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REVIEW

Paediatrics: how to manage acute asthma exacerbations

James S Leung

McMaster University, Faculty of Health Sciences, Department of Pediatrics, McMaster Children's Hospital, Hamilton, ON, Canada

Abstract

Background: Asthma is the most common chronic disease of childhood and a major source of childhood health burden worldwide. These burdens are particularly marked when children experience characteristic 'symptom flare-ups' or acute asthma exacerbations (AAEs). AAE are associated with significant health and economic impacts, including acute Emergency Department visits, occasional hospitalizations, and rarely, death. To treat children with AAE, several medications have been studied and used.

Methods: We conducted a narrative review of the literature with the primary objective of understanding the evidence of their efficacy. We present this efficacy evidence in the context of a general stepwise management pathway for paediatric AAEs. This framework is developed from the combined recommendations of eight established (inter)national paediatric guidelines.

Discussion: Management of paediatric AAE centres around four major care goals: (1) immediate and objective assessment of AAE severity; (2) prompt and effective medical interventions to decrease respiratory distress and improve oxygenation; (3) appropriate disposition of patient; and (4) safe discharge plans. Several medications are currently recommended with varying efficacies, including heliox, systemic corticosteroids, first-line bronchodilators (salbutamol/albuterol), adjunctive bronchodilators (ipratropium bromide, magnesium sulfate) and second-line bronchodilators (aminophylline, i.v. salbutamol, i.v. terbutaline, epinephrine, ketamine). Care of children with AAE is further enhanced using clinical severity scoring, pathway-driven care and after-event discharge planning.

Conclusions: AAEs in children are primarily managed by medications supported by a growing body of literature. Continued efforts to study the efficacy of second-line bronchodilators, integrate AAE management with long-term asthma control and provide fair/equitable care are required.

Keywords: algorithms, asthma, bronchodilator agents, glucocorticoids, paediatric emergency medicine, paediatrics.

Citation

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Introduction

Asthma is the most common chronic disease affecting children worldwide.[1] According to international consensus, asthma is defined as a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyper-responsiveness. Globally, ~11–14% of all children report asthma symptoms, with increasing prevalence reported worldwide.[2]

Measured by school absences, Emergency Department (ED) visits, hospitalization and parental work absence, paediatric asthma is a major burden on childhood and family health worldwide.[3,4] Poorly controlled childhood asthma is associated with a lower quality of life, lower cardiovascular fitness, increased missed school days in children and decreased caregiver productivity.[4,5] The resulting economic costs are substantial, including 10 million school days lost, $726.1 million lost from parental work absence in the United States and $120–140 million in direct patient care costs in Canada.[4]

These human and economic impacts are critically apparent when children experience acute asthma exacerbations (AAEs). AAEs or 'flare-ups' are defined as acute or subacute episodes of progressive increases in asthma symptoms associated with airflow obstruction.[6,7] AAEs are associated with high morbidity and, on rare occasions, mortality, particularly with children from visible minorities and living in socioeconomically disadvantaged environments.[3–5,8] As such, AAEs are one of the most common reasons children seek ED care worldwide. In the United States, 3 million asthma exacerbations in children <18 years of age were reported in 2017, leading to 626,923 ED visits and 75,905 admissions (a top-three cause).[9] In Canada, between

2015 and 2016, 3–10% of all ED visits by children were due to asthma exacerbations, leading to ~6000 hospitalizations and ~8 ED visits for every hospitalization.[5,10]

Timely and appropriate management of an AAE is lifesaving. Multiple medications have been recommended based on varying degrees of evidence of their efficacy, creating some confusion. As such, we felt it was necessary to provide an evidence-based review of the medications used to manage paediatric AAEs. The primary objective of this review is to understand the effectiveness of medications used to manage children presenting with AAEs. Our secondary objective is to contextualize how these drugs are utilized by healthcare providers. We compare and contrast medication recommendations and discuss general care principles described in several national and international paediatric guidelines on AAE management. These descriptions are embedded within a stepwise approach to acute AAE paediatric management synthesized from the included guidelines.

Methods

This review focuses on acute pharmacotherapy for the treatment of paediatric AAE. Baseline asthma control strategies (including allergen avoidance and therapies, harm reduction, and smoking cessation) were determined to be beyond the scope of this review according to the *a priori* determined objectives described earlier. The author recognizes the significant negative impact of economic, ethnic and social inequality on children with asthma.[5,8] However, an in-depth discussion on this important topic is also beyond the scope of this review. Finally, mechanical ventilation strategies were deemed beyond the review's scope.

To identify relevant articles, the author conducted a search literature using OVID Medline between 1946 and December 1, 2020, including articles (Epub Ahead of Print, Abstracts, English, Humans, In-process and other nonindexed citations) with the following MESH terms: 'asthma' (with subheadings drug therapy (/dh), epidemiology (/ep), physiology (/ph), statistics & numerical data (/sn), therapy (/th)) AND 'pediatrics', revealing 460 articles. When multiple studies were found on a topic, the author prioritized systematic review and meta-analysis data when available. A search of the Cochrane Review Library was completed with the search terms 'asthma' (all dates, status, language, type but limited to child health topics), revealing 204 articles. All results were manually reviewed for inclusion and appropriate information abstracted. With review articles, references were assessed and primary evidence sought. Epidemiological data were pulled from United States and Canadian government sources. Finally, the author reviewed the most current AAE management guidelines from the eight most prominent (inter)national organizations[6,7,11–16] (Table 1). These guidelines were selected as they were publicly available, free of major financial influence, and developed by reputed experts with clearly reported methodologies and references.

Table 1. International and national-level guidelines for paediatric acute asthma exacerbations included in this review.[6,7,11–16]

Guideline abbreviation (Reference Number)	Most recent publication year	Country of origin	Rationale for inclusion				
			English language	Industry sponsored	Clear methods and expert involved	Clear presentation	Clear references
GINA (7)	2020	International	Y	N	Y	Y	Y
ICON (6)	2012	International	Y	N	Y	Y	Y
NHLBI (11)	2007	United States	Y	N	Y	Y	Y
PRACTALL (12)	2007	Europe and North America	Y	Y	Y	Y	Y
National Asthma Council (13)	2019	Australia	Y	N	Y	Y	Y
BTS/SIGN (14)	2016	United Kingdom	Y	N	Y	Y	Y
CPS (15)	2012	Canada	Y	N	Y	Y	Y
TREKK (16)	2020	Canada	Y	N	Y	Y	Y

BTS/SIGN, British Thoracic Society/Scottish Intercollegiate Guidelines Network, CPS, the Canadian Paediatric Society; GINA, the Global Initiative for Asthma; ICON, International Consensus on Pediatric Asthma; NHLBI, National Heart, Lung, and Blood Institute Expert Panel 3; PRACTALL, joint guidelines from the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology; TREKK, Translating Emergency Knowledge for Kids.

In lieu of standard reporting guidelines for narrative reviews, this article aims to fulfil criteria from the SANRA scale for assessing narrative review quality.[17]

Results

Overall goals of care

The goals of care for managing children with AAEs are generally understood and shared across multiple guidelines.[15] These goals are the basis of a stepwise approach to managing paediatric AAEs and are (1) immediate and objective assessment of AAE severity; (2) prompt and effective medical interventions to decrease respiratory distress and improve oxygenation; (3) appropriate disposition of patient and (4) a safe discharge home plan. The majority of this review is organized around this stepwise approach.

Immediate and objective assessment of asthma exacerbation severity

A focused history and physical examination are recommended to (1) confirm the diagnosis of an AAE, (2) determine aetiology, (3) determine AAE severity and (4) estimate the risk factors for intensive care unit (ICU) admission.[15] In order to provide appropriate and effective treatment, it is crucial to promptly determine the severity of the AAE. Children with a critical AAE should not have their treatment delayed.

Pertinent clinical information includes previous asthma history, exposure to triggers and asthma medications administered (adherence, dose, timing of medications, social barriers to care). Of critical importance are questions on risk factors for fatal asthma (Table 2). Children with these risk factors require caution and specialist involvement with their care.

By far, respiratory viral infections are the most common trigger for AAEs in children, accounting for ~85% of cases.[18,19] The most common identified virus is human rhinovirus (74%), whereas respiratory syncytial virus and influenza can also trigger severe AAEs. Additional triggers include allergens, drugs (i.e. nicotine smoking), exercise and environmental irritants.[20] Of note, long-term asthma control significantly reduces the likelihood that exposure to the previously mentioned triggers results in an AAE and that medications fail to treat an AAE.[7] Pathophysiologically, AAEs evolve from a complex interplay of three processes, namely airway inflammation, bronchiolar hyper-responsiveness and bronchial constriction[20–23] (Figure 1). Children with poorly controlled baseline asthma have structural remodelling, such as hypertrophic smooth muscle, thickened basement membranes and collagen deposition, resulting in decreased compliance.[23,24] Pharmacological management of AAEs is the mainstay of therapy and targets multiple steps of the previous pathophysiology. However, the previous medications do not address permanent changes from poorly controlled asthma.

In contrast to adults, supplemental pulmonary function tests (PFTs) measuring peak expiratory flow (PEF) and/or forced expiratory volume (FEV1) are de-emphasized in young children. Most children <5 years of age are not developmentally capable of performing these tests appropriately. In a prospective single-centre cohort study, only 54% of children performed initial bedside PEF measures and 48% of tests led to valid information at the start and end of treatment. Children that completed PEF were older (mean 11.2 ± 3.2 years).[25] Likewise, chest x-rays are

Table 2. Risk factors for dying from acute asthma exacerbations.[11,98]

Asthma history:
– Previous severe exacerbation (intubation or intensive care unit admission)
– >2 hospitalization for asthma in the past year
– >3 emergency department visits for asthma in the past year
– >2 canisters of SABAs/month
– Difficulty perceiving AAE symptoms or severity of AAE
– Lack of written asthma action plan
– Currently using or recently stopped oral corticosteroids (a severe AAE marker)
Social history:
– Low socioeconomic status or inner-city residence
– Illicit drug use
– Major psychosocial problems
Comorbidities:
– Cardiovascular disease
– Another chronic lung disease
– Chronic psychiatric disease
– Food allergy

AAE, acute asthma exacerbation; SABA, short-acting β-agonist.

Figure 1. Pathophysiology of an acute asthma exacerbation. At baseline, children with asthma are primed with increased inflammatory cell populations. In response to trigger exposure, these inflammatory cells, along with hyperactive structural bronchial cells, produced excess inflammatory mediators. These inflammatory mediators interact with s mooth muscle and epithelial lung cells to result in early bronchospasm. Continued production of inflammatory mediators results in later-stage inflammation leading to increased mucus production and edema. Both early and late bronchospasms result in progressive bronchiolar obstruction leading to hypoxia and hypoventilation.

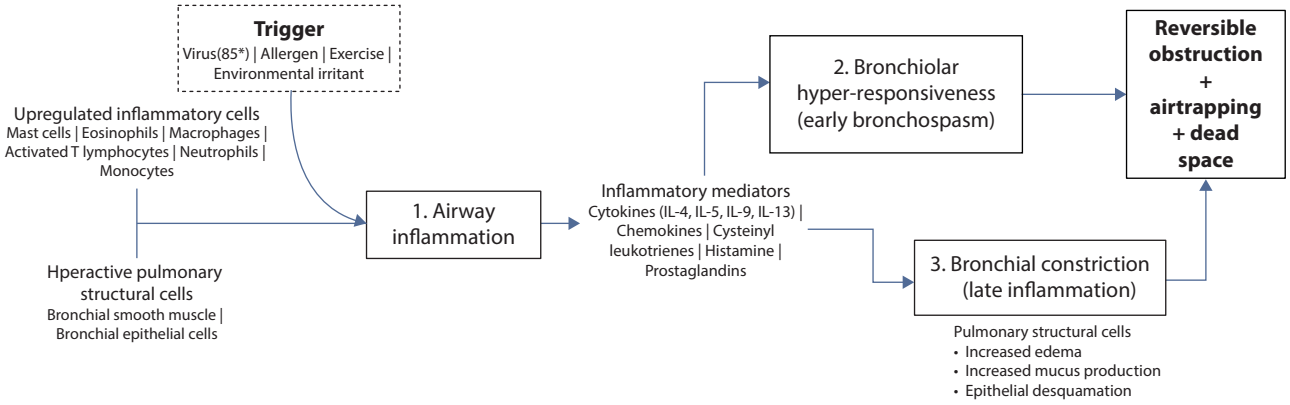

Table 3. Classification of acute asthma exacerbation severity in children.[11,15]

	Mild	Moderate	Severe	Critical
Symptoms				
Breathlessness/speech	Whilst walking	At rest	At rest (sits upright)	
Talks in	Sentences	Phrases	Words	
Mental status	Normal	May be agitated	Usually agitated	Drowsy or confused
Signs				
Work of breathing	Minimal intercostal retraction	Intercostal and substernal retraction	Significant distress; all accessory muscles involved; possible nasal flaring, paradoxical breathing	Marked respiratory distress OR exhaustion/ decreasing effort
Wheeze	Moderate wheeze	Loud expiratory and inspiratory wheeze	Audible wheezing	Silent chest
Oxygen saturations	>94%	91–94%	<90%	<90%
Peak expiratory flow *versus* personal best	>80%	60–80%	Best <60%	Unable to perform

not routinely indicated but are useful in excluding alternative diagnoses. Indications to consider imaging include first wheezing episodes, asymmetric lung findings, unexplained fevers, lack of response to treatment and critical illness.[21] Likewise, routine arterial or capillary blood gases generally do not play much of a role unless the child is critically ill, where they can guide ICU interventions.[15] Children with 'normal range' carbon dioxide levels, despite respiratory distress and tachypnoea, are at high risk for hypercarbic respiratory failure as this value is inappropriately high.[11]

Based on clinical assessment, AAEs are classified by clinicians as either mild, moderate, severe or critical (also referred to as near-fatal or life-threatening AAE in some guidelines) (Table 3).[11,15] There are minor variations in these AAE severity definitions across different guidelines but they are conceptually similar and all largely derived from US guidelines. Several validated clinical scoring tools have been developed to better aid the accuracy and precision of determining AAE severity.[26] These scores include the modified Pulmonary Index Score (PIS),[27,28] the Paediatric Asthma Severity Score (PASS),[29] the

Childhood Asthma Score (CAS)[30] and the Paediatric Respiratory Assessment Measure (PRAM).[31,32] PRAM is the only score endorsed by the one Canadian guideline reviewed.[1] The PRAM score accurately reflects severity of airway obstruction, response to treatment[33,34] and predicts the need for hospitalization 3 hours after initial ED presentation.[35] In a single-centre cohort study of children aged 5–17 years, PRAM was more sensitive to clinical changes than spirometry.[34]

Of note, the classification of severe asthma exacerbation should be differentiated from severe asthma (referring to the degree of baseline disease control). The terms 'severe asthma', 'poorly controlled' and 'persistent asthma' have overlapping definitions and are used interchangeably or in combination (i.e. persistent–severe) by different guidelines. Differentiating between these baseline control terms is beyond the scope of this review.

Subgoal: consideration of alternative and additional diagnoses

Especially for patients with previous AAEs, it is crucial to avoid anchoring bias and exclude alternative causes for wheeze/respiratory distress. Critical differential diagnoses include bronchiolitis, anaphylaxis, pertussis, vocal cord dysfunction, heart failure, foreign body aspiration, cystic fibrosis and lower airway mass effects.[20] Of note, in children <1 year of age, bronchiolitis is the most common reason for wheeze. Bronchiolitis is classically refractory to asthma pharmacotherapy and current treatment guidelines recommend against routine asthma medication 'trials' in children with this suspected diagnosis.[36,37] Conversely, preschool children (aged 1–5 years) are classically underdiagnosed with asthma as they are too young to perform a PFT. A new Canadian guideline details a pragmatic approach to diagnosing asthma in preschool children and advocates that they receive asthma medications.[38]

Furthermore, clinicians should consider comorbid diagnoses requiring additional treatments alongside AAEs. In the correct circumstances, concurrent anaphylaxis should always be considered, with intramuscular epinephrine administered in suspected cases. In younger children, underlying lung pathology, such as bronchopulmonary dysplasia, cystic fibrosis and triggers from nonaccidental injury, should be managed concurrently with AAEs. In toddlers and school-aged children, attention should be paid to concurrent atypical pneumonia requiring antibiotic therapy. A prospective study of 119 children aged 2–15 years hospitalized for severe asthma revealed that up to 20% had mycoplasma pneumonia, particularly in children experiencing their first AAE (50%).[39] Finally, in older adolescents, clinicians should concurrently manage potential coingestions (i.e. smoking, cannabinoids, opioids), withdrawals, vaping-related lung injuries and comorbid mental health concerns.

Prompt and effective medical intervention

Upon diagnosing an AAE and determining its severity, therapy should be promptly initiated. Evidence recommends using clinical pathways to improve the quality of care in acute settings. Clinical pathways are knowledge translation tools providing evidence-based, stepwise guidance on management goals, appropriate medications, doses, plans for escalating care and predefined admissions criteria. In a systematic review of seven studies involving 2600 asthmatic children in ED or inpatient settings, clinical pathway use was associated with decreased hospital length of stay.[40] Additional data from multiple, large single-centre studies also found decreased odds of admission, after implementation of a pathway and a decrease in costs of patients seen in the ED (but not for inpatients).[41–45] Furthermore, a recently published multisite study of ED asthma pathway implementation (83 ED with 22,963 visits) found that it was associated with significantly decreased odds of admission, increased odds of early systemic corticosteroid administration and triage severity assessments.[46]

Several institution-specific pathways have been utilized in the previous studies with similar outcomes, suggesting no one superior pathway exists. Multiple pathways for the management of paediatric asthma exacerbations have been published by large, (inter)national paediatric asthma working groups.[6,7,11–16] The recommended interventions are mostly shared and focus on five subgoals: (1) treatment of hypoxemia (if needed); (2) early administration of corticosteroids; (3) administration of bronchodilators; (4) administration additional critical care medications (if needed); and (5) regular reassessment for treatment response.

Subgoal: treatment of hypoxemia (if needed)

Children with resting hypoxemia and spontaneous respiration require urgent supplemental oxygen. There is no consensus oxygen threshold, with cut-offs ranging between 90% and 94%.[7,11,15] Hypoxemia prior to bronchodilator treatment is a marker of AAE severity. Children with hypoxemia seen in an ambulatory clinic should be transferred to an ED setting with prehospital services involved. Baseline saturations of <92% have been correlated with AAE severity and prolonged frequent bronchodilator therapy.[11,47] Hypoxemia after 1 hour of bronchodilator treatment is a risk factor for hospitalization.[7,11]

For children with mild hypoxemia and severe AAE, heliox is a potential adjunct therapy.[7,11,15] Heliox is a low-density premixed mixture of helium and oxygen (70:30% or 79:21%), allowing improved laminar flow and decreased resistance that theoretically improves oxygenation and ventilation in constricted airways with AAEs. The efficacy of heliox remains unclear, with five randomized control trials (RCT) finding improved PFT and clinical symptoms but no decreased admissions or lengths of hospitalization.[48–52] Of note, heliox is contraindicated in children with higher oxygen requirements (>30%).

Subgoal: early administration of systemic corticosteroids

Systemic corticosteroids are the foundation to 'controlling' AAEs. Steroids decrease airway inflammation by reducing the numbers and activation of inflammatory cells and suppressing the production of immune modulators.[52]

Whereas bronchodilators are critical for acute 'rescue' and stabilization, they are ultimately temporizing measures until corticosteroids take effect after 4–8 hours. As such, early administration of oral steroids within 1 hour of presentation has been strongly associated with reduced hospitalization, the need for ED presentation and duration of symptoms.[53–55] This review deliberately places the administration of systemic corticosteroids in advance of bronchodilator therapy to emphasize early administration. The recommended steroids and dosages are listed Table 4.[6,7,11,38]

For children with mild AAEs, oral corticosteroids are not routinely indicated but may be prescribed based on the child's underlying control and previous history.[7] Of note, for children aged 5–11 years with mild AAE managing at home, increasing inhaled corticosteroid doses (traditionally 4–5× baseline controller doses) is no longer recommended due to new evidence suggesting no effect.[7,56]

For children with moderate/severe AAEs, oral systemic corticosteroids are strongly recommended.[6,7,11–16] Historically, oral prednisolone (active metabolite)/prednisone (prodrug) are recommended with good evidence. A systematic review and meta-analysis of 12 RCTs (863 children and adults) found that early ED administration of prednisolone/prednisone significantly reduced admission rates.[54] The duration of this course ranges from 3 to 5 days, with evidence showing equal benefit from both durations.[57] Recently, guidelines have recommended the administration of oral dexamethasone as an alternative to oral prednisolone/prednisone.[11,15] Dexamethasone, a long-acting corticosteroid (half-life: 36–72 hours) that is six times more potent than prednisone (half-life: 18–36 hours), offers the theoretical advantage of single-dose administration and thereby greater adherence.[58] A high-quality meta-analysis including data from 6 RCTs comparing children receiving 1–2 day courses of oral or intramuscular dexamethasone compared to 3–5 day courses of prednisolone or prednisone in children seen in ED with severe AAEs found no difference in relapse rates but significantly decreased vomiting in children receiving dexamethasone.[59] Regardless of oral corticosteroid use, systematic review and meta-analysis suggest that they are generally safe with few acute systemic adverse drug events, including vomiting, hyperglycaemia and transient mood change. The impact of growth suppression from intermittent systemic corticosteroid doses remain uncertain from current studies.[60,61]

In children with severe/critical AAEs, intravenous (i.v.) methylprednisolone (preferred for minimal mineralocorticoid effects) or i.v. hydrocortisone is recommended as oral medications may not be safely tolerated due to concerns of vomiting.[15,52] However, there is no data suggesting that i.v. formulations provide additional efficacy benefits over oral formulations.[52] Similarly, there is insufficient evidence to support increased intramuscular corticosteroids over oral formulations.[62]

Subgoal: administration of bronchodilators

The cornerstone acute AAE 'rescue' management therapeutics are short-acting bronchodilators. These are divided into first-line and second-line agents and described in the following sections.

First-line bronchodilators Across all major guidelines, short-acting β-agonists (SABAs) are the first-line bronchodilators of choice.6,7,11–16 SABAs activate β2 receptors in medium

Table 4. Recommended corticosteroids for acute asthma medications in children.[7,11,15,16]

Name	AAE severity indication	Route	Dosage[a]	Frequency/ course	Comments
Prednisone/ prednisolone	Moderate/severe (consider in mild)	Oral	1 mg/kg/dose (max 60 mg/ dose)	Once or twice daily x 3–5 days	Adrenal suppression may occur with repeat doses
Dexamethasone	Moderate/severe (consider in mild)	Oral	0.15–0.3 mg/ kg/dose (max 10–16mg)	One dose or two doses spaced 24 hours apart	i.v. administration possible but less preferred Decreased vomiting compared to prednisone/prednisolone
Methylprednisolone	Severe/critical	i.v.	1–2 mg/kg/day (max 60 mg/ day)	Every 6 or 12 hours × 3–5 days	Less mineralocorticoid effects than hydrocortisone
Hydrocortisone	Severe/critical	i.v.	5–7 mg/kg dose (max 400 mg/dose)	Every 6 hours	

[a]Disclaimer: Suggested doses are from North American and International Guidelines. Please refer and adhere to guidelines and recommendations to your local institution, pharmacist or regulatory board.
AAE, acute asthma exacerbation; i.v., intravenous.

and large airways, increasing intracellular cyclic adenosine monophosphate (cAMP).52 cAMP inhibits calcium release from intracellular stores, inhibiting smooth muscle contraction and reversing bronchoconstriction. Salbutamol (international nonproprietary name) or albuterol (US adopted name) is the general SABA of choice and is available in inhalational and i.v. formulations. Salbutamol is a 50:50 mixture of R-(active) and S-(inactive) enantiomers. Whilst levosalbutamol, a pure R-enantiomer theoretically offers more benefit, it is substantially more costly and limited RCT evidence does not support its superiority.[63,64] In general, salbutamol is a safe medication, with adverse effects including transient tachycardia, tremors and hypokalaemia with repeated doses.[61] Recommended dosages are listed in Table 5.

For children with mild/moderate AAEs, evidence strongly suggests salbutamol administered using metered-dose inhalers (MDIs) and spacer devices. A Cochrane systematic review and meta-analysis including 1897 children with mild/moderate AAEs in 39 trials found no significant difference (noninferior) in admission rates and PFT outcomes between children administered salbutamol compared to those administered MDIs and nebulizers.[65] MDIs were associated with decreased lengths of stay, pulse rates and risks of tremor. A further incremental cost-effectiveness analysis of this Cochrane review revealed that MDIs were associated with major cost savings (~$155 Canadian per patient) to healthcare systems.[66] Homemade spacer devices have similar efficacies compared to commercial versions.[65]

However, there is less evidence to support the use of MDIs with spacer devices in children with severe/critical AAEs as the previous studies excluded these patients. There is concern that children with severe/critical AAEs do not have adequate inspirational forces to sufficiently administer salbutamol via MDIs and spacers.[52] As such, most guidelines recommend nebulized salbutamol for severe/critical AAEs.[7,11–16] Evidence from adult studies suggests that continuous nebulization over 60–180 minutes results in significantly improved PFT at 2–3 hours and reduced admission rates compared to intermittent (1 nebulization every 15 minutes) nebulization.[67]

Adjunct bronchodilators Along with salbutamol, several adjunct bronchodilators play an important role in augmenting its effects in children with moderate-to-critical AAEs. The recommended doses of these adjunct bronchodilators are listed in Table 6.

Ipratropium bromide is a short-acting anticholinergic emerging in the early 2000s. Ipratropium bromide is indicated for moderate-to-critical AAEs showing no initial response to SABAs.[7,11,13,15] It produces a mild bronchodilator effect by blocking the interaction of acetylcholine with muscarinic receptors on bronchial smooth muscle cells whilst also decreasing mucosal oedema and secretion.[52] As it does not cross mucous membranes, the central anticholinergic side effects are minimal, with occasional mydriasis, dry mucous membranes and blurred vision reported.[52] Several studies have been conducted, with strong evidence supporting reduced hospitalization rates in children with moderate-to-severe AAE. A systematic review of 2697 children (20 trials) aged 1–18 years with moderate/severe exacerbations found that adding nebulized ipratropium bromide to salbutamol in ED settings significantly reduced the odds of hospital admission.[68] The addition of ipratropium bromide also significantly improved PFT and clinical scores at 120 minutes, oxygen saturation at 60 minutes and the need for repeat salbutamol use as well as decreasing nausea (but not vomiting) and tremor compared to salbutamol alone.[68]

Several limitations of ipratropium bromide should be noted. The majority of children studied were >2 years old. A systematic review and meta-analysis of 321 infants aged <2 years from six parallel control trials found a decreased need for additional treatment compared to salbutamol alone in an

Table 5. Recommended primary bronchodilators for acute asthma exacerbations in children.[7,11,15,16]

Name	AAE severity indication	Route	Dosage[a]	Frequency/course	Comments
Salbutamol (albuterol)	Home/mild/ moderate	MDI with spacer	(100 µg/puff) Home: 2–6 puffs Mild/moderate: 4 puffs (<20 kg) or 8 puffs (>20 kg)	Home: every 20 minutes (max: 2 sets) Mild/moderate: every 20 min for the first hour, then every 30–60 min as needed	Repeat doses optional for mild AAE
Salbutamol (albuterol)	Severe/critical	Nebulizer	2.5 mg (<20 kg) or 5 mg (>20 kg)	Every 20 minutes for the first hour OR continuous for 60–180 min, then every 30–60 min as needed	– If available, continuous is preferred – Monitor potassium

[a]Disclaimer: Suggested doses are from North American and International Guidelines. Please refer and adhere to guidelines and recommendations to your local institution, pharmacist or regulatory board.
AAE, acute asthma exacerbation; MDI, metered dose inhaler.

Table 6. Recommended adjunct bronchodilators for acute asthma exacerbations in children.[7,11,15,16]

Name	AAE severity indication	Route	Dosage[a]	Frequency/course	Comments
Ipratropium bromide	Moderate/severe	MDI with spacer	(17 µg/puff) 3–4 puffs (<20 kg) 6–8 puffs (>20 kg)	Every 20 minutes for first hour	
Ipratropium bromide	Severe/critical	Nebulizer	250 µg (<20 kg) or 500 µg (>20 kg)	Every 20 minutes for first hour	Can mix with salbutamol nebulization
Magnesium sulfate	Moderate/severe/critical	i.v.	25–50 mg/kg i.v. bolus over 20–30 min (maximum 2 g)		– Watch for hypotension – Consider higher doses (75 mg/kg i.v.) for critical AAE

[a]Disclaimer: Suggested doses are from North American and International Guidelines. Please refer and adhere to guidelines and recommendations to your local institution, pharmacist or regulatory board.
AAE, acute asthma exacerbation; MDI, metered dose inhaler.

ED setting but no changes in the length of stay in hospitalized children, symptom improvement in ED or in the number of hospitalized patients.[69] Furthermore, the beneficial effects of ipratropium as an adjunct agent appear to decline with repeated doses. Numerous studies have found that ipratropium bromide with salbutamol in hospitalized children does not result in reduced lengths of stay or symptom improvements compared to salbutamol alone.[70] As such, several guidelines for acute asthma exacerbation limit ipratropium bromide to the initial first hour of management only.[7,11–13,15,16] Finally, several guidelines extrapolate the benefits of MDI and spacer with salbutamol with emerging evidence suggesting that ipratropium bromide delivered in this fashion does not reduce admission rates.[7,11,15,71,72]

Magnesium sulfate (i.v.) also emerged in the early 2000s as a key adjunctive bronchodilator in children with severe-to-critical AAE not responding to repeated or continuous salbutamol and/or ipratropium bromide nebulization.[7,11,15,16] Magnesium is a competitive antagonist for calcium receptors. In addition to inactivating inflammatory cells, magnesium causes bronchiolar smooth muscle relaxation by inhibiting the calcium uptake of myosin fibres required for smooth muscle contraction.[52] Several meta-analyses, combining small numbers from heterogenous studies have shown significant decreases in rates of hospitalization of children with severe AAEs refractory to repeated/continuous nebulized SABAs (at high likelihood of admission) when administered i.v. magnesium sulfate compared to placebo.[73–75] However, as the prevalence of children with severe AAEs is relatively low, there is less evidence for magnesium compared to other bronchodilators. There is limited evidence on the effects of i.v. magnesium on ICU admission rates or length of stay. Most studies utilized dosages from 25 to 50 mg/kg/dose, with occasional studies and ICU experts recommending doses of 75 mg/kg for children with critical AAEs to more rapidly achieve higher serum magnesium concentrations.[52,73] Generally, i.v. magnesium sulfate is safe, with side effects including hypotension under rapid infusion, respiratory depression, facial warmth/flushing, muscle weakness, vision changes and dry mouth.[76] Of note, recently, nebulized magnesium sulfate has been shown to be ineffective as an adjunct therapy in a randomized placebo-controlled, multi-centre parallel trial of 508 children.[77]

Subgoal: administration of critical care medications/therapies (if needed)

On occasions where children with severe/critical AAEs are refractory to the previous medications, second-line bronchodilators and additional critical care medications as well as ventilation interventions are required. These children, classically termed to be in 'status asthmaticus', are at high risk of respiratory failure and require ICU management. Evidence supporting these interventions in children is sparse, owing, fortunately, to the rarity of critical AAEs. As a result, international guidelines do not take a position on these medications,[7] whilst national guidelines diverge, resulting in more variability in care[78] (Table 7).

Classically, the methylxanthine aminophylline (an i.v. form of theophylline) is recommended for the treatment of critical AAEs. Whilst their precise mechanism of action is unclear, methylxanthines are thought to primarily produce a bronchodilator effect by inhibiting phosphodiesterase enzymes that break down cAMP. This increase in cAMP, combined with a possible increase in respiratory drive, catecholamine release, prostaglandin antagonism and inhibition of afferent neuronal activity, is thought to improve pulmonary function.[52] However, in recent years, methylxanthines have fallen out of favour due to concerns of adverse events outweighing the clinical benefit. A systematic review of 7 controlled trials and 380 children admitted with critical AAEs found that the addition of aminophylline to systemic steroids and nebulized SABAs improved PFTs but did not affect symptoms, length of stay, ICU admission and mechanical ventilation rates, whilst leading to a three-fold

Table 7. Recommended secondary bronchodilators and critical care medicines for acute asthma exacerbations in children.[7,11,15,16]

Name	AAE severity indication	Route	Dosage[a]	Frequency/course	Guidelines endorsed by
Aminophylline	Critical	i.v.	5 mg/kg loading dose (omit if on baseline oral theophylline) followed by 1 mg/kg/h infusion	Infusion monitored by ICU Narrow therapeutic index	CPS, ICON, BTS/SIGN, PRACTALL Not recommended by NHLBI, GINA
Salbutamol	Critical	i.v.	7.5 µg/kg bolus over 5 min OR 15 µg/kg bolus over 10 min, followed by 1–2 µg/kg/min infusion (max 5 µg/kg/min)	Infusion monitored by ICU	CPS, ICON, Australia, BTS/SIGN, PRACTALL, TREKK
Terbutaline	Critical	s.c./i.v.	s.c.: 0.01 mg/kg (max 0.25 mg/dose) i.v.: 2–10 µg/kg over 10 min, then 0.1–10 µg/kg/min infusion	s.c.: Every 20 min for first hour, then every 2–6 hours as needed	NHLBI (s.c. – transport setting only)
Epinephrine	Critical	i.m.	1 mg/mL (1:1000) 0.01 mg/kg (max 0.5 mg)	Every 20 min for first hour	NHLBI, GINA (if concerned anaphylaxis only)
Ketamine	Critical	i.v.	Bolus 1–2 mg/kg, followed by 20–60 µg/kg/min infusion		BTS/SIGN

[a]Disclaimer: Suggested doses are from North American and International Guidelines. Please refer and adhere to guidelines and recommendations to your local institution, pharmacist or regulatory board.
AAE, acute asthma exacerbation; BTS/SIGN, British Thoracic Society/Scottish Intercollegiate Guidelines Network, CPS, the Canadian Paediatric Society; GINA, the Global Initiative for Asthma; ICON, International Consensus on Pediatric Asthma; i.m., intramuscular; i.v., intravenous; NHLBI, National Heart, Lung, and Blood Institute Expert Panel 3; PRACTALL, joint guidelines from the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology; s.c., subcutaneous; TREKK, Translating Emergency Knowledge for Kids.

increase in vomiting.[79] Similarly, a systematic review of 15 pooled studies found no significant effect on admissions and PFTs but a significant increase in palpitations/arrythmias and vomiting.[80] This effect is likely due to the narrow therapeutic range of aminophylline (10–20 µg/mL) and its overlap with toxic concentrations (>15 µg/mL).[52] Consequently, some guidelines no longer suggest aminophylline.[7,11]

In contrast, i.v. SABAs are increasingly recommended despite somewhat limited evidence. Currently, two i.v. SABAs are indicated, namely terbutaline and salbutamol. These two SABAs are pharmacologically similar, with terbutaline commonly used in the United States[52] and salbutamol elsewhere. Evidence for i.v. SABAs is limited, with a 2012 systematic review identifying only two RCTs with 46 children in an ICU setting and 29 children in an ED setting. These studies report earlier reductions in the need for recurrent SABA and slight increases in PFT but no reductions in lengths of ICU admission or length of hospitalization.[81] However, a more recent retrospective chart review of 120 children found an association between early initiation of i.v. terbutaline and reduced respiratory failure, ICU admission, and mechanical ventilation.[82] A systematic review comparing the efficacy of i.v. aminophylline and i.v. SABAs in children and adults of status asthmaticus revealed no significant difference in lengths of stay and pulmonary function but a markedly increased risk of adverse effects of giddiness, vomiting and nausea in children administered i.v. aminophylline.[83] The adverse effects of i.v. SABAs include tachycardia, diastolic hypotension, hypokalaemia and cardiac ischaemia.[52] Regarding the latter, multiple prospective case series in children on i.v. terbutaline infusions have found transient increases in troponins but no clinically significant cardiac injury.[84–86]

Injected β-agonists, subcutaneous terbutaline and intramuscular epinephrine are recommended exclusively by one US guideline as a secondary bronchodilator primarily in a prehospital setting or suspected comorbid anaphylaxis.[11] Evidence supporting these medications is especially sparse, originating in the early 1980s from multiple small single-centre studies.[87–89]

Finally, ketamine, a dissociative anaesthetic, analgesic and sedative, is a known bronchodilator indicated for children in truly refractory status asthmaticus with impending respiratory failure/death requiring mechanical ventilation.[52,90] Ketamine produces bronchodilator effects through various mechanisms, including N-methyl-D-aspartic acid receptor antagonism (which normally cause bronchial smooth muscle contraction),

endogenous catecholamine release, anticholinergic effects and immunomodulation.[91] The evidence to support ketamine in critical AAEs with children is mixed, with one placebo-controlled RCT in nonventilated children in an ED setting demonstrating no differences in clinical status, admission, and mechanical ventilation and another observational study finding improved clinical status and PFT.[90,92] In ventilated children in the paediatric ICU with bronchospasm and asthma, retrospective chart reviews have demonstrated improved PFT and compliance.[93,94] The adverse effects of ketamine are minimal with occasional sialorrhea and hallucinations.

Mechanical ventilation A detailed discussion on mechanical ventilation is beyond the scope of this review. Indications to consider mechanical ventilation include impending respiratory arrest, cardiopulmonary arrest, severe hypoxia refractory to second-line bronchodilators and rapid deterioration in a child's mental state.[11,15,52,78] Intubated children are at risk of air trapping and overinflation, requiring specific ventilatory strategies, including permissive hypercapnia (contraindicated if increased intracranial pressure, cardiac failure, toxic overdose), low peak inspiratory pressures, low tidal volumes and longer expiratory times. Critical care expertise is required.

Subgoal: regular reassessment of treatment response
All medications and interventions require repeated assessment and adjustments based on patient status. AAE management pathways/protocols and clinical scoring tools such as PRAM are particularly helpful by inserting time posts for regular reassessments, suggested interventions and objective reassessment criteria. Important reassessment points include the reassessment of AAE severity at 1 and 2 hours postadministration of SABAs (usual endpoints for repeat salbutamol MDI or continuous nebulized salbutamol) and 3–4 hours after systemic corticosteroid administration (usual time of onset). Children showing improvements in AAE severity can have bronchodilator therapy gradually tapered under close supervision. Conversely, children with AAEs that do not improve or worsen require continued or escalated therapy.

Appropriate patient disposition
Children with AAEs can present in the ambulatory clinic, urgent care or ED settings. In some cases, children will arrive after home management adhering to written asthma action plans. Regardless of location, assessing disposition for safe ongoing care is a continuous process.

For children managing at home or presenting to clinical settings, determination of the need to transfer to ED care is critical. The children meeting the following criteria should be immediately transferred for ED care:[7] failure of SABA response (home action plans: symptoms are not relieved promptly with inhaled SABAs – >6 puffs of SABAs for symptom relief in the first 2 hours or no recovery after 24 hours; ambulatory settings: severe AAE failing to resolve within 1–2 hours despite three repeated doses of inhaled SABA); persistent tachypnoea (>40) despite repeated SABA treatment, even if the child shows other clinical signs of improvement; severe/critical AAE signs; lack of capacity for ongoing care; recurrence of signs of severe exacerbation within 48 hours of therapy (especially if systemic corticosteroids already administered); or the child has risk factors for fatal asthma.[11]

For children in an ED, indications for hospitalization and ICU consultation can vary considerably. In general, children that should be admitted include those with[7,11,13] ongoing need for supplemental oxygen; severe AAE despite 1–2 hours of continuous nebulization salbutamol (potential ICU admission); continued moderate AAE for more than 4–6 hours after corticosteroid administration; continued deterioration on conventional treatments; social environment limiting the delivery of care; and risk factors for fatal asthma with a child living at a major geographic distance from appropriate care.

In contrast, children can be considered for ED discharge if they have[7,11,14,15] SABA use <4-hour intervals after 4–8 hours of treatment; adequate oxygen saturations on room air; minimal signs of respiratory distress; improved PFTs (if capable to perform); baseline ambulation and drinking; and safe ongoing monitoring at home.

Appropriate discharge and follow-up instructions
Fortunately, the estimated mortality rate of children with AAEs is low, with a mortality rate of 2.6 per million in 2018 in the United States.[9] Whilst this value does reflect asthma's burden of illness, it highlights that the vast majority of children with appropriately managed AAE will be eventually discharged home. To reduce future AAEs, guidelines suggest that all children being discharged home from medical care should have the following:[7,14–16,95,96] written and verbal instructions on signs of recurrence and worsening asthma; assessment of chronic asthma control (triggers for the AAE should be identified and risks mitigated); a written, individualized action plan, with details for ED care; review of MDI and spacer technique and medications; prescriptions and adequate supplies of SABAs and remaining courses of oral corticosteroids (if applicable); follow-up arranged with primary healthcare providers within 1–2 days of discharge and another in 1–2 months (evidence suggests that telephone follow-up may be a feasible option; social supports improve adherence with low-income families); and paediatric allergist or respirology referrals for critical AAEs.

Discussion

Several advances in medications and strategies in managing paediatric AAEs have been highlighted. Intriguingly, despite the increasing global prevalence, rates of hospitalization in all asthmatic children in North America and high-income countries have declined from the 1980s to date, suggesting improved AAE care and underlying control.[5,9]

In most guidelines, AAE management exists independent and in parallel to long-term disease control. Whereas control strategies focus on individualized care plans to manage the highly heterogenous phenotypes of asthma, guidelines advocate for pathway/protocol-driven care, except in extreme circumstances of critical AAEs.[52] These AAE pathways are guided by the severity of the AAE with treatment largely independent of baseline control. These treatment pathways revert more to expert opinion and individualistic approaches as available evidence diminishes with managing the rare child that presents with status asthmaticus.

In reality, the integral relationship between AAE and long-term asthma control is less distinct than currently conceptualized. On the one hand, the majority of AAEs are preventable and their occurrence reflects disease control. On the other, chronic control influences serial reoccurrences of AAEs and affect AAE severity and therapy responsiveness.[6] It is critical that all caregivers consider both the acute and chronic implications of AAEs in children.

Conclusion

Ultimately, AAEs in children remain a significant burden on children's health and substantial work is required to improve the care of children with AAEs. Identified directions for continued growth include[6,7,11,61,97] higher quality studies on ideal dosing, duration, and efficacy of existing pharmacotherapies and mechanical ventilation (particularly with critical AAEs) targeting outcomes such as hospitalization rates and including data from diverse populations; increased understanding of adverse drug events and developmental impacts of AAE; novel pharmacotherapies; strategies to deliver equitable care for children from identified racial minority and disadvantaged socioeconomic backgrounds; improved knowledge translation and implementation of AAE pathways; and improved integration of AAEs and long-term asthma care approaches.

Key practice points

- Viral infections are the most common trigger for acute asthma exacerbations (AAEs) in children. Some children may need concurrent treatments for other disease processes (i.e. atypical pneumonia, anaphylaxis) that occur in addition to their AAE.
- AEs in children are classified by severity as mild, moderate, severe or critical based on clinical criteria. Bedside pulmonary function testing is de-emphasized in children, as many cannot accurately or reliably perform the test. There is a limited role for routine lab-work and diagnostic imaging.
- The goals of care in managing children with AAEs are (1) immediate and objective assessment of AAE severity; (2) prompt and effective medical interventions; (3) appropriate disposition of patient; and (4) safe discharge home plans.
- Prompt and effective medical interventions for children with AAEs include (1) treatment of hypoxemia (if needed); (2) early administration of corticosteroids; (3) administration of bronchodilators with frequent reassessment; (4) administration of additional critical care medications (if needed); and (5) regular reassessment for treatment response.
- Strong evidence supports the early administration of oral corticosteroids and short-acting β-agonists as primary bronchodilators. Adhering to an asthma pathway based on the severity of the AAE improves the quality of care delivered.
- In contrast with long-term asthma control strategies that are individualized for each patient, AAEs are generally managed by generic stepwise pathways based on illness severity. However, critically ill children with AAEs frequently receive individualized management in the ICU as there is less evidence of efficacy for secondary bronchodilators in this group.

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Correspondence: James Sze-Chuck Leung, 1200 Main Street West, Room 2R104, Hamilton, ON, L8N3Z5, Canada.
Email: leungj16@mcmaster.ca

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