Respiratory Care
Volume 70, Number 5, 2025

DOI: 10.1089/respcare.12897
Published by Mary Ann Liebert, Inc.

RESPIRATORY CARE

CLINICAL PRACTICE GUIDELINES

AARC and PALISI Clinical Practice Guideline: Pediatric Critical Asthma

Benjamin R. White,[1,*] Andrew G. Miller,[2–4] Joyce Baker,[5] Sangita Basnet,[6] Christopher L. Carroll,[7] Hannah Craven,[8] Abdallah Dalabih,[9] Anne M. Fitzpatrick,[10,11] Joel Glogowski,[12] Jose Enrique Irazuzta,[7] Christine A. Kapuscinski,[13] Jesslyn Lenox,[14] Stephanie Lovinsky-Desir,[15] Danielle K. Maue,[16] Gerald Moody,[17] Christopher Newth,[18] Kyle J. Rehder,[2] Anthony A. Sochet,[19] Sana J. Said,[20] L. Denise Willis,[21,22] Elizabeth C. Whipple,[8,23] Lynda Goodfellow,[24,25] and Samer Abu-Sultaneh[26]

Methods
Clinical practice guidelines panel composition and disclosures
Formulation of definition, questions, and outcomes prioritization
Literature review, study selection, and data analysis
Development of clinical practice guidelines
Results
Definition of pediatric critical asthma
Introduction
Recommendations
Limitations
Summary

[1]Dr. White is affiliated with Division of Pediatric Critical Care Medicine, University of Utah, Salt Lake City, Utah, USA.
[2]Mr. Miller and Dr. Rehder are affiliated with Division of Pediatric Critical Care Medicine, Duke University Medical Center, Durham, North Carolina, USA.
[3]Mr. Miller is affiliated with Respiratory Care Services, Duke University Medical Center, Durham, North Carolina, USA.
[4]Mr. Miller is affiliated with Thomas Jefferson University, Philadelphia, Pennsylvania, USA.
[5]Mrs. Baker is affiliated with Breathing Institute, Children's Hospital Colorado Aurora, Colorado, USA.
[6]Dr. Basnet is affiliated with Division of Pediatric Critical Care Medicine, Department of Pediatrics, Southern Illinois University School of Medicine, Springfield, Illinois, USA.
[7]Drs. Carroll and Irazuzta are affiliated with Division of Pediatric Critical Care Medicine, Department of Pediatrics, School of Medicine, University of Florida, Jacksonville, Florida, USA.
[8]Ms. Craven and Ms. Whipple are affiliated with Ruth Lilly Medical Library, Indiana University School of Medicine, Indianapolis, Indiana, USA.
[9]Dr. Dalabih is affiliated with Driscoll Children's Health System, Corpus Christi, Texas, USA.
[10]Dr. Fitzpatrick is affiliated with Division of Pulmonology, Emory University, Atlanta, Georgia, USA.
[11]Dr. Fitzpatrick is affiliated with Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, Georgia, USA.
[12]Mr. Glogowski is affiliated with Georgia State University Library, Atlanta, Georgia, USA.
[13]Dr. Kapuscinski is affiliated with Department of Pharmacy, John R. Oishei Children's Hospital, Buffalo, New York, USA.
[14]Ms. Lenox is affiliated with Respiratory Care Services, South Shore Health System, South Weymouth, Massachusetts, USA.
[15]Dr. Lovinsky-Desir is affiliated with Departments of Pediatrics and Environmental Health Sciences, Columbia University Medical Center, New York, New York, USA.
[16]Dr. Maue is affiliated with Division of Pediatric Critical Care Medicine, Cincinnati Children's Hospital, Cincinnati, Ohio, USA.
[17]Mr. Moody is affiliated with Department of Respiratory Care, Children's Health – Children's Medical Center, Plano, Texas, USA.
[18]Dr. Newth is affiliated with Division of Pediatric Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, California, USA.
[19]Dr. Sochet is affiliated with Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Johns Hopkins All Children's Hospital, St. Petersburg, Florida, USA.
[20]Dr. Said is affiliated with Department of Pharmacy, Comer Children's Hospital, University of Chicago Medicine, Chicago, Illinois, USA.
[21]Ms. Willis is affiliated with Respiratory Care Services, Arkansas Children's Hospital, Little Rock, Arkansas, USA.
[22]Ms. Willis is affiliated with Department of Respiratory Care, College of Health Professions, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.
[23]Ms. Whipple is affiliated with Welch Medical Library, Johns Hopkins University, Baltimore, Maryland, USA.
[24]Dr. Goodfellow is Director of Clinical Practice Guideline Development at the American Association for Respiratory Care, Irving, TX, USA.
[25]Dr. Goodfellow is affiliated with Georgia State University, Atlanta, Georgia, USA.
[26]Dr. Abu-Sultaneh is affiliated with Division of Pediatric Critical Care Medicine, Department of Pediatrics, Indiana University School of Medicine and Riley Hospital for Children, Indiana University Health, Indianapolis, Indiana, USA.

*Address correspondence to: Benjamin R. White, MD, Department of Pediatrics, School of Medicine, University of Utah, PO Box 581289, Salt Lake City, UT 84158-1289, USA, Email: benjaminrobertwhite@gmail.com

Abstract

To address the lack of guidance for clinicians in their care of children with critical asthma, a multidisciplinary team of medical providers used Grading of Recommendations, Assessment, Development, and Evaluation methodology to make the following recommendations:

1. We suggest the use of continuous inhaled short-acting β agonist (SABA) over frequent intermittent SABA in children treated for critical asthma. (Conditional recommendation, very low certainty of evidence)
2. We suggest the use of either high- or low-dose continuous inhaled SABA regimens in children treated for critical asthma. (Conditional recommendation, very low certainty of evidence)
3. We suggest the use of either dexamethasone or methylprednisolone (or an equivalent dose of prednisone/prednisolone) for children treated for critical asthma. (Conditional recommendation, very low certainty of evidence)
4. We suggest the use of intravenous (IV) magnesium (intermittent or continuous) as an adjunct therapy in children treated for critical asthma. (Conditional recommendation, low certainty of evidence)
5. We cannot recommend for or against the use of IV methylxanthines as an adjunct therapy in children treated for critical asthma. (Conditional recommendation, very low certainty of evidence)
6. We suggest the use of an IV SABA infusion as an adjunct therapy in children treated for critical asthma. (Conditional recommendation, low certainty of evidence)
7. We cannot recommend for or against the application of high-flow nasal cannula versus conventional oxygen therapy in children presenting with critical asthma with persistent hypoxemia and/or respiratory distress. (Conditional recommendation, very low certainty of evidence)
8. We suggest the use of bi-level positive airway pressure over conventional oxygen therapy in children presenting with critical asthma with persistent hypoxemia and/or respiratory distress. (Conditional recommendation, very low certainty of evidence)
9. We cannot recommend for or against the application of bi-level positive airway pressure over high-flow nasal cannula for children hospitalized with critical asthma with persistent hypoxemia and/or respiratory distress. (Conditional recommendation, very low certainty of evidence)
10. We cannot recommend for or against the application of heliox in children treated for critical asthma. (Conditional recommendation, very low certainty of evidence)
11. We suggest the use of a dedicated protocol or pathway for managing children treated for critical asthma. (Conditional recommendation, low certainty of evidence)

Keywords: status asthmaticus, bronchodilator, glucocorticoids, magnesium, aminophylline, terbutaline, heliox, high-flow nasal cannula, bi-level positive airway pressure, noninvasive ventilation, asthma, children, clinical practice guideline, noninvasive respiratory support, evidenced-based guideline

Introduction

Pediatric asthma results in a tremendous burden on children, families, and medical systems worldwide. In the United States, 7% of those under 18 years of age suffer from asthma, affecting over 5 million children. As a result, there are approximately 750,000 emergency department visits and 74,000 hospital admissions annually for pediatric asthma exacerbations, contributing nearly $6 billion in yearly costs.[1,2] Asthma is rarely fatal in children, but those with severe exacerbations commonly present to an emergency department (ED) and require admission to the general ward or the pediatric intensive care unit (PICU).[3–5] Once in these settings, if initial therapy fails to adequately resolve symptoms, clinicians are left to choose between an array of different pharmaceutical agents and respiratory support modalities with limited evidence-based guidance. As a result, practice variability is high.[5,6]

To improve the care of children affected by asthma, multiple national and international guidelines have been developed to guide its diagnosis and management, including the National Asthma Education and Prevention Program in the United States and the Global Initiative for Asthma, among others.[7,8] These guidelines provide limited guidance for hospitalized children with severe asthma exacerbations and have not produced a consensus definition of critical asthma that would guide research in this population. As a result, providers who care for these patients are left to derive best practices from institutional protocols and narrative reviews.[9–14] To address these gaps in knowledge and facilitate a shared understanding among providers, we aim to establish a contemporary

definition and the first clinical practice guidelines for pediatric critical asthma.

Methods

Clinical practice guidelines panel composition and disclosures

The project co-chairs (B.R.W., A.G.M., and S.A.-S.) with the help of a guideline methodologist (L.G.) identified potential experts who had published studies related to pediatric critical asthma in the last 10 years. Including the co-chairs, the panel consisted of 11 physicians (10 pediatric intensivists and 1 pediatric pulmonologist), 5 respiratory therapists (RTs), 2 pharmacists, and 1 advanced practice registered nurse. Three medical librarians (H.C., J.G., and E.C.W.) with experience in systematic reviews assisted the panel with creating search strategies, performing literature searches, and systematic reviews. Conflict-of-interest disclosure forms were reviewed, and no disqualifying conflicts were noted (see Supplementary Data).

Formulation of definition, questions, and outcomes prioritization

The definition of pediatric critical asthma was developed using modified Delphi process with 2 rounds of voting to reach an agreement level >80%. The initial definition was created based on detailed discussions among the panel prior to any data extraction and allowed for a shared inclusion criteria for studies in the systematic review. Subsequently, the panelists had a series of meetings and revised the definition using data extracted from studies included in the systematic reviews before the final voting.

Clinical questions were chosen based on perceived importance and priority. These questions were related to continuous or intermittent use of inhaled short-acting β agonist (SABA), systemic corticosteroids, intravenous (IV) magnesium, IV methylxanthines, IV SABA, the use of noninvasive respiratory support (NRS), the use of heliox, and the use of protocols or care pathways. Eight PICO (Population, Intervention, Comparators, and Outcomes) questions were developed from these topics by the project co-chairs after extensive literature review and presented to the project panel. After discussion and refinement of the PICO questions, initial outcomes were narrowed through voting to critical and important outcomes, which included intubation rate, mortality, hospital admission, hospital stay, NRS use rate, PICU admission, PICU stay, and change in acute asthma severity score. The protocol for the systematic reviews was registered on PROSPERO (CRD42023409281). Details of the PICO questions considered are shown in Table 1.

Literature review, study selection, and data analysis

Comprehensive search strategies were composed and conducted by the medical librarians based on panel members feedback and provided target articles. Multidatabase literature search was performed in Ovid for MEDLINE and Embase simultaneously. CINAHL Complete (EBSCO) was also searched. The initial literature searches were performed in 2023 and updated on July 3, 2024. No search filters or limitations were used. The complete search strategies for each PICO question are provided in the Supplementary Data.

The returned references were screened for inclusion in Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Studies were included if their subjects were children with asthma requiring treatment in the ED, hospital ward, intermediate care unit or critical care unit, involved an intervention delineated in the chosen PICO questions, and had subjects ≥2 years of age and <18 years of age. Study designs included human studies, randomized controlled trials (RCTs), and observational studies. Systematic reviews were reviewed to ensure all relevant articles were included in the abstract screening stage. Studies were excluded if they met any of the following criteria: only included subjects whose asthma exacerbations were managed in the out-patient setting, only included subjects 18 years of age and older, animal studies, laboratory studies, physiological studies, expert opinions, or case studies. Studies that examined ED management of subjects with asthma, as well as included data on in-patient management and outcomes, were included if they met the other inclusion criteria. For each PICO question, at least 2 panelists screened each abstract in Covidence to determine if the article met inclusion and/or exclusion criteria. Once the initial screening was completed, conflicts in screening agreement were resolved via discussion among panel members or by the co-chair assigned to that PICO question. Full-text articles were then dually screened using the Covidence platform and conflicts were resolved similar to the abstract screening stage. Included full-text articles were uploaded for data extraction to REDCap (Research Electronic Data Capture), a secure, web-based software platform designed to support data extraction for research studies.[15,16] Once full-text data were extracted, odds ratios were obtained when available to report the results for binary outcomes and mean differences or standardized mean differences. To report the results for continuous outcomes, a 95% CI was used. Meta-analyses were performed when studies had consistent outcomes that allowed pooling of data.

Table 1. List of PICO questions and recommendations

#	PICO question	Recommendations	Strength of recommendation	Certainty of evidence
1	In children presenting with critical asthma, should frequent intermittent (hourly or every 2 h) or continuous inhaled SABA be administered?	We suggest the use of continuous inhaled SABA over frequent intermittent regimens in children treated for critical asthma.	Conditional	Very low
2	In children presenting with critical asthma, should high- or low-dose continuous inhaled SABA be administered?	We suggest the use of either high- or low-dose continuous inhaled SABA regimens in children treated for critical asthma.	Conditional	Very low
3	In children presenting with critical asthma, should dexamethasone or methylprednisolone (or an equivalent dose of prednisone/prednisolone) be administered as the systemic corticosteroid regimen?	We suggest the use of either dexamethasone or methylprednisolone (or an equivalent dose of prednisone/prednisolone) for children treated for critical asthma.	Conditional	Very low
4	In children presenting with critical asthma, should IV magnesium (continuous or intermittent) be administered as an adjunct therapy?	We suggest the use of IV magnesium (intermittent or continuous) as an adjunct therapy in children treated for critical asthma.	Conditional	Low
5	In children with critical asthma, should IV methylxanthines (continuous or intermittent) be administered as an adjunct therapy?	We cannot recommend for or against the use of IV methylxanthines as an adjunct therapy in children treated for critical asthma.	Conditional	Very low
6	In children with critical asthma, should an IV SABA infusion be administered as an adjunct therapy?	We suggest the use of IV SABA as an adjunct therapy in children treated for critical asthma.	Conditional	Low
7	In children presenting with critical asthma with persistent hypoxemia and/or respiratory distress, should NRS be initiated?	We cannot recommend for or against the application of HFNC versus conventional oxygen therapy in children presenting with critical asthma with persistent hypoxemia and/or respiratory distress.	Conditional	Very low
8		We suggest the use of NIV over conventional oxygen therapy in children presenting with critical asthma with persistent hypoxemia and/or respiratory distress.	Conditional	Very low
9	In children presenting with critical asthma who are initiated on NRS, which NRS modality (HFNC or CPAP or NIV) should be administered?	We cannot recommend for or against the application of NIV over HFNC for children hospitalized with critical asthma with persistent hypoxemia and/or respiratory distress.	Conditional	Very low
10	In children presenting with critical asthma, should heliox be administered?	We cannot recommend for or against the application of heliox in children treated for critical asthma.	Conditional	Very low
11	In children presenting with critical asthma, should a dedicated protocol or pathway be used to manage care?	We suggest the use of a dedicated protocol or pathway for managing children treated for critical asthma.	Conditional	Low

NIV, noninvasive ventilation; HFNC, high-flow nasal cannula; IV, intravenous; NRS, noninvasive respiratory support; SABA, short-acting β agonist.

Development of clinical practice guidelines

For each PICO question, the committee developed recommendations based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology, (https://gdt.gradepro.org/app/handbook/handbook.html).[17] Recommendations for each PICO question considered the quality of evidence, a balance of desirable and undesirable effects, assumptions of patient values and preferences, use of resources, health equity, acceptability of an intervention, and the feasibility of implementation. According to the GRADE process, the certainty of effect estimates for each outcome were then categorized as high, moderate, low, or very low. Evidence tables were created to assess the quality of the evidence (see Supplementary Data). In addition to clinical data, risk of bias was assessed using risk of bias 2 for RCTs and ROBINS-I for observational studies.[18] Evidence profiles for each question were prepared and reviewed by PICO members and co-chairs (see Evidence to Decision tables for each PICO question; Supplementary Data). The committee discussed recommendations and their strength until agreement of >80% was achieved on the final wording and rationale with qualifications for each PICO question using 2 rounds of anonymous electronic voting. Recommendations were designated as strong or conditional and the terminology "we recommend" was used for strong recommendations and "we suggest" for conditional recommendations (Table 2).[18] Further descriptions and details of the methodology used can be found in section A of the

Supplementary Data. Abbreviations used in guideline statements are summarized in Table 3.

Results

This guideline includes the definition of pediatric critical asthma and 11 recommendations developed from 8 PICO questions. These are included in Table 1 with the coinciding strength of recommendation and quality of evidence rating.

Definition of pediatric critical asthma

The pediatric critical asthma definition is shown below. The discussions among the panelists resulted in a definition that prioritized treatment-based criteria over location or physiologic-based criteria owing to the variability in where children with severe asthma are placed within hospitals and owing to the challenges of physiologic testing during severe exacerbations. Additionally, although the panelists acknowledged that bronchospastic disease can occur at any age, the definition excludes children under 2 years of age to prevent confounding the defined population with children whose primary pathology is bronchiolitis. This definition is also presented in Table 4.

Recommendations

Inhaled SABA. In children presenting with critical asthma, should frequent intermittent (hourly or every 2 h) or continuous inhaled SABA be administered?

Sub-question: In children presenting with critical asthma, should high- or low-dose continuous inhaled SABA be administered?

Recommendation 1. We suggest the use of continuous inhaled SABA over frequent intermittent SABA in children treated for critical asthma.

(Conditional recommendation, very low certainty of evidence).

Recommendation 2. We suggest the use of either high- or low-dose continuous inhaled SABA regimens in children treated for critical asthma.

(Conditional recommendation, very low certainty of evidence).

Background. Continuous SABA nebulization is widely used in the treatment of critical asthma in children, and experts have recommended its use in children who are not sufficiently improved following intermittent SABA therapy.[19–26] Despite widespread use, it remains unclear if there is adequate evidence to support its efficacy compared with intermittently delivered inhaled SABA.

Summary of evidence. We identified 3 RCTs[27–29] and 1 observational study[30] examining the use of inhaled continuous SABA compared with intermittently delivered SABA (see Supplementary Data). The SABA agent used varied between the studies: 1 used albuterol,[27] 1 used terbutaline,[28] and 2 used salbutamol.[29,30] One study was performed in the PICU[27] and 3 were performed in a non-ICU ward.[28–30]

Intubation rate was not different between the 2 interventions in 2 RCTs.[27,30] There was no difference in PICU or hospital stay in 2 RCTs or 1 observational study.[27,29,30] One RCT noted faster improvement in acute asthma severity score in the continuous group,[27] whereas 1 observational study noted less escalation in respiratory support with continuous nebulization.[30] Duration of SABA administration was longer in the continuous SABA group in 1 RCT and 1 observational study.[27,30] Continuous SABA required significantly less RT time to administer compared with intermittent SABA in 1 RCT.[27] Adverse events (increase in heart rate, systolic and diastolic blood pressure hypotension, and the incidence of arrythmia) were similar between the 2 interventions in the 3 RCTs.[27–29]

Two observational studies compared the use of high- with low-dose (10 vs 25 mg/h and ≤0.58 mg/kg/h vs >0.58 mg/kg/h) continuously inhaled SABA, and both used albuterol as the SABA agent.[31,32] Intubation rate, NRS use rate, PICU stay, and hospital stay were not different between the 2 groups.[31,32] Adjunct therapy use was similar between the interventions, though the high-dose continuous albuterol group received more fluid blouses than the low-dose continuous group.[31,32]

Justification. Despite the lack of significant clinical outcome benefit from continuous compared with intermittent inhaled SABAs, the benefit of continuous SABA to RT

Table 2. Implications of strength of recommendations to stakeholders

Stakeholder	*Strong recommendation*	*Conditional recommendation*
Patients	Most individuals in this situation would want the *recommended* course of action and only a small proportion would not.	The majority of individuals in this situation would want the *suggested* course of action, but many would not.
Clinicians	Most individuals should receive the *recommended* course of action.	Recognize that different choices will be appropriate for different patients and that you must help each patient arrive at a management decision consistent with her or his values and preferences.
Policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions.

Table 3. List of abbreviations

ED	Emergency department
HFNC	High-flow nasal cannula
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IV	Intravenous
Mg	Magnesium
NRS	Noninvasive respiratory support
PICO	Population, Intervention, Comparators, and Outcomes
PICU	Pediatric intensive care unit
QI	Quality improvement
RCT	Randomized controlled trial
RT	Respiratory therapist
SABA	Short-acting β agonist

staffing is significant. Continuously delivered medication requires significantly less time and staffing than intermittent therapy. Papo et al found that continuous SABA required fewer total relative value units than intermittent (14 [range 6–26] vs 33 relative value units [range 25–45], $P = .01$).[27] In a busy hospital setting where bedside provider time can be limited, this staffing benefit may be clinically important, especially since many RT departments have struggled with burnout and staffing challenges.[33] The optimal duration of continuous SABA and the ideal transition point to less frequent administration (≥2 h) when a patient's clinical status has improved remain unclear. The use of a validated acute asthma severity score may help in the decision-making process of that transition and has been shown to result in shorter PICU and hospital stay (see Recommendation #11).

The evidence for the benefits of high-dose versus low-dose continuous SABA was also very low. In the studies examined, there was no significant improvement with higher-dose SABA and the use of lower dose may be associated with fewer fluid boluses.[31] Of note, other investigators have reported the use of very high doses of albuterol (75 mg/h and 150 mg/h) far exceeding the doses used in the included studies, though they did not compare this usage to lower-dose regimens.[34]

Table 4. Definition of pediatric critical asthma

Pediatric critical asthma is defined as a severe asthma exacerbation in children ≥2 and <18 years of age which:

- Requires hospital admission.
- Is refractory to intermittent inhaled short-acting β agonists (SABA) and systemic corticosteroids.
- Necessitates continued management with continuous inhaled SABA and/or adjunctive asthma therapies, which include:
  - Continuous IV SABA (terbutaline, salbutamol, epinephrine)
  - IV methylxanthines (aminophylline)
  - IV magnesium
  - Helium-oxygen mixture
  - Noninvasive respiratory support (NRS) (high-flow nasal cannula [HFNC], CPAP, noninvasive ventilation [NIV]).
  - Invasive mechanical ventilation
  - Inhaled anesthetics
  - Extracorporeal membrane oxygenation

Future research opportunities. Studies are needed to determine optimal times for transition from continuous to intermittent SABA, utilizing the known effectiveness of implementing nurse- or RT-led protocols to ensure timely adherence to those clinical time points. These studies should also include how to best utilize SABA therapies in those patients who require HFNC, CPAP, NIV, and invasive mechanical ventilation. Interventional trials examining the use of very high doses of SABA (eg, >25 mg/h of albuterol) to more commonly used doses (10–20 mg/h of albuterol) are needed to compare the efficacy and adverse effects of the 2 regimens. As delivery of SABA to lower airways can be affected by the nebulizer type (mesh vs other nebulization methods)[35] and respiratory support devices (aerosol mask vs HFNC vs CPAP vs NIV),[13] high-quality physiological and clinical studies are needed to compare delivery methods for inhaled SABA in the pediatric population.

Systemic corticosteroid.

In children presenting with critical asthma, should dexamethasone or methylprednisolone (or an equivalent dose of prednisone/prednisolone) be administered as the systemic corticosteroid regimen?

Recommendation 3. We suggest the use of either dexamethasone or methylprednisolone (or an equivalent dose of prednisone/prednisolone) for children treated for critical asthma.

(Conditional recommendation, very low certainty of evidence).

Background. Recent evidence has suggested that dexamethasone may be similarly effective to prednisone for the management of asthma exacerbations in the ED and hospital setting and may even be favored because of palatability, reduced treatment course, and comparable outcomes, although the quality of this evidence is low.[36–38] Evaluation of studies comparing dexamethasone versus methylprednisolone (or equivalent doses of prednisone) for the management of critical asthma is needed to determine if similar benefits may be present in this population.

Summary of Evidence. We identified 2 RCTs,[39,40] 1 quasi-randomized trial,[41] and 6 observational studies[42–47] comparing dexamethasone and prednisone derivatives in children with critical asthma (see Supplementary Data). Four observational studies examined outcomes before and after an institutional protocol change that transitioned to the use of dexamethasone for acute asthma management[43–45,47] and 2 additional studies examined this comparison leveraging the multihospital system Pediatric Health Information System database.[42,46] These studies had significant variation in the corticosteroid formulation used and hospital

setting. Three studies were performed in the PICU[39,40,46] and 6 in a non-ICU ward.[41–45,47]

The intubation rate was lower among those treated with dexamethasone compared with methylprednisolone in 1 observational study.[46] The same study showed no difference in mortality or NIV use but did report reduced CPAP usage in the dexamethasone group. The children in the dexamethasone group had lower chronic asthma severity, which may have affected the measured outcomes. In 4 pooled observational studies, PICU admissions were not different between groups.[42,44,45,47] PICU stay was assessed in 1 RCT and showed no difference between groups.[39] Hospital stay was evaluated in 2 RCTs,[39,40] 1 quasi-randomized trial,[41] and 6 observational studies,[42–47] which showed a small decrease in the dexamethasone group. Use of adjunct asthma therapies showed no difference in 1 quasi-randomized trial[41] and was lower in the dexamethasone group in 1 observational study.[46] Three observational studies[42,43,46] reported reduced costs with dexamethasone compared with methylprednisolone, whereas a fourth showed no difference.[44] Adverse events were lower in the dexamethasone group in 1 observational study[46] but were not different between groups in 1 RCT and 1 quasi-randomized trial.[40,41]

Justification. The certainty of existing evidence was not sufficient to favor the intervention (dexamethasone) or the comparison (methylprednisolone). There were few high-quality RCTs and results were mixed across the studies. The observational studies also offered conflicting results and were difficult to compare owing to variability in study designs, variability in corticosteroid dosing and formulations, and the use of historical controls. Additionally, though hospital stay was decreased for dexamethasone in most of the evaluated studies, this outcome may not be well suited for comparisons of pharmacologic effectiveness in observational studies given all the confounding factors that affect it. Other comparisons, such as time to weaning of respiratory support, symptom trajectories, and patient-reported outcomes such as tolerability, may add important additional context, though these continue to be affected by confounders.

The comparative effectiveness of dexamethasone versus methylprednisolone remains an important question, particularly as many hospital systems have transitioned to using dexamethasone for the acute management of asthma in ED settings. Continued management with dexamethasone in the PICU may be desirable in those hospitals with dexamethasone-based ED protocols for continuation of therapies and may possibly be associated with more favorable outcomes.

Future research opportunities. Future research with rigorous RCT design including double blinding of providers and subjects with placebo control is needed to evaluate the best corticosteroid regimen for children with critical asthma. These studies may need to be informed by future pharmacokinetic and pharmacodynamic studies as well as careful consideration of the best outcomes of pharmacologic effectiveness to measure in this complex population. Pharmacologic and clinical studies are needed to investigate the optimal equivalent dosing and duration of dexamethasone compared with the traditional methylprednisolone dosing and whether dosing regimens including both medications can be effective.

IV magnesium.

In children presenting with critical asthma, should IV magnesium (continuous or intermittent) be administered as an adjunct therapy?

Recommendation 4. We suggest the use of IV magnesium (intermittent or continuous) as an adjunct therapy in children treated for critical asthma.

(Conditional recommendation, low certainty of evidence).

Background. IV magnesium has been frequently utilized in pediatric asthma and offers several advantages as an adjunct therapy for critical asthma including ease of administration, low cost, wide availability, and a favorable safety profile.[14] Proposed mechanisms of action include direct bronchodilation via an increase in calcium uptake into the sarcoplasmic reticulum and subsequent smooth muscle relaxation, reduced inflammation via inhibition of histamine release, enhanced β agonist activity via regulation of adenylyl cyclase and sodium and potassium ATPase, and inhibition of acetylcholine release at motor nerve terminals.[48,49] IV magnesium use has been described in the ED, hospital ward, and PICU settings (both as intermittent dosing and continuous infusion), but rigorous evaluation of its use in pediatric critical asthma has been lacking.

Summary of evidence. We identified 3 RCTs[50–52] and 5 retrospective observational studies[53–57] evaluating the impact of IV magnesium administration on clinical outcomes for pediatric patients with critical asthma (see Supplementary Data). The studies differed significantly in the dosing, administration timing, and hospital setting; 4 studies were conducted in the ED,[50,51,55,57] 2 in a non-ICU ward,[54,56] and 2 in PICU/hospital ward.[52,53]

Two RCTs[51,52] demonstrated lower intubation rates with the use of IV magnesium, whereas 1 observational study[56] showed no benefit of IV magnesium over placebo. The use of NRS was lower in the IV magnesium group in 1 RCT,[51] higher in 1 observational study,[53] and similar in 2 others.[56,57] The need for NRS or invasive mechanical ventilation was higher in the IV magnesium

group in 1 RCT[51] but lower in 1 observational study.[54] NRS duration was lower with IV magnesium use in 1 observational study.[56] Duration of invasive mechanical ventilation was shorter in the IV magnesium group in 1 RCT[51] but similar in 1 observational study.[56] PICU admission was higher in the IV magnesium group in 1 observational study[53] but lower in another observational study.[54] PICU stay was shorter in 1 RCT[51] but longer in another RCT.[52]

A meta-analysis of 3 RCTs[50–52] showed shorter hospital stay in the IV magnesium group; however, 2 observational studies[53,54] showed longer stay or no difference. Change in acute asthma severity score was evaluated in 1 RCT,[50] which showed that acute asthma severity score improved at 3 h with IV magnesium. Nebulized bronchodilator use was lower with IV magnesium in 1 RCT,[52] whereas duration of continuous SABA was longer in the IV magnesium group in 2 observational studies, likely related to higher illness severity.[53,54] In a cost simulation analysis,[55] IV magnesium use was associated with lower total cost compared with no IV magnesium. One RCT did not report hypotension associated with IV magnesium administration,[50] whereas hypotension during magnesium administration that resolved within 1 h was observed in another RCT.[52] Similarly, an observational study found that hypotension was not increased with IV magnesium administration.[53]

Justification. IV magnesium is readily available, relatively inexpensive, possesses a favorable safety profile, and is easily administered. These qualities allow it to be deployed widely, even in many resource-limited settings. Although observational studies presented conflicting results, the more rigorous study designs (RCTs and meta-analyses) suggested a benefit to IV magnesium for intubation rates, stay, acute asthma severity score, nebulization rates, and cost. With these advantages and the aggregate evaluation of outcomes favoring IV magnesium, our panel believes the benefits of this intervention justify its use in pediatric critical asthma. The observed dose of IV magnesium administered in these studies varies significantly with intermittent doses ranging from 25 mg/kg to 100 mg/kg over 20–35 min, whereas other studies showed efficacy and safety of continuous infusions at approximately 20 mg/kg/h.[58] Additional studies have shown that higher-dose continuous infusions may also be feasible and effective.[59,60] As a result, we cannot recommend a specific dosing regimen. Patients should be monitored for adverse effects including hypotension and drug reactions (redness, warmth, tingling) at the infusion site. When hypotension occurs, it is usually mild and can be treated with fluid boluses or slowing the rate of IV magnesium infusion.

Future research opportunities. There is a need for large, high-quality RCTs to evaluate the efficacy and safety of IV magnesium in children with critical asthma as well as a need for investigation into the appropriate triggers to start IV magnesium, the optimal administration regimens, and the proper duration of use in this population. Additionally, the utility of monitoring serum magnesium levels (or ionized magnesium levels) should be studied to determine whether targeted ranges affect clinical outcomes.

IV methylxanthines.

In children with critical asthma, should IV methylxanthines (continuous or intermittent) be administered as an adjunct therapy?

Recommendation 5. We cannot recommend for or against the use of IV methylxanthines as an adjunct therapy in children treated for critical asthma.

(Conditional recommendation, very low certainty of evidence).

Background. Theophylline, a methylxanthine, commonly administered in its compounded form aminophylline, is a naturally occurring xanthine derivative with mechanisms of action that include smooth muscle relaxation through inhibition of phosphodiesterase isoenzymes, antagonizing adenosine receptors, and enhancing histone deacetylase activity.[61] Though methylxanthine agents remain commonly used for pediatric asthma worldwide because of their availability and affordability, their narrow therapeutic window, potential serious adverse effects, and the advent of widely available inhaled SABAs have led to their decreased use.[62] The most recent National Institutes of Health guidelines on asthma management recommends against their use in asthma exacerbations in children either in the ED or in-patient, citing no benefit and increased toxicity, but their utility in pediatric critical asthma remains an important unanswered question.[21]

Summary of Evidence. We identified 9 RCTs[63–71] and 1 observational study[72] comparing IV methylxanthine with placebo (see Supplementary Data). One RCT was conducted in the PICU,[70] one in both PICU and non-ICU ward,[69] 2 in the ED,[66,71] and 5 in a non-ICU ward.[63–65,67,68] The observational study was conducted in the PICU.[72]

The intubation rate was lower in the IV methylxanthine group in 1 RCT,[69] and no difference was found between groups in a second RCT.[70] One RCT[69] found a decrease in oxygen requirements in the IV methylxanthine group, whereas 3 others found no difference.[64,66,71] One observational study found no difference in NIV rate between groups.[72] Duration of invasive mechanical ventilation was evaluated by 1 RCT,[69] with no difference between groups. PICU stay was not different between

groups in 1 RCT,[70] and 1 observational study[72] reported a lower likelihood of discharge from PICU in the IV methylxanthine group. Two RCTs[69,71] showed no difference in PICU admission rate between groups. Five RCTs[65,67,69–71] evaluated hospital stay, and although one[70] found a decrease in the IV methylxanthine group, no difference was found in the remaining studies, and a pooled analysis also found no difference. Changes in acute asthma severity score were evaluated by 7 RCTs[63,64,66–70] and 1 retrospective observational study.[72] Two RCTs[69,70] demonstrated a significant reduction in acute asthma severity score in the IV methylxanthine group at 6 and 24 h, respectively, with no difference found in the remaining studies. Adverse events (nausea, emesis, insomnia, headache, and abdominal pain) were found to be more frequent in the IV methylxanthine group in 4 RCTs[64–66,69] and in a pooled analysis of their results.

Justification. Although individual studies[69,70] reported some positive outcomes favoring IV methylxanthine over placebo, pooled effect models did not demonstrate statistical significance, and the certainty of those effects was determined to be low or very low. The increased rates of adverse events in the IV methylxanthine group in 4 RCTs, however, were felt to have a high certainty of evidence. Additionally, doses of IV methylxanthine and goal drug levels were not standardized between studies, which could contribute to differences in efficacy and toxicity. Given these findings, our panel did not consider the evidence available strong enough to recommend for or against IV methylxanthine. It would be reasonable for clinicians, especially those in low-resource environments, to consider IV methylxanthines in children with refractory critical asthma when other therapies have failed or are unavailable. When used, it is crucial to closely monitor serum levels (if available) and adverse events.

Future Research Opportunities. Well-designed, multicenter RCTs are necessary to further evaluate the use of IV methylxanthines in pediatric critical asthma. These studies should focus on key outcomes such as intubation rate, hospital and PICU stay, adverse events, and change in acute asthma severity score. Additionally, pharmacokinetic evaluations are needed to explore optimal dosing strategies and therapeutic serum levels of IV methylxanthines.

IV β 2 agonist.

In children with critical asthma, should an IV SABA infusion be administered as an adjunct therapy?

Recommendation 6. We suggest the use of an IV SABA infusion as an adjunct therapy in children treated for critical asthma.

(Conditional recommendation, low certainty of evidence).

Background. The use of IV SABA therapy in pediatric critical asthma offers an attractive treatment option as it bypasses the drug delivery difficulties inherent in using inhaled medications in patients with respiratory distress and air flow limitation. Use of various agents including IV albuterol (not commercially available in the United States and commonly referred to by its alternate name salbutamol), isoproterenol, epinephrine, and terbutaline have been described in various phases of critical asthma treatment, although questions about the efficacy and safety of these agents persist.[73,74]

Summary of evidence. We identified 4 RCTs[52,75–77] and 1 observational study[78] comparing the use of IV SABA to placebo in pediatric critical asthma (see Supplementary Data). Salbutamol was evaluated in 3 studies[52,75,76] with terbutaline studied in the remaining 2.[77,78] One study was performed in the PICU,[77] 3 in a non-ICU ward,[52,75,76] and 1 in the ED.[78]

Intubation rate was reported in 1 study and showed no subjects were intubated in the IV SABA arm compared with a 12–19% rate in the other arms, though statistical analysis was not performed.[52] Measures of oxygenation were evaluated in 1 RCT[52] where improvement was greater in the IV SABA group but not statistically analyzed and in 1 observational study[78] where oxygen use was higher in the IV SABA group in an unadjusted analysis. Measures of ventilation were assessed in 2 included RCTs and IV SABA statistically significantly improved pH, P_{aCO_2}, and breathing frequency in 1 study,[52] and there was no difference in the second.[77] NRS use was not different between groups in 1 observational study.[78] PICU admission was evaluated in 1 observational study and found to be higher in the IV SABA group but showed no difference when corrected for other factors.[78] PICU stay was evaluated by 2 RCTs with no difference found between groups.[52,77] Hospital stay was evaluated by 1 RCT[52] and 1 observational study[78] with no difference found between groups. IV SABA showed a benefit in acute asthma severity scores in 1 RCT[75] and a trend toward improvement in another.[77] Adverse events were reported in 2 RCTs[52,77] with one study showing no increased hypotension in the IV SABA group and another showing a not statistically significant increase in troponin I elevation at 12 and 24 h with IV SABA.

Justification. The evidence available for the use of IV SABA therapy in critical asthma continues to be of low quality and quantity. Although this treatment modality is appealing for patients with severe bronchoconstriction who are unable to experience adequate delivery of inhaled therapies to distal airways, the paucity of data for benefit persists. IV SABA therapy may improve acute asthma severity scoring when added to conventional

therapies, but other objective outcomes for expedited recovery from critical asthma remain unchanged with its addition. In balance given this evidence, our panel suggests the use of IV SABA in pediatric critical asthma refractory to standard therapies.

It is important to consider the products used in the studies included when considering implementation. Salbutamol, which is only available in IV formulation in some regions, is the most commonly used agent in the studies reviewed. Questions continue for the use of less β_2 receptor selective and more widely available infusions such as epinephrine whose use was not represented in the included studies. Although less utilized in current practice, isoproterenol presents another appealing option for IV SABA therapy because of its short half-life and rapid treatment effect.[79] A more widely utilized IV SABA agent, terbutaline, presents an advantage in its availability but can also result in a profound IV volume load for patients receiving treatment as well as operational hurdles with infusion preparation (limited vial sizes). Additionally, terbutaline and salbutamol have prolonged half-lives compared with the other agents mentioned, requiring bolus dosing for attainment of steady state with infusion initiation as well as with dose escalations. Safety outcomes for all these therapies are not well described, and the incidence and, more importantly, clinical importance of lactic acidosis, hypokalemia, and tachyarrhythmias with all IV SABA treatment remain an area of ambiguity, especially at low and moderate dosing.

Future Research Opportunities. Future research for IV SABA use should focus on their addition to inhaled SABA. Protocolized dose escalation studies should aim to match dosing and up titration frequency to each agent's half-life. Dose titration should aim to improve IV SABA delivery while limiting toxicities at higher dosing ranges of infused IV SABA. As data regarding β_2 receptor polymorphisms and their role in treatment response to conventional critical asthma therapy expands, IV SABA may present a unique and rapid test for β_2 agonist responsiveness at the bedside when genetic profiles are unavailable.[80]

Noninvasive respiratory support.

In children presenting with critical asthma with persistent hypoxemia and/or respiratory distress, should NRS be initiated?

Sub-question: In children presenting with critical asthma who are initiated on NRS, which NRS modality (HFNC, CPAP, or NIV) should be administered?

Recommendation 7. We cannot recommend for or against the application of HFNC versus conventional oxygen therapy in children presenting with critical asthma with persistent hypoxemia and/or respiratory distress.

(Conditional recommendation, very low certainty of evidence).

Recommendation 8. We suggest the use of NIV over conventional oxygen therapy in children presenting with critical asthma with persistent hypoxemia and/or respiratory distress.

(Conditional recommendation, very low certainty of evidence).

Recommendation 9. We cannot recommend for or against the application of NIV over HFNC for children hospitalized with critical asthma with persistent hypoxemia and/or respiratory distress.

(Conditional recommendation, very low certainty of evidence).

Remark. In patients where conventional oxygen therapy or HFNC is used as a first-line respiratory support modality, a trial of NIV should be considered prior to intubation if hypoxemia or respiratory distress persists.

Background. NRS (HFNC, CPAP, and NIV) is a commonly utilized therapy for pediatric critical asthma, though there is wide institutional variability in the frequency of NRS utilization.[81] Proposed mechanisms for HFNC are decreasing work of breathing by increased clearance of carbon dioxide through dead space washout, conditioning of inspired gases, reduced nasopharyngeal resistance, and possibly providing a small amount of PEEP.[13] The primary mechanisms of CPAP and NIV are augmentation of the respiratory muscles during inspiration, increase in tidal volume, equilibration with alveolar pressure, and potential stenting of airways during exhalation to reduce gas trapping.[82–85]

Summary of evidence. We identified 1 RCT[86] and 4 observational studies[87–90] evaluating the impact of HFNC compared with conventional oxygen therapy in pediatric critical asthma (see Supplementary Data). These studies varied in study design, study setting (ED,[86,88] hospital ward,[90] PICU[87,89,90]), ages of subjects included, and flows utilized for HFNC.

Intubation rate was evaluated in 1 observation study and was not different between groups.[89] Measures of oxygenation were evaluated in 1 RCT[86] and found to have no difference between groups. Escalation in respiratory support was not different between groups in 1 RCT[86] and 1 observational study[89] but was increased in the HFNC group in 1 observational study.[90] PICU admission was not different between groups in 1 RCT[86] and 1 observational study.[88] PICU stay was not different between groups in 1 RCT[86] and 2 observational studies.[87,89] Hospital stay was evaluated in 3 observational studies,[88–90] 2 of which[88,90] observed an increase in the HFNC group,

though there was high risk of bias toward subjects with higher severity of illness in the intervention groups. Improvement in acute asthma severity score was greater in HFNC in 1 RCT, though unquantified,[86] and showed no difference in 1 observational study.[89] Adverse events were not different between groups in 1 RCT.[86]

Additionally, our search identified 1 RCT[91] and 2 observational studies[92,93] evaluating the impact of NIV compared with conventional oxygen therapy and 1 observational study comparing NIV and CPAP with conventional oxygen therapy[94] in pediatric critical asthma. The studies were variable in design, and the NIV support was not controlled in the observational studies. Intubation rate was not different between groups in 1 observational study.[94] One RCT[91] showed a small improvement in oxygenation compared with conventional oxygen therapy. PICU admission was higher in the NIV group in 1 observational study in an unadjusted analysis.[93] PICU stay showed no difference between groups in 1 RCT[91] and 2 observational studies.[92,94] Hospital stay was also no different between groups in 1 RCT[91] and in 2 observational studies.[92,93] Change in acute asthma severity score was improved in the NIV group in 1 RCT.[91] Duration of continuous albuterol was reported in 1 observational study[94] and found to be longer in the NIV group compared with CPAP and conventional oxygen therapy. No adverse events were reported in any study other than a single subject who did not tolerate NIV.[91]

Three observational studies[81,95,96] compared HFNC to NIV in pediatric critical asthma. Only one study controlled the NIV and HFNC settings.[95] Duration of NRS support was evaluated in 2 studies, 1[95] showing no difference between groups and 1 showing longer duration in the HFNC group compared with NIV.[81,95] PICU stay was not different between groups in 2 studies[95,96] and had a very small increase in the third.[81] Hospital stay was not different between groups in 1 single center study.[96] Escalation to mechanical ventilation was described in 1 study and found to be higher in the NIV or CPAP groups compared with HFNC in an unadjusted comparison.[81] Sedation use was higher with NIV in 1 observational study.[96] One study showed an increased rate of cardiac arrest in the NIV group, though it was not adjusted for illness severity.[81]

Justification. Although HFNC is increasingly commonly used to support children with critical asthma, there remains inadequate evidence to recommend for or against its use. HFNC may decrease work of breathing in these patients as is seen in other pediatric respiratory disorders[97] and does not appear to affect hospital stay in our identified evidence, but concerns remain that HFNC administration in pediatric critical asthma could lead to longer hospital stay as seen in other forms of pediatric respiratory failure.[98] Available studies were highly variable in study design, and most were unable to account for differences in admission illness severity.

Although the available evidence supporting the use of NIV in pediatric critical asthma is limited, these data suggest NIV is well tolerated and can decrease work of breathing.[13] The data also indicate that NIV likely does not increase stay, despite being typically used for a sicker cohort of patients. Given the risks associated with invasive mechanical ventilation in this population, we feel it is reasonable to trial NIV prior to escalating to more invasive options. Based on the published data, it is unclear how to determine when NIV should be initiated and applying NIV in most patients with critical asthma may not be warranted. To avoid overutilization, centers should consider developing guidelines for NIV initiation, titration, de-escalation, and discontinuation.

There is little evidence comparing HFNC with NIV for pediatric critical asthma; therefore, we cannot judge if one modality is superior. If there is benefit to both HFNC and NIV, it may require much larger RCTs to differentiate any discernable advantages. Although we have suggested the use of NIV over conventional oxygen therapy, and it may be reasonable for clinicians to infer a benefit of NIV over HFNC, we could not make that recommendation based on the limited evidence directly comparing the two.

Future Research Opportunities. There is a need for large, multi-center, high-quality RCTs to evaluate the efficacy and safety of NRS in children with critical asthma. Future research should aim to identify the indications for starting NRS, comparing HFNC and NIV with conventional oxygen therapy as well as with each other, and to better delineate optimal settings. Stratification based on initial disease severity should also be considered to compare HFNC with conventional oxygen therapy and NIV with HFNC (Fig. 1).[14] Implementation/quality improvement (QI) studies in different settings (ED, hospital ward, PICU) are needed to optimize the use of NRS in pediatric critical asthma to avoid overuse.

Heliox. In children presenting with critical asthma, should heliox be administered?

Recommendation 10. We cannot recommend for or against the application of heliox in children treated for critical asthma.

(Conditional recommendation, very low certainty of evidence).

Background. Helium-oxygen mixtures (heliox) are used as an adjuvant respiratory intervention for cases of upper and lower airway obstruction, including pediatric critical asthma.[99,100] By replacing nitrogen with helium and thus

lowering the density of inspired gas, heliox optimizes the Reynold's number and Hagen-Poiseuille principles that result in increased laminar flow. This effect translates into decreased turbulence and airway resistance in areas of obstruction, potentially improving alveolar ventilation and the deposition of aerosolized bronchodilators.[101–105] The role of heliox in pediatric critical asthma remains a question of interest including defining relevant efficacy outcomes and, pragmatically, optimal timing of initiation as compared with other asthma-related interventions.

Summary of Evidence. We identified 1 single-center RCT[106] and 2 multi-center, registry-based observational studies[107,108] examining clinical outcomes of administering heliox for pediatric critical asthma (see Supplementary Data). The RCT[106] was performed in the PICU and a non-ICU ward, whereas the observational studies were PICU subjects.[107,108]

Intubation rate was lower in the heliox group in 1 observational study unadjusted for severity of illness[108] and was no different between groups in another study where adjustment was performed.[107] NRS use rate was lower in the heliox group in 1 observational study in an unadjusted comparison.[108] Duration of invasive mechanical ventilation was not different between groups in 1 observational study.[107] PICU stay was not different between groups in 1 RCT[106] and 1 observational study.[107] Hospital stay was no different between groups in 1 RCT[106] and was lower in the heliox group in 1 unadjusted comparison in 1 observational study.[108] Change in acute asthma severity score was no different between groups in 1 RCT.[106] One RCT showed no differences between groups in adverse events.[106]

Justification. Our review of the literature and the methodological limitations of disease and context-applicable studies led to the determination that there is insufficient evidence for or against the application of heliox for pediatric patients with critical asthma. Heliox may remain a reasonable choice for clinicians in institutions with the experience and availability to administer it to children with critical asthma refractory to initial management. Institutional protocols should be established to define when and how heliox will be used to avoid overutilization of this noble gas.

Future research opportunities. Future research of heliox use in pediatric critical asthma must establish strict and explicit study enrollment criteria to yield generalizable

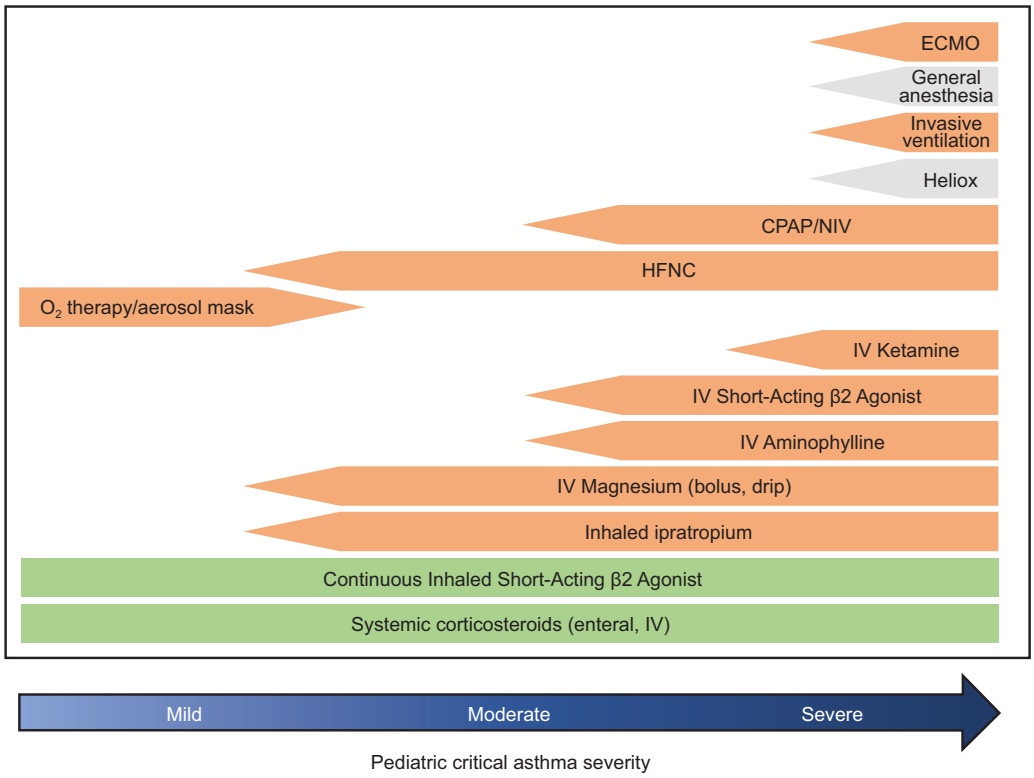

Fig. 1. Conceptual diagram of pediatric critical asthma therapies in context of disease severity. ECMO = extracorporeal membrane oxygenation, NIV = noninvasive ventilation, HFNC = high-flow nasal cannula.

findings given the various delivery methods and support devices available in children presenting with critical asthma. Future studies should also control for the potential impact of concurrent adjuvant interventions including their timing, dose, and cumulative exposure. In addition to the methodological considerations, research must clearly distinguish the delivery method and dosing of heliox interventions. Finally, clinical trials must consider clinical and physiological efficacy end points beyond those commonly studied (eg, avoidance of rare outcomes such as endotracheal intubation, mortality, and invasive mechanical ventilation duration).

Clinical protocol or pathway.

In children presenting with critical asthma, should a dedicated protocol or pathway be used to manage care?

Recommendation 11. We suggest the use of a dedicated protocol or pathway for managing children treated for critical asthma.

(Conditional recommendation, low certainty of evidence).

Background. Unwarranted variation in patient care results in low quality of care and potentially worse outcomes among critically ill children. Standardization of care is key to quality monitoring and the evolution of value-based care.[109] Research regarding, and interest in, protocols or pathways in health care is not new, and rigorous scholarly application of protocols has increased in recent years. Benefits of protocolized care include prompt and efficient delivery of evidenced-based therapies, reduced waste and associated cost, and often improved outcomes. Protocols or pathways may be applied to all hospital care settings and have demonstrated reproducible, favorable effects when measured against multiple outcome variables.

Summary of evidence. We identified 15 QI studies,[110–124] 6 observational studies,[125–130] 1 RCT,[131] and 1 quasi-randomized study,[132] evaluating the impact of using a dedicated protocol or pathway in the treatment of pediatric critical asthma (see Supplementary Data). Fifteen studies were done in the PICU[112,114,115,117,119–129] and 7 in a non-ICU ward.[110,113,116,118,130–132]

Intubation rate was lower in the protocol group in 1 QI study[123] but showed no difference in 2 other QI studies[117,119] or in the pooled analysis. Mortality was reported in 1 QI study with no difference between groups.[124] NRS use rate was evaluated by 5 QI studies,[112,117,120,121,123] and no difference was found between groups in a pooled analysis. Escalation of respiratory support was found to be lower in the protocol group in a pooled analysis of 1 observational[127] and 2 QI studies.[112,119] PICU stay was evaluated by 1 observational[126] and 3 QI studies[120,122,124] and was found to be decreased in the protocol group in 2 pooled analyses, 1 including all 4 studies and 1 including only the 3 QI studies. Hospital stay was evaluated by 4 observational studies,[125,126,129,130] 1 quasi-randomized study,[132] and 12 QI studies.[110–114,116–120,122,124] One pooled analysis of the QI studies showed a decrease in hospital stay in the protocol group, and a separate meta-analysis on the observational and quasi-randomized studies also showed a decrease in hospital stay. Change in respiratory score was improved in the protocol group in 1 observational study[126] and was not different between groups in 1 QI study.[116] Duration of continuous inhaled β agonist was found to be improved in the protocol group in 2 observational[126,129] and 3 QI studies[117,120,128] but showed no difference in 2 other QI studies.[122,123] Readmission rate was lower in the protocol group in 1 QI study[119] but no different in 3 others.[114,116,124] Cost savings from protocol use were reported in 1 quasi-RCT,[132] 1 RCT,[131] 2 observational studies,[125,126] and 3 QI studies,[113,114,124] though these studies were highly variable on methodology of cost calculation and significance testing. Additionally, 1 QI study did not show any decrease in cost.[118] Adverse events were not different between groups in 1 observational study[127] and 3 QI studies,[112,115,116] and 1 QI study showed an increased PICU readmission rate in the protocol group.[123]

Justification. Overall, the certainty of evidence was regarded as low because of the types of studies, their inherent limitations, and the varying types of interventions. Each of the included studies was conducted in single centers, and the majority were QI or observational except 2 randomized/quasi-randomized studies. Interventions ranged from inhaled SABA (intermittent and continuous) weaning and/or escalation, initiation and titration of IV terbutaline, score-based protocols, standardized order-sets, standardized treatment protocols/pathways, and HFNC initiation and weaning. Although most of the included studies favored the intervention, inconsistency in results for some interventions that demonstrated no change in outcomes contributed to the decision for a conditional recommendation. Importantly, no protocols were associated with worse outcomes.

Based on the quality of the evidence and variability in types of interventions, we are unable to recommend a specific pathway or protocol. Overall, the available evidence suggests the interventions were effective in decreasing hospital and PICU stay. Such protocols also have potential for benefit in other outcomes including improved quality of care, patient safety, efficiency, and cost reduction. Realizing those benefits requires stakeholder buy-in to ensure the success of any standardized process. Nonadherence may be encountered owing to staff turnover or

because some clinicians may not fully endorse the pathway or protocol. As such, auditing protocol adherence and staff re-education is an essential component of implementing a new process, and all clinicians who will utilize the protocol should be trained in its aspects.

Future Research Opportunities. High-quality, multicenter RCTs are needed to evaluate the effectiveness of protocols and pathways to manage the care of children with critical asthma. Future research should examine score-based protocols to initiate, titrate, and discontinue inhaled SABA and IV adjunct medications, heliox, NRS, and invasive mechanical ventilation.

Limitations

Despite our use of rigorous methodology recommended by the GRADE framework, this clinical practice guideline has some limitations. Our systematic reviews revealed a paucity of high-quality RCTs evaluating different pediatric critical asthma interventions. Those RCTs that were available were small or older or used a lower-quality methodology. Additionally, there was significant heterogeneity between studies that presents significant difficulty in attempting to perform meta-analyses. As a result, our recommendations were largely based on studies with many weaknesses, resulting in conditional recommendations and, in some, an inability to recommend for or against an intervention. Clinicians reading these guidelines should take these limitations into consideration as they incorporate the evidence into their bedside decisions, and we look forward to future work that will better guide these difficult clinical choices.

Summary

We provide a contemporary definition and the first clinical practice guidelines for pediatric critical asthma. The resulting recommendations are limited by the lack of high-quality studies, but we believe these guidelines will help lay the groundwork for future investigations.

Acknowledgments

We offer our sincere gratitude to Yuedi Yang (Department of Biostatistics and Health Data Science, Indiana University) and Terri Pigott (College of Education and Human Development, Georgia State University) for their work in performing the statistical analyses for this study and to Dean Hess for his guidance throughout the guideline development process.

Author Disclosure Statement

Dr. Abu-Sultaneh has a relationship with Indiana University School of Medicine. Mrs. Baker has a relationship with Children's Hospital Colorado, president-elect of the National Board for Respiratory Care. Dr. Basnet has a relationship with Southern Illinois University School of Medicine and Patan Academy of Health Sciences. Dr. Carroll has a relationship with the University of Florida at Jacksonville and College Regent-at-Large, Board of Regents, American College of Chest Physicians. Ms. Craven has a relationship with Indiana University, School of Medicine. Dr. Dalabih has a relationship with Driscoll Children's Hospital. Dr. Fitzpatrick has a relationship with Emory University and Children's Healthcare of Atlanta. Mr. Glogowski has a relationship with Georgia State University. Dr. Goodfellow has a relationship with the AARC/Daedalus Enterprises, Section Editor for *Respiratory Care*, and Georgia State University. Dr. Irazuzta has a relationship with the University of Florida at Jacksonville. Dr. Kapuscinski has a relationship with Kaleida Health. Ms. Lenox has a relationship with Southshore Health. Dr. Lovinsky-Desir has a relationship with Columbia University Medical Center. Dr. Maue has a relationship with Cincinnati's Children Medical Center. Mr. Miller has a relationship with Duke University, a Section Editor for *Respiratory Care*, and the Board of Directors for the Carolina/Virginias Chapter of SCCM; Mr. Miller has received gifts from Aerogen and has received an AARC Vision Grant. Mr. Moody has a relationship with Children's Health and Spero Therapeutics. Prof. Newth has a relationship with Children's Healthcare of Los Angeles, the Kirk School of Medicine of University of Southern California, and Economedtrx—Chair, Data Safety Monitoring Committee. Dr. Rehder has a relationship with Duke University. Received funds from the American Hospital Association for teaching. Dr. Said has a relationship with University of Chicago Medicine. Dr. Sochet has a relationship with the Johns Hopkins All Children's Medical Center. Ms. Whipple has a relationship with Johns Hopkins University & Medicine. Dr. White has a relationship with the University of Utah. Mrs. Willis has a relationship with Arkansas Children's Hospital and Section Editor for *Respiratory Care*.

Funding Information

This study has not received any funding.

Supplementary Material

Supplementary Data

References

1. Perry R, Braileanu G, Palmer T, et al. The economic burden of pediatric asthma in the United States: Literature review of current evidence. Pharmacoeconomics 2019;37(2):155–167; doi: 10.1007/s40273-018-0726-2
2. Anonymous. Most recent national asthma data. CDC; 2020. Available from: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm [Last accessed: May 15, 2022].
3. Sol IS, Jang H, Noh J, et al. Mortality and morbidity in children with asthma: A nationwide study in Korea. Respir Med 2021;177:106306; doi: 10.1016/j.rmed.2021.106306

4. Mukherjee M, Cunningham S, Bhuia MR, et al. Asthma in paediatric intensive care in England residents: observational study. Sci Rep 2022; 12(1):1315; doi: 10.1038/s41598-022-05414-5
5. Craig S, Powell CVE, Nixon GM, et al. Treatment patterns and frequency of key outcomes in acute severe asthma in children: A Paediatric Research in Emergency Departments International Collaborative (PREDICT) multicentre cohort study. BMJ Open Respir Res 2022;9(1): e001137; doi: 10.1136/bmjresp-2021-001137
6. Bratton SL, Newth CJL, Zuppa AF, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Critical care for pediatric asthma: wide care variability and challenges for study. Pediatr Crit Care Med 2012;13(4):407–414; doi: 10.1097/PCC.0b013e318238b428
7. Cloutier MM, Baptist AP, Blake KV, et al. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol 2020;146(6):1217–1270; doi: 10.1016/j.jaci.2020.10.003
8. Reddel HK, Bacharier LB, Bateman ED, et al. Global initiative for asthma strategy 2021: executive summary and rationale for key changes. Am J Respir Crit Care Med 2022;205(1):17–35; doi: 10.1164/rccm.202109-2205PP
9. Nievas IFF, Anand KJS. Severe acute asthma exacerbation in children: a stepwise approach for escalating therapy in a pediatric intensive care unit. J Pediatr Pharmacol Ther 2013;18(2):88–104; doi: 10.5863/1551-6776-18.2.88
10. Wong JJM, Lee JH, Turner DA, et al. A review of the use of adjunctive therapies in severe acute asthma exacerbation in critically ill children. Expert Rev Respir Med 2014;8(4):423–441; doi: 10.1586/17476348.2014.915752
11. Rehder KJ. Adjunct therapies for refractory status asthmaticus in children. Respir Care 2017;62(6):849–865; doi: 10.4187/respcare.05174
12. Craig SS, Dalziel SR, Powell CV, et al. Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2020;8(8):CD012977; doi: 10.1002/14651858.CD012977.pub2
13. Miller AG, Rotta AT. Noninvasive respiratory support for pediatric critical asthma. Respir Care 2025;69(5):534–540; doi: 10.4187/respcare.12487
14. Rogerson CM, White BR, Abu-Sultaneh S. Pharmacological management of pediatric critical asthma. Respir Care 2025; doi: 10.4187/respcare.12458
15. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–381; doi: 10.1016/j.jbi.2008.08.010
16. Harris PA, Taylor R, Minor BL, et al.; REDCap Consortium. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208; doi: 10.1016/j.jbi.2019.103208
17. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4):383–394; doi: 10.1016/j.jclinepi.2010.04.026
18. Schünemann H, Brożek J, Guyatt G, et al. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations: The GRADE Working Group; 2013.
19. Portnoy J, Nadel G, Amado M, et al. Continuous nebulization for status asthmaticus. Ann Allergy 1992;69(1):71–79.
20. Camargo CA, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. Cochrane Database Syst Rev 2003;2003(4):CD001115; doi: 10.1002/14651858.CD001115
21. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120(5 Suppl):S94–S138; doi: 10.1016/j.jaci.2007.09.043
22. Carroll CL, Sala KA. Pediatric status asthmaticus. Crit Care Clin 2013; 29(2):153–166; doi: 10.1016/j.ccc.2012.12.001
23. Castro-Rodriguez JA, J Rodrigo G, E Rodríguez-Martínez C. Principal findings of systematic reviews of acute asthma treatment in childhood. J Asthma 2015;52(10):1038–1045; doi: 10.3109/02770903.2015.1033725
24. Wade A, Chang C. Evaluation and treatment of critical asthma syndrome in children. Clin Rev Allergy Immunol 2015;48(1):66–83; doi: 10.1007/s12016-014-8408-0
25. Shein SL, Speicher RH, Filho JOP, et al. Contemporary treatment of children with critical and near-fatal asthma. Rev Bras Ter Intensiva 2016; 28(2):167–178; doi: 10.5935/0103-507X.20160020
26. Pollock M, Sinha IP, Hartling L, et al. Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. Allergy 2017;72(2):183–200; doi: 10.1111/all.13039
27. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. Crit Care Med 1993;21(10):1479–1486; doi: 10.1097/00003246-199310000-00015
28. Moler FW, Johnson CE, Van Laanen C, et al. Continuous versus intermittent nebulized terbutaline: plasma levels and effects. Am J Respir Crit Care Med 1995;151(3 Pt 1):602–606; doi: 10.1164/ajrccm.151.3.7881645
29. Alba R, Vegas Munoz E, Torrijos Roman C, et al. Continuous albuterol nebulization in the treatment of acute asthma in children. Acta Pediatr Esp 2000;58(9):508–512.
30. Kulalert P, Phinyo P, Patumanond J, et al. Continuous versus intermittent short-acting β2-agonists nebulization as first-line therapy in hospitalized children with severe asthma exacerbation: a propensity score matching analysis. Asthma Res Pract 2020;6(1):6; doi: 10.1186/s40733-020-00059-5
31. Lin AT, Moore-Clingenpeel M, Karsies TJ. Comparison of two continuous nebulized albuterol doses in critically ill children with status asthmaticus. J Asthma 2020;57(9):980–986; doi: 10.1080/02770903.2019.1623249
32. Parlar-Chun R, Arnold K. Association of various weight-based doses of continuous albuterol on hospital length of stay. J Asthma 2021;58(5): 645–650; doi: 10.1080/02770903.2020.1723622
33. Miller AG, Burr KL, Juby J, et al. Enhancing respiratory therapists' well-being: battling burnout in respiratory care. Respir Care 2023;68(5): 692–705; doi: 10.4187/respcare.10632
34. Phumeetham S, Bahk TJ, Abd-Allah S, et al. Effect of high-dose continuous albuterol nebulization on clinical variables in children with status asthmaticus. Pediatr Crit Care Med 2015;16(2):e41–e46; doi: 10.1097/PCC.0000000000000314
35. Li J, Fink JB. Narrative review of practical aspects of aerosol delivery via high-flow nasal cannula. Ann Transl Med 2021;9(7):590–590; doi: 10.21037/atm-20-7383
36. Qureshi F, Zaritsky A, Poirier MP. Comparative efficacy of oral dexamethasone versus oral prednisone in acute pediatric asthma. J Pediatr 2001;139(1):20–26; doi: 10.1067/mpd.2001.115021
37. Cronin JJ, McCoy S, Kennedy U, et al. A randomized trial of single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children who attend the emergency department. Ann Emerg Med 2016;67(5):593–601.e3; doi: 10.1016/j.annemergmed.2015.08.001
38. Normansell R, Kew KM, Mansour G. Different oral corticosteroid regimens for acute asthma. Cochrane Database Syst Rev 2016;2016(5): CD011801; doi: 10.1002/14651858.CD011801.pub2
39. Doymaz S, Ahmed YE, Francois D, et al. Methylprednisolone, dexamethasone or hydrocortisone for acute severe pediatric asthma: does it matter? J Asthma 2022;59(3):590–596; doi: 10.1080/02770903.2020.1870130
40. Hussain N, Suleman, Javed A, et al. Comparison of outcome between dexamethasone versus prednisolone administration in acute moderate asthma. Pjmhs 2023;17(4):31–32; doi: 10.53350/pjmhs202317431
41. Roddy MR, Sellers AR, Darville KK, et al. Dexamethasone versus methylprednisolone for critical asthma: A single center, open-label, parallel-group clinical trial. Pediatr Pulmonol 2023;58(6):1719–1727; doi: 10.1002/ppul.26386
42. Parikh K, Hall M, Mittal V, et al. Comparative effectiveness of dexamethasone versus prednisone in children hospitalized with asthma. J Pediatr 2015;167(3):639–644.e1; doi: 10.1016/j.jpeds.2015.06.038
43. Bohannon K, Machen R, Ragsdale C, et al. Dexamethasone associated with significantly shorter length of hospital stay compared with a prednisolone-based regimen in pediatric patients with mild to moderate acute asthma exacerbations. Clin Pediatr (Phila) 2019;58(5): 521–527; doi: 10.1177/0009922819832091
44. Tyler A, Cotter JM, Moss A, et al. Outcomes for pediatric asthmatic inpatients after implementation of an emergency department dexamethasone treatment protocol. Hosp Pediatr 2019;9(2):92–99; doi: 10.1542/hpeds.2018-0099
45. Hemani SA, Glover B, Ball S, et al. Dexamethasone versus prednisone in children hospitalized for acute asthma exacerbations. Hosp Pediatr 2021;11(11):1263–1272; doi: 10.1542/hpeds.2020-004788

46. Sellers AR, Roddy MR, Darville KK, et al. Dexamethasone for pediatric critical asthma: a multicenter descriptive study. J Intensive Care Med 2022;37(11):1520–1527; doi: 10.1177/08850666221082540
47. Hoefgen ER, Huang B, Schuler CL, et al. Dexamethasone versus prednisone in children hospitalized with asthma exacerbation. Hosp Pediatr 2022;12(3):325–335; doi: 10.1542/hpeds.2021-006276
48. Irazuzta JE, Chiriboga N. Magnesium sulfate infusion for acute asthma in the emergency department. J Pediatr (Rio J) 2017;93(Suppl 1):19–25; doi: 10.1016/j.jped.2017.06.002
49. Kapuscinski CA, Stauber SD, Hutchinson DJ. Escalation in therapy based on intravenous magnesium sulfate dosing in pediatric patients with asthma exacerbations. J Pediatr Pharmacol Ther 2020;25(4): 314–319; doi: 10.5863/1551-6776-25.4.314
50. Devi PR, Kumar L, Singhi SC, et al. Intravenous magnesium sulfate in acute severe asthma not responding to conventional therapy. Indian Pediatr 1997;34(5):389–397
51. Torres S, Sticco N, Bosch JJ, et al. Effectiveness of magnesium sulfate as initial treatment of acute severe asthma in children, conducted in a tertiary-level university hospital: a randomized, controlled trial. Arch Argent Pediatr 2012;110(4):291–296; doi: 10.5546/aap.2012.eng.291
52. Santana JC, Barreto SSM, Piva JP, et al. Controlled study on intravenous magnesium sulfate or salbutamol in early treatment of severe acute asthma attack in children. J Pediatr (Rio J) 2001;77(4):279–287; doi: 10 .2223/JPED.235
53. DeSanti RL, Agasthya N, Hunter K, et al. The effectiveness of magnesium sulfate for status asthmaticus outside the intensive care setting. Pediatr Pulmonol 2018;53(7):866–871; doi: 10.1002/ppul.24013
54. Shein SL, Farhan O, Morris N, et al. Adjunctive pharmacotherapies in children with asthma exacerbations requiring continuous albuterol therapy: findings from the Ohio pediatric asthma repository. Hosp Pediatr 2018;8(2):89–95; doi: 10.1542/hpeds.2017-0088
55. Buendia JA, Acuña-Cordero R, Rodriguez-Martinez CE. The cost-utility of intravenous magnesium sulfate for treating asthma exacerbations in children. Pediatr Pulmonol 2020;55(10):2610–2616; doi: 10.1002/ppul.25024
56. Antoon JW, Hall M, Mittal V, et al. Intravenous magnesium and hospital outcomes in children hospitalized with asthma. Hosp Pediatr 2021; 11(8):785–793; doi: 10.1542/hpeds.2020-004770
57. Arnold DH, Gong W, Antoon JW, et al. Prospective observational study of clinical outcomes after intravenous magnesium for moderate and severe acute asthma exacerbations in children. J Allergy Clin Immunol Pract 2022;10(5):1238–1246; doi: 10.1016/j.jaip.2021.11.028
58. Glover ML, Machado C, Totapally BR. Magnesium sulfate administered via continuous intravenous infusion in pediatric patients with refractory wheezing. J Crit Care 2002;17(4):255–258; doi: 10.1053/jcrc.2002.36759
59. Egelund TA, Wassil SK, Edwards EM, et al. High-dose magnesium sulfate infusion protocol for status asthmaticus: a safety and pharmacokinetics cohort study. Intensive Care Med 2013;39(1):117–122; doi: 10 .1007/s00134-012-2734-6
60. Vaiyani D, Irazuzta JE. Comparison of two high-dose magnesium infusion regimens in the treatment of status asthmaticus. J Pediatr Pharmacol Ther 2016;21(3):233–238; doi: 10.5863/1551-6776-21.3.233
61. Barnes PJ. Theophylline. Am J Respir Crit Care Med 2013;188(8): 901–906; doi: 10.1164/rccm.201302-0388PP
62. Rogerson CM, Hogan AH, Waldo B, et al. Wide institutional variability in the treatment of pediatric critical asthma: a multicenter retrospective study. Pediatr Crit Care Med 2024;25(1):37–46; doi: 10.1097/PCC .0000000000003347
63. Carter E, Cruz M, Chesrown S, et al. Efficacy of intravenously administered theophylline in children hospitalized with severe asthma. J Pediatr 1993;122(3):470–476; doi: 10.1016/s0022-3476(05)83443-2
64. DiGiulio GA, Kercsmar CM, Krug SE, et al. Hospital treatment of asthma: lack of benefit from theophylline given in addition to nebulized albuterol and intravenously administered corticosteroid. J Pediatr 1993; 122(3):464–469; doi: 10.1016/S0022-3476(05)83442-0
65. Strauss RE, Wertheim DL, Bonagura VR, et al. Aminophylline therapy does not improve outcome and increases adverse effects in children hospitalized with acute asthmatic exacerbations. Pediatrics 1994;93(2): 205–210; doi: 8121733
66. Bien JP, Bloom MD, Evans RL, et al. Intravenous theophylline in pediatric status asthmaticus. A prospective, randomized, double-blind, placebo-controlled trial. Clin Pediatr (Phila) 1995;34(9):475–481; doi: 10 .1177/000992289503400905
67. Needleman JP, Kaifer MC, Nold JT, et al. Theophylline does not shorten hospital stay for children admitted for asthma. Arch Pediatr Adolesc Med 1995;149(2):206–209; doi: 10.1001/archpedi.1995 .02170140088016
68. Nuhoğlu Y, Dai A, Barlan IB, et al. Efficacy of aminophylline in the treatment of acute asthma exacerbation in children. Ann Allergy Asthma Immunol 1998;80(5):395–398; doi: 10.1016/S1081-1206(10)62990-0
69. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. Arch Dis Child 1998;79(5):405–410; doi: 10. 1136/adc.79.5.405
70. Ream RS, Loftis LL, Albers GM, et al. Efficacy of IV theophylline in children with severe status asthmaticus. Chest 2001;119(5):1480–1488; doi: 10.1378/chest.119.5.1480
71. D'Avila RS, Piva JP, Marostica PJC, et al. Early administration of two intravenous bolus of aminophylline added to the standard treatment of children with acute asthma. Respir Med 2008;102(1):156–161; doi: 10.1016/j.rmed.2007.07.030
72. Dalabih AR, Bondi SA, Harris ZL, et al. 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. Pulm Pharmacol Ther 2014;27(1):57–61; doi: 10.1016/j .pupt.2013.03.001
73. Stein SW, Thiel CG. The history of therapeutic aerosols: a chronological review. J Aerosol Med Pulm Drug Deliv 2017;30(1):20–41; doi: 10.1089/ jamp.2016.1297
74. Tobin A. Intravenous salbutamol: too much of a good thing? Crit Care Resusc 2005;7(2):119–127; doi: 10.1016/S1441-2772(23)01644-7
75. Browne GJ, Penna AS, Phung X, et al. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. Lancet 1997;349(9048):301–305; doi: 10.1016/S0140-6736(96)06358-1
76. Browne GJ, Trieu L, Van Asperen P. Randomized, double-blind, placebo-controlled trial of intravenous salbutamol and nebulized ipratropium bromide in early management of severe acute asthma in children presenting to an emergency department. Crit Care Med 2002; 30(2):448–453; doi: 10.1097/00003246-200202000-00030
77. Bogie AL, Towne D, Luckett PM, et al. Comparison of intravenous terbutaline versus normal saline in pediatric patients on continuous high-dose nebulized albuterol for status asthmaticus. Pediatr Emerg Care 2007;23(6):355–361; doi: 10.1097/01.pec.0000278397.63246.33
78. Adair E, Dibaba D, Fowke JH, et al. The impact of terbutaline as adjuvant therapy in the treatment of severe asthma in the pediatric emergency department. Pediatr Emerg Care 2022;38(1):e292–e294; doi: 10 .1097/PEC.0000000000002269
79. Herman JJ, Noah ZL, Moody RR. Use of intravenous isoproterenol for status asthmaticus in children. Crit Care Med 1983;11(9):716–720; doi: 10.1097/00003246-198309000-00009
80. Carroll CL, Stoltz P, Schramm CM, et al. β 2—Adrenergic receptor polymorphisms affect response to treatment in children with severe asthma exacerbations. Chest 2009;135(5):1186–1192; doi: 10.1378/chest.08-2041
81. Russi BW, Roberts AR, Nievas IF, et al. Noninvasive respiratory support for pediatric critical asthma: a multicenter cohort study. Respir Care 2024;69(5):534–540; doi: 10.4187/respcare.11502
82. Korang SK, Feinberg J, Wetterslev J, et al. Non-invasive positive pressure ventilation for acute asthma in children. Cochrane Database Syst Rev 2016;9(9):CD012067; doi: 10.1002/14651858.CD012067.pub2
83. Pavone M, Verrillo E, Caldarelli V, et al. Non-invasive positive pressure ventilation in children. Early Hum Dev 2013;89(Suppl 3):S25–S31; doi: 10.1016/j.earlhumdev.2013.07.019
84. Gomes EL de FD, Cavassini CLF, David MCM, et al. Does bilevel noninvasive ventilation have a bronchodilating effect and alter respiratory mechanics in asthmatic individuals after bronchoprovocation? Randomized, crossover study. J Aerosol Med Pulm Drug Deliv 2021; 34(2):124–133; doi: 10.1089/jamp.2020.1608
85. Korang SK, Baker M, Feinberg J, et al. Non-invasive positive pressure ventilation for acute asthma in children. Cochrane Database Syst Rev 2024;10(10):CD012067; doi: 10.1002/14651858.CD012067.pub3
86. Ballestero Y, De Pedro J, Portillo N, et al. Pilot clinical trial of high-flow oxygen therapy in children with asthma in the emergency service. J Pediatr 2018;194:204–210.e3; doi: 10.1016/j.jpeds.2017.10.075
87. Baudin F, Buisson A, Vanel B, et al. Nasal high flow in management of children with status asthmaticus: a retrospective observational study. Ann Intensive Care 2017;7(1):55; doi: 10.1186/s13613-017-0278-1
88. González Martínez F, González Sánchez MI, Toledo del Castillo B, et al. Tratamiento con oxigenoterapia de alto flujo en las crisis asmáticas en la planta de hospitalización de pediatría: nuestra

experiencia. An Pediatr (Engl Ed) 2019;90(2):72–78; doi: 10.1016/j.anpedi.2018.06.015
89. Gates RM, Miller AG, Haynes KE, et al. High-flow nasal cannula in pediatric critical asthma. Respir Care 2021;66(8):1240–1246; doi: 10.4187/respcare.08740
90. Rogerson C, Owora A, He T, et al. High flow nasal cannula use is associated with increased hospital length of stay for pediatric asthma. Pediatr Pulmonol 2023;58(11):3046–3053; doi: 10.1002/ppul.26617
91. Basnet S, Mander G, Andoh J, et al. Safety, efficacy, and tolerability of early initiation of noninvasive positive pressure ventilation in pediatric patients admitted with status asthmaticus. Pediatr Crit Care Med 2012; 13(4):393–398; doi: 10.1097/PCC.0b013e318238b07a
92. Kang C-M, Wu E-T, Wang C-C, et al. Bilevel positive airway pressure ventilation efficiently improves respiratory distress in initial hours treating children with severe asthma exacerbation. J Formos Med Assoc 2020;119(9):1415–1421; doi: 10.1016/j.jfma.2019.11.013
93. Golden C, Xu M, Estrada CM, et al. Clinical outcomes after bilevel positive airway pressure treatment for acute asthma exacerbations. JAMA Pediatr 2015;169(2):186–188; doi: 10.1001/jamapediatrics.2014.2767
94. Usala C, Wilson P. Noninvasive ventilation use in pediatric status asthmaticus. J Asthma 2022;59(7):1338–1342; doi: 10.1080/02770903.2021.1941085
95. Pilar J, Modesto I Alapont V, Lopez-Fernandez YM, et al. High-flow nasal cannula therapy versus non-invasive ventilation in children with severe acute asthma exacerbation: An observational cohort study. Med Intensiva 2017;41(7):418–424; doi: 10.1016/j.medin.2017.01.001
96. Russi BW, Lew A, McKinley SD, et al. High-flow nasal cannula and bilevel positive airway pressure for pediatric status asthmaticus: a single center, retrospective descriptive and comparative cohort study. J Asthma 2022;59(4):757–764; doi: 10.1080/02770903.2021.1872085
97. Guglielmo RD, Hotz JC, Ross PA, et al. High-flow nasal cannula reduces effort of breathing but not consistently via positive end-expiratory pressure. Chest 2022;162(4):861–871; doi: 10.1016/j.chest.2022.03.008
98. Franklin D, Babl FE, George S, et al. Effect of early high-flow nasal oxygen vs standard oxygen therapy on length of hospital stay in hospitalized children with acute hypoxemic respiratory failure. JAMA 2023; 329(3):224–234; doi: 10.1001/jama.2022.21805
99. Ho AM-H, Lee A, Karmakar MK, et al. Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma: a systematic overview. Chest 2003;123(3):882–890; doi: 10.1378/chest.123.3.882
100. Reuben AD, Harris AR. Heliox for asthma in the emergency department: a review of the literature. Emerg Med J 2004;21(2):131–135; doi: 10.1136/emj.2002.003483
101. Hess DR, Fink JB, Venkataraman ST, et al. The history and physics of heliox. Respir Care 2006;51(6):608–612
102. Kim IK, Saville AL, Sikes KL, et al. Heliox-driven albuterol nebulization for asthma exacerbations: an overview. Respir Care 2006;51(6):613–618
103. Myers TR. Use of heliox in children. Respir Care 2006;51(6):619–631
104. Goode ML, Fink JB, Dhand R, et al. Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation. Am J Respir Crit Care Med 2001;163(1):109–114; doi: 10.1164/ajrccm.163.1.2003025
105. Anderson M, Svartengren M, Bylin G, et al. Deposition in asthmatics of particles inhaled in air or in helium-oxygen. Am Rev Respir Dis 1993; 147(3):524–528; doi: 10.1164/ajrccm/147.3.524
106. Bigham MT, Jacobs BR, Monaco MA, et al. Helium/oxygen-driven albuterol nebulization in the management of children with status asthmaticus: a randomized, placebo-controlled trial. Pediatr Crit Care Med 2010;11(3):356–361.
107. Lew A, Morrison JM, K Amankwah E, et al. Heliox prescribing trends for pediatric critical asthma. Respir Care 2022;67(5):510–519; doi: 10.4187/respcare.09385
108. Lew A, Morrison JM, Amankwah E, et al. Heliox for pediatric critical asthma: a multicenter, retrospective, registry-based descriptive study. J Intensive Care Med 2022;37(6):776–783; doi: 10.1177/08850666211026550
109. Porter ME. What is value in health care? N Engl J Med 2010;363(26): 2477–2481; doi: 10.1056/NEJMp1011024
110. Lierl MB, Pettinichi S, Sebastian KD, et al. Trial of a therapist-directed protocol for weaning bronchodilator therapy in children with status asthmaticus. Respir Care 1999;44(5):497–505.
111. Cunningham S, Logan C, Lockerbie L, et al. Effect of an integrated care pathway on acute asthma/wheeze in children attending hospital: cluster randomized trial. J Pediatr 2008;152(3):315–320; doi: 10.1016/j.jpeds.2007.09.033
112. Wong J, Agus MSD, Graham DA, et al. A critical asthma standardized clinical and management plan reduces duration of critical asthma therapy. Hosp Pediatr 2017;7(2):79–87; doi: 10.1542/hpeds.2016-0087
113. Magruder TG, Narayanan S, Walley S, et al. Improving inpatient asthma management: the implementation and evaluation of a pediatric asthma clinical pathway. Pediatr Qual Saf 2017;2(5):e041; doi: 10.1097/pq9.0000000000000041
114. Bartlett KW, Parente VM, Morales V, et al. Improving the efficiency of care for pediatric patients hospitalized with asthma. Hosp Pediatr 2017;7(1):31–38; doi: 10.1542/hpeds.2016-0108
115. Maue DK, Tori AJ, Beardsley AL, et al. Implementing a respiratory therapist-driven continuous albuterol weaning protocol in the pediatric ICU. Respir Care 2019;64(11):1358–1365; doi: 10.4187/respcare.06447
116. Smith A, Banville D, Gruver EJ, et al. A clinical pathway for the care of critically ill patients with asthma in the community hospital setting. Hosp Pediatr 2019;9(3):179–185; doi: 10.1542/hpeds.2018-0197
117. Miller AG, Haynes KE, Gates RM, et al. A respiratory therapist-driven asthma pathway reduced hospital length of stay in the pediatric intensive care unit. Respir Care 2019;64(11):1325–1332; doi: 10.4187/respcare.06626
118. Shakirah MS, Jamalludin AR, Hasniah AL, et al. Paediatric asthma clinical pathway: Impact on cost and quality of care. Med J Malaysia 2019; 74(2):138–144
119. Melendez E, Dwyer D, Donelly D, et al. Standardized protocol is associated with a decrease in continuous albuterol use and length of stay in critical status asthmaticus. Pediatr Crit Care Med 2020;21(5):451–460; doi: 10.1097/PCC.0000000000002239
120. Kucher NM, S Dhaliwal D, Fischer GA, et al. Implementation of a critical asthma protocol in a pediatric ICU. Respir Care 2021;66(4):635–643; doi: 10.4187/respcare.07944
121. Miksa M, Kaushik S, Antovert G, et al. Implementation of a critical care asthma pathway in the PICU. Crit Care Explor 2021;3(2):e0334; doi: 10.1097/CCE.0000000000000334
122. Flaherty MR, Whalen K, Lee J, et al. Implementation of a nurse-driven asthma pathway in the pediatric intensive care unit. Pediatr Qual Saf 2021;6(6):e503; doi: 10.1097/pq9.0000000000000503
123. Maue DK, Cater DT, Rogerson CM, et al. Outcomes of a respiratory therapist driven high flow nasal cannula management protocol for pediatric critical asthma patients. Pediatr Pulmonol 2023;58(10):2881–2888; doi: 10.1002/ppul.26606
124. Lopez M, Wilson M, Cobbina E, et al. Decreasing ICU and hospital length of stay through a standardized respiratory therapist-driven electronic clinical care pathway for status asthmaticus. Pediatr Qual Saf 2023;8(6):e697; doi: 10.1097/pq9.0000000000000697
125. Kelly CS, Andersen CL, Pestian JP, et al. Improved outcomes for hospitalized asthmatic children using a clinical pathway. Ann Allergy Asthma Immunol 2000;84(5):509–516; doi: 10.1016/S1081-1206(10)62514-8
126. Carroll CL, Schramm CM. Protocol-based titration of intravenous terbutaline decreases length of stay in pediatric status asthmaticus. Pediatr Pulmonol 2006;41(4):350–356; doi: 10.1002/ppul.20394
127. Phillips M, Fahrenbach J, Khanolkar M, et al. The effect of a pediatric intensive care severity-tiered pathway for status asthmaticus on quality measures and outcomes. Pediatr Allergy Immunol Pulmonol 2017; 30(4):246–251; doi: 10.1089/ped.2017.0777
128. Brennan S, Lowrie L, Wooldridge J. Effects of a PICU status asthmaticus de-escalation pathway on length of stay and albuterol use. Pediatr Crit Care Med 2018;19(7):658–664; doi: 10.1097/PCC.0000000000001551
129. Okada Y, Nakamura T, Maeda M, et al. Utility of therapeutic strategy based on the modified Pulmonary Index Score for childhood asthma exacerbation. Allergy Asthma Proc 2019;40(2):111–115; doi: 10.2500/aap.2019.40.4203
130. Sjoerdsma MH, Bongaerts THG, van Lente L, et al. Nurse-driven clinical pathway based on an innovative asthma score reduces admission time for children. Pediatr Qual Saf 2020;5(5):e344; doi: 10.1097/pq9.0000000000000344
131. Johnson KB, Blaisdell CJ, Walker A, et al. Effectiveness of a clinical pathway for inpatient asthma management. Pediatrics 2000;106(5): 1006–1012; doi: 10.1542/peds.106.5.1006
132. McDowell KM, Chatburn RL, Myers TR, et al. A cost-saving algorithm for children hospitalized for status asthmaticus. Arch Pediatr Adolesc Med 1998;152(10):977–984; doi: 10.1001/archpedi.152.10.977