

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-Sultaneh²⁶

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¹Dr. White is affiliated with Division of Pediatric Critical Care Medicine, University of Utah, Salt Lake City, Utah, USA.

²Mr. Miller and Dr. Rehder are affiliated with Division of Pediatric Critical Care Medicine, Duke University Medical Center, Durham, North Carolina, USA.

³Mr. Miller is affiliated with Respiratory Care Services, Duke University Medical Center, Durham, North Carolina, USA.

⁴Mr. Miller is affiliated with Thomas Jefferson University, Philadelphia, Pennsylvania, USA.

⁵Mrs. Baker is affiliated with Breathing Institute, Children's Hospital Colorado Aurora, Colorado, USA.

⁶Dr. Basnet is affiliated with Division of Pediatric Critical Care Medicine, Department of Pediatrics, Southern Illinois University School of Medicine, Springfield, Illinois, USA.

⁷Drs. Carroll and Irazuzta are affiliated with Division of Pediatric Critical Care Medicine, Department of Pediatrics, School of Medicine, University of Florida, Jacksonville, Florida, USA.

⁸Ms. Craven and Ms. Whipple are affiliated with Ruth Lilly Medical Library, Indiana University School of Medicine, Indianapolis, Indiana, USA.

⁹Dr. Dalabih is affiliated with Driscoll Children's Health System, Corpus Christi, Texas, USA.

¹⁰Dr. Fitzpatrick is affiliated with Division of Pulmonology, Emory University, Atlanta, Georgia, USA.

¹¹Dr. Fitzpatrick is affiliated with Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, Georgia, USA.

¹²Mr. Glogowski is affiliated with Georgia State University Library, Atlanta, Georgia, USA.

¹³Dr. Kapuscinski is affiliated with Department of Pharmacy, John R. Oishei Children's Hospital, Buffalo, New York, USA.

¹⁴Ms. Lenox is affiliated with Respiratory Care Services, South Shore Health System, South Weymouth, Massachusetts, USA.

¹⁵Dr. Lovinsky-Desir is affiliated with Departments of Pediatrics and Environmental Health Sciences, Columbia University Medical Center, New York, New York, USA.

¹⁶Dr. Maue is affiliated with Division of Pediatric Critical Care Medicine, Cincinnati Children's Hospital, Cincinnati, Ohio, USA.

¹⁷Mr. Moody is affiliated with Department of Respiratory Care, Children's Health – Children's Medical Center, Plano, Texas, USA.

¹⁸Dr. 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.

¹⁹Dr. 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.

²⁰Dr. Said is affiliated with Department of Pharmacy, Comer Children's Hospital, University of Chicago Medicine, Chicago, Illinois, USA.

²¹Ms. Willis is affiliated with Respiratory Care Services, Arkansas Children's Hospital, Little Rock, Arkansas, USA.

²²Ms. Willis is affiliated with Department of Respiratory Care, College of Health Professions, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA.

²³Ms. Whipple is affiliated with Welch Medical Library, Johns Hopkins University, Baltimore, Maryland, USA.

²⁴Dr. Goodfellow is Director of Clinical Practice Guideline Development at the American Association for Respiratory Care, Irving, TX, USA.

²⁵Dr. Goodfellow is affiliated with Georgia State University, Atlanta, Georgia, USA.

²⁶Dr. 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. Multi-database 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.gradeapro.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 study³⁰ 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 PICU²⁷ 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 arrhythmia) were similar between the 2 interventions in the 3 RCTs.^{27–29}

Two observational studies compared the use of high- vs 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 boluses 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 <i>recommended</i> course of action and only a small proportion would not.	The majority of individuals in this situation would want the <i>suggested</i> course of action, but many would not.
Clinicians	Most individuals should receive the <i>recommended</i> 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 trial⁴¹ 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 study⁴⁶ 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 study⁵⁶ 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 RCT⁵¹ 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 RCT⁵¹ but similar in 1 observational study.⁵⁶ PICU admission was higher in the IV magnesium group in 1 observational study⁵³ but lower in another observational study.⁵⁴ PICU stay was shorter in 1 RCT⁵¹ 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 study⁷² 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 RCT⁶⁹ 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 study⁷² 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 one⁷⁰ 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 study⁷⁸ 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 RCT⁵² where improvement was greater in the IV SABA group but not statistically analyzed and in 1 observational study⁷⁸ 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 RCT⁵² and 1 observational study⁷⁸ with no difference found between groups. IV SABA showed a benefit in acute asthma severity scores in 1 RCT⁷⁵ 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 RCT⁸⁶ 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 RCT⁸⁶ and found to have no difference between groups. Escalation in respiratory support was not different between groups in 1 RCT⁸⁶ and 1 observational study⁸⁹ but was increased in the HFNC group in 1 observational study.⁹⁰ PICU admission was not different between groups in 1 RCT⁸⁶ and 1 observational study.⁸⁸ PICU stay was not different between groups in 1 RCT⁸⁶ 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 RCT⁹¹ 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 therapy⁹⁴ 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 RCT⁹¹ 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 RCT⁹¹ and 2 observational studies.^{92,94} Hospital stay was also no different between groups in 1 RCT⁹¹ 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 study⁹⁴ 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, 1⁹⁵ 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 disorders⁹⁷ 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 RCT¹⁰⁶ and 2 multi-center, registry-based observational studies^{107,108} examining clinical outcomes of administering heliox for pediatric critical asthma (see Supplementary Data). The RCT¹⁰⁶ 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 illness¹⁰⁸ 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 RCT¹⁰⁶ and 1 observational study.¹⁰⁷ Hospital stay was no different between groups in 1 RCT¹⁰⁶ 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 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

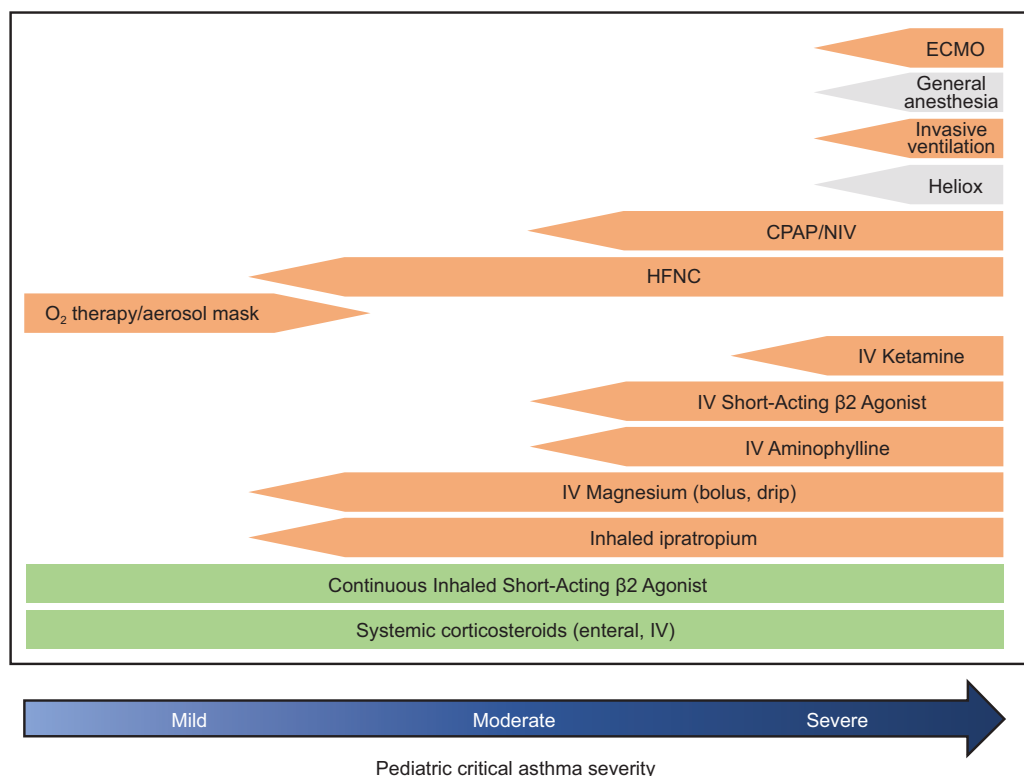


Fig. 1. Conceptual diagram of pediatric critical asthma therapies in context of disease severity. ECMO = extracorporeal membrane oxygenation, NIV = noninvasive ventilation, HFNC = high-flow nasal cannula.

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 study¹²³ 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 observational¹²⁷ and 2 QI studies.^{112,119} PICU stay was evaluated by 1

observational¹²⁶ 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 study¹²⁶ 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 study¹¹⁹ 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 study¹²⁷ 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, multi-center 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.

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Supplementary Material

Supplementary Data

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