, Rebuck AS, et al. Acute asthma: observations regarding the management of a pediatric emergency room. Pediatrics 1989;83:507–512.
38. Kerem E, Canny G, Tibshirani R, Reisman J, Bentur L, Schuh S, et al. Clinical-physiologic correlations in acute asthma of childhood. Pediatrics 1991;87:481–486.
39. Arnold DH, Gebretsadik T, Sheller JR, Abramo TJ, Hartert TV. Accessory muscle use in pediatric patients with acute asthma exacerbations. Ann Allergy Asthma Immunol 2011;106:344–346.
40. Arnold DH, Gebretsadik T, Abramo TJ, Moons KG, Sheller JR, Hartert TV. The RAD score: a simple acute asthma severity score compares favorably to more complex scores. Ann Allergy Asthma Immunol 2011;107:22–28.
41. Arnold DH, Saville BR, Wang W, Hartert TV. Performance of the Acute Asthma Intensity Research Score (AAIRS) for acute asthma research protocols. Ann Allergy, Asthma Immunol 2012;109:78–79.
42. Busse WW, Lemanske Jr RF, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. The Lancet 2010;376:826–834.
43. Khetsuriani N, Kazerouni NN, Erdman DD, Lu X, Redd SC, Anderson LJ, et al. Prevalence of viral respiratory tract infections in children with asthma. J Allergy Clin Immunol 2007;119:314–321.
44. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ 1995;310:1225–1229.
45. Leung TF, To MY, Yeung ACM, Wong YS, Wong GWK, Chan PKS. MUltiplex molecular detection of respiratory pathogens in children with asthma exacerbation. Chest 2010;137:348–354.
46. Sanders DL, Gregg W, Aronsky D. Identifying asthma exacerbations in a pediatric ED: a feasibility study. Into J Med Inform 2006;76:557–564.
47. Gershel JC, Goldman HS, Stein RE, Shelov SP, Ziprkowski M. The usefulness of chest radiographs in first asthma attacks. N Engl J Med 1983;309:336–339.
48. Swischuk LE. Asthma attack: is a chest X-ray necessary? Pediatr Emerg Care 2005;21:468–470.
49. Lewis LM, Ferguson I, House SL, Aubuchon K, Schneider J, Johnson K, Matsuda K. Albuterol administration is commonly associated with increases in serum lactate in patients with asthma treated for acute exacerbation of asthma. Chest 2014;145:53–59.
50. Rodrigo GJ, Rodrigo C. Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. Emerg Med J 2005;22:404–408.
51. Meert KL, McCaulley L, Sarnaik AP. Mechanism of lactic acidosis in children with acute severe asthma. Pediatr Crit Care Med 2012;13:28–31.
52. Arnold DH, Moore PE, Abramo TJ, Hartert TV. The dilemma of albuterol dosing for acute asthma exacerbations in pediatric patients. Chest 2011;139:472.
53. Arnold DH, Saville BR, Moore PE, Abramo TJ, Resha DJ, Wang W, Hartert TV. Changes of serum potassium and spirometry during treatment for acute asthma: a double-blind, randomized pilot

trial of four albuterol regimens. Proc Ped Acad Soc E- PAS 2011;754618:2011.
54. Arnold DH, Hartert TV. What we need to know about long-acting ss(2)-agonists: deja vu all over again? Am J Respir Crit Care Med 2010;182:1219–1220.
55. Salpeter SR, Wall AJ, Buckley NS. Long-acting beta-agonists with and without inhaled corticosteroids and catastrophic asthma events. Am J Med 2010;123:322–328.e2.
56. Shore SA, Moore PE. Regulation of beta-adrenergic responses in airway smooth muscle. Respir Physiol Neurobiol 2003;137:179–195.
57. Leikin JB, Linowiecki KA, Soglin DF, Paloucek F. Hypokalemia after pediatric albuterol overdose: a case series. Am J Emerg Med 1994;12:64–66.
58. Rakhmanina NY, Kearns GL, Farrar III HC. Hypokalemia in an asthmatic child from abuse of albuterol metered dose inhaler. Pediatr Emerg Care 1998;14:145–147.
59. Phumeetham S, Bahk TJ, Abd-Allah S, Mathur M. Effect of high-dose continuous albuterol nebulization on clinical variables in children with status asthmaticus. Pediatr Crit Care Med 2015;16:e41–e46.
60. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev (Online) 2013;9:Cd000052.
61. Doan Q, Shefrin A, Johnson D. Cost-effectiveness of metered-dose inhalers for asthma exacerbations in the pediatric ED. Pediatrics 2011;127:e1105–e1111.
62. Kaashmiri M, Shepard J, Goodman B, Lincourt WR, Trivedi R, Ellsworth A, Davis AM. Repeat dosing of albuterol via metered-dose inhaler in infants with acute obstructive airway disease: a randomized controlled safety trial. Pediatr Emerg Care 2010;26:197–202.
63. Aaron SD. The use of ipratropium bromide for the management of acute asthma exacerbation in adults and children: a systematic review. J Asthma 2001;38:521–530.
64. Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. Cochrane Database Syst Rev 2013;8:CD000060.
65. Pollack Jr CV, Pollack ES, Baren JM, Smith SR, Woodruff PG, Clark S, Camargo CA. A prospective multicenter study of patient factors associated with hospital admission from the ED among children with acute asthma. Arch Pediatr Adolesc Med 2002;156:934–940.
66. Goggin N, Macarthur C, Parkin PC. Randomized trial of the addition of ipratropium bromide to albuterol and corticosteroid therapy in children hospitalized because of an acute asthma exacerbation. Arch Pediatr Adolesc Med 2001;155:1329–1334.
67. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early ED treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev 2001;1:Cd002178.
68. Keeney GE, Gray MP, Morrison AK, Levas MN, Kessler EA, Hill GD, et al. Dexamethasone for acute asthma exacerbations in children: a meta-analysis. Pediatrics 2014;133:493–499.
69. Ducharme FM, Chabot G, Polychronakos C, Glorieux F, Mazer B. Safety profile of frequent short courses of oral glucocorticoids in acute pediatric asthma: impact on bone metabolism, bone density, and adrenal function. Pediatrics 2003;111:376–383.
70. Derendorf H, Hochhaus G, Mollmann H, Barth J, Krieg M, Tunn S, Mollmann C. Receptor-based pharmacokinetic–harmacodynamic analysis of corticosteroids. J Clin Pharmacol 1993;33:115–123.
71. Cross KP, Paul RI, Goldman RD. Single-dose dexamethasone for mild-to-moderate asthma exacerbations: effective, easy, and acceptable. Can Fam Phys 2011;57:1134–1136.
72. Andrews AL, Wong KA, Heine D, Scott Russell W. A costeffectiveness analysis of dexamethasone versus prednisone in pediatric acute asthma exacerbations. Acad Emerg Med 2012;19:943–948.
73. Szlam S, Arnold DH. Identifying parental preferences for corticosteroid and inhaled beta-agonist delivery mode in children with acute asthma exacerbations. Clin Pediatr 2015;54:15–18.
74. Rowe BH, Camargo Jr CA. The role of magnesium sulfate in the acute and chronic management of asthma. Curr Opin Pulmon Med 2008;14:70–76.
75. Shan Z, Rong Y, Yang W, Wang D, Yao P, Xie J, Liu L. Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: a systematic review and meta-analysis. Respir Med 2013;107:321–330.
76. Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. Arch Pediatr Adolesc Med 2000;154:979–983.
77. Ciarallo L, Sauer AH, Shannon MW. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. J Pediatr 1996;129:809–814.
78. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emerg Med J 2007;24:823–830.
79. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo Jr CA. Intravenous magnesium sulfate treatment for acute asthma in the ED: a systematic review of the literature. Ann Emerg Med 2000;36:181–190.
80. Kokotajlo S, Degnan L, Meyers R, Siu A, Robinson C. Use of intravenous magnesium sulfate for the treatment of an acute asthma exacerbation in pediatric patients. J Pediatr Pharmacol Ther 2014;19:91–97.
81. Mutlu GM, Factor P. Alveolar epithelial beta2-adrenergic receptors. Am J Respir Cell Mol Biol 2008;38:127–134.
82. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for non-intubated acute asthma patients. Cochrane Database Syst Rev 2006;4:Cd002884.
83. Rodrigo GJ, Castro-Rodriguez JA. Heliox-driven beta2-agonists nebulization for children and adults with acute asthma: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2014;112:29–34.
84. Golden C, Xu M, Estrada CM, Arnold DH. Clinical outcomes after bilevel positive airway pressure treatment for acute asthma exacerbations. JAMA Pediatr 2014;169:186–188.
85. Wing R, James C, Maranda LS, Armsby CC. Use of high-flow nasal cannula support in the ED reduces the need for intubation in pediatric acute respiratory insufficiency. Pediatr Emerg Care 2012;28:1117–1123.
86. Jat KR, Chawla D. Ketamine for management of acute exacerbations of asthma in children. Cochrane Database Syst Rev (Online) 2012;11:CD009293.
87. Allen JY, Macias CG. The efficacy of ketamine in pediatric ED patients who present with acute severe asthma. Ann Emerg Med 2005;46:43–50.
88. Denmark TK, Crane HA, Brown L. Ketamine to avoid mechanical ventilation in severe pediatric asthma. J Emerg Med 2006;30:163–166.
89. Green SA, Malice MP, Tanaka W, Tozzi CA, Reiss TF. Increase in urinary leukotriene LTE4 levels in acute asthma: correlation with airflow limitation. Thorax 2004;59:100–104.
90. Reiss TF, Hill JB, Harman E, Zhang J, Tanaka WK, Bronsky E, Guerreiro D, Hendeles L. Increased urinary excretion of LTE4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. Thorax 1997;52:1030–1035.
91. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2012;380:2095–2128.
92. Sampson AP, Green CP, Spencer DA, Piper PJ, Price JF. Leukotrienes in the blood and urine of children with acute asthma. Ann NY Acad Sci 1991;629:437–439.
93. Drazen JM, O'Brien J, Sparrow D, Weiss ST, Martins MA, Israel E, Fanta CH. Recovery of leukotriene E4 from the urine of patients with airway obstruction. Am Rev Respir Dis 1992;146:104–108.
94. Dockhorn RJ, Baumgartner RA, Leff JA, Noonan M, Vandormael K, Stricker W, Weinland DE, Reiss TF. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. Thorax 2000;55:260–265.
95. Camargo Jr CA, Gurner DM, Smithline HA, Chapela R, Fabbri LM, Green SA, Malice MP, et al. A randomized placebocontrolled study of intravenous montelukast for the treatment of acute asthma. J Allergy Clin Immunol 2010;125:374–380.

96. Camargo Jr CA, Smithline HA, Malice MP, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. Am J Respir Crit Care Med 2003;167:528–533.
97. Morris CR, Becker AB, Pinieiro A, Massaad R, Green SA, Smugar SS, Gurner DM. A randomized, placebo-controlled study of intravenous montelukast in children with acute asthma. Ann Allergy Asthma Immunol 2010;104:161–171.
98. Ramakrishnan R, Migoya E, Knorr B. A population pharmacokinetic model for montelukast disposition in adults and children. Pharm Res 2005;22:532–540.
99. Cheng H, Leff JA, Amin R, Gertz BJ, De Smet M, Noonan N, Rogers JD, et al. Pharmacokinetics, bioavailability, and safety of montelukast sodium (MK-0476) in healthy males and females. Pharm Res 1996;13:445–448.
100. Migoya E, Kearns GL, Hartford A, Zhao J, van Adelsberg J, Tozzi CA, Knorr B, et al. Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. J Clin Pharmacol 2004;44:487–494.
101. Knorr B, Larson P, Nguyen HH, Holland S, Reiss TF, Chervinsky P, Blake K, et al. Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. J Clin Pharmacol 1999;39:786–793.
102. Schoors DF, De Smet M, Reiss T, Margolskee D, Cheng H, Larson P, Amin R, Somers G. Single dose pharmacokinetics, safety and tolerability of MK-0476, a new leukotriene D4-receptor antagonist, in healthy volunteers. Br J Clin Pharmacol 1995;40:277–280.
103. Alansari K, Ahmed W, Davidson BL, Alamri M, Zakaria I, Alrifaai M. Nebulized magnesium for moderate and severe pediatric asthma: a randomized trial. Pediatr Pulmonol 2015 doi: 10.1002/ppul.23158. [Epub ahead of print].
104. Chande VT, Skoner DP. A trial of nebulized magnesium sulfate to reverse bronchospasm in asthmatic patients. Ann Emerg Med 1992;21:1111–1115.
105. Dalabih A, Harris ZL, Bondi SA, Arnold DH. Contemporary aminophylline use for status asthmaticus in pediatric ICUs. Chest 2012;141:1122–1123.
106. Dalabih AR, Bondi SA, Harris ZL, Saville BR, Wang W, Arnold DH. Aminophylline infusion for status asthmaticus in the pediatric critical care unit setting is independently associated with increased length of stay and time for symptom improvement. Pulmon Pharm Ther 2014;27:57–61.
107. Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, Baker T, et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. Thorax 2011;66:937–941.
108. Bohn D, Kissoon N. Acute asthma. Pediatr Crit Care Med 2001;2:151–163.
109. Bratton SL, Newth CJ, Zuppa AF, Moler FW, Meert KL, Berg RA, Berger J, et al. Critical care for pediatric asthma: wide care variability and challenges for study. Pediatr Crit Care Med 2012;13:407–414.
110. Bratton SL, Odetola FO, McCollegan J, Cabana MD, Levy FH, Keenan HT. Regional variation in ICU care for pediatric patients with asthma. J Pediatr 2005;147:355–361.
111. Roberts JS, Bratton SL, Brogan TV. Acute severe asthma: differences in therapies and outcomes among pediatric intensive care units. Crit Care Med 2002;30:581–585.
112. Newth CJ, Meert KL, Clark AE, Moler FW, Zuppa AF, Berg RA, Pollack MM, et al. Fatal and near-fatal asthma in children: the critical care perspective. J Pediatr 2012;161:214–221.e3.
113. Fernandez MM, Villagra A, Blanch L, Fernandez R. Non-invasive mechanical ventilation in status asthmaticus. Intensive Care Med. 2001;27:486–492.
114. Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV. Noninvasive positive pressure ventilation in status asthmaticus. Chest 1996;110:767–774.
115. Basnet S, Mander G, Andoh J, Klaska H, Verhulst S, Koirala J. Safety, efficacy, and tolerability of early initiation of noninvasive positive pressure ventilation in pediatric patients admitted with status asthmaticus: a pilot study. Pediatric Crit Care Med 2012;13:393–398.
116. Thill PJ, McGuire JK, Baden HP, Green TP, Checchia PA. Noninvasive positive-pressure ventilation in children with lower airway obstruction. Pediatr Crit Care Med 2004;5:337–342.
117. Williams AM, Abramo TJ, Shah MV, Miller RA, Burney-Jones C, Rooks S, Estrada C, Arnold DH. Safety and clinical findings of BiPAP utilization in children 20 kg or less for asthma exacerbations. Intens Care Med 2011;37:1338–1343.
118. Levy BD, Kitch B, Fanta CH. Medical and ventilatory management of status asthmaticusIntensive Care Medicine 1998;24:105–117.
119. Reddy VG. Auto-PEEP: how to detect and how to prevent – a review. Middle East Journal of Anaesthesiology 2005;18:293–312.
120. Martin JG, Shore SA, Engel LA. Mechanical load and inspiratory muscle action during induced asthma. The American Review of Respiratory Disease 1983;128:455–460.
121. Martin JG, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. The American Review of Respiratory Disease 1982;126:812–817.
122. Zimmerman JL, Dellinger RP, Shah AN, Taylor RW. Endotracheal intubation and mechanical ventilation in severe asthma. Critical Care Medicine 1993;21:1727–1730.
123. Baren JM, Boudreaux ED, Brenner BE, Cydulka RK, Rowe BH, Clark S, Camargo Jr CA. Randomized controlled trial of ED interventions to improve primary care follow-up for patients with acute asthma. Chest 2006;129:257–265.
124. Zorc JJ, Scarfone RJ, Li Y, Hong T, Harmelin M, Grunstein L, Andre JB. Scheduled follow-up after a pediatric ED visit for asthma: a randomized trial. Pediatrics 2003;111:495–502.
125. Liberman DB, Shelef DQ, He J, McCarter R, Teach SJ. Low rates of follow-up with primary care providers after pediatric ED visits for respiratory tract illnesses. Pediatr Emerg Care 2012;28:956–961.
126. Scarfone RJ, Zorc JJ, Angsuco CJ. Emergency physicians' prescribing of asthma controller medications. Pediatrics 2006;117:821–827.
127. Lehman HK, Lillis KA, Shaha SH, Augustine M, Ballow M. Initiation of maintenance antiinflammatory medication in asthmatic children in a pediatric ED. Pediatrics 2006;118:2394–2401.
128. Andrews AL, Russell WS, Titus MO, Braden J, Word C, Cochran C, Adams S, Roberts JR. Quality improvement methods improve inhaled corticosteroid prescribing in the ED. J Asthma 2014;51:737–742.
129. Sampayo EM, McLoughlin RJ, Tsevdos D, Alam S, Zorc JJ. Pediatricians support initiation of asthma controller medications in the ED: a national survey. Pediatr Emerg Care 2015;31:545–550.
130. Strikas RA. Advisory committee on immunization practices recommended immunization schedules for persons aged 0 through 18 years – United States, 2015. MMWR 2015;64:93–94.
131. Dawood FS, Kamimoto L, D'Mello TA, Reingold A, Gershman K, Meek J, Arnold KE, et al. Children with asthma hospitalized with seasonal or pandemic influenza, 2003–2009. Pediatrics 2011;128:e27–e32.
132. Center for Disease Control and Prevention (CDC). Vaccination coverage among persons with asthma – United States, 2010–2011 influenza season. MMWR 2013;62:973–978.
133. Venkat A, Chan-Tompkins NH, Hegde GG, Chuirazzi DM, Hunter R, Szczesiul JM. Feasibility of integrating a clinical decision support tool into an existing computerized physician order entry system to increase seasonal influenza vaccination in the ED. Vaccine 2010;28:6058–6064.