This article has been accepted for publication in ADC following peer review.
The definitive copyedited, typeset version is available online at 10.1136/archdischild-2023-326739

An analysis of guideline recommendations for treatment of asthma exacerbations in children: a Pediatric Emergency Research Networks (PERN) study.

Word count – up to 3500 (currently 2717)
Title – up to 20 words (currently 19)
Structured abstract – up to 250 words (currently 245)
References – up to 40 (currently 39)
Figures – not limited

Corresponding author

Prof Simon Craig

Simon.Craig@monash.edu

Abstract

Rationale

There is significant practice variation in acute paediatric asthma, particularly severe exacerbations. It is unknown whether this is due to differences in clinical guidelines.

Objectives

To describe and compare the content and quality of clinical guidelines for the management of acute exacerbations of asthma in children between geographic regions.

Methods

Observational study of guidelines for the management of acute paediatric asthma from institutions across a global collaboration of six regional paediatric emergency research networks.

Measurements and main results

158 guidelines were identified. Half provided recommendations for at least two age groups, and most guidelines provided treatment recommendations according to asthma severity.

There were consistent recommendations for the use of inhaled short-acting beta-agonists and systemic corticosteroids. Inhaled anticholinergic therapy was recommended in most guidelines for severe and critical asthma, but there were inconsistent recommendations for its use in mild and moderate exacerbations. Other inhaled therapies such as helium-oxygen mixture (Heliox™) and nebulised magnesium were inconsistently recommended for severe and critical illness.

Parenteral bronchodilator therapy and adrenaline were mostly reserved for severe and critical asthma, with intravenous magnesium most recommended. There were regional differences in the use of other parenteral bronchodilators, particularly aminophylline.

Guideline quality assessment identified high ratings for clarity of presentation, scope and purpose, but low ratings for stakeholder involvement, rigour of development, applicability, and editorial independence.

Conclusions

Current guidelines for the management of acute paediatric asthma exacerbations have substantial deficits in important quality domains and provide limited and inconsistent guidance for severe exacerbations.

What is already known on this topic

There is significant practice variation in acute paediatric asthma, particularly regarding severe exacerbations where there is inconsistent selection and utilisation of parenteral bronchodilators.

What this study adds

This observational study of 158 clinical guidelines from a global paediatric emergency research network found that current guidelines for the management of acute paediatric asthma exacerbations have substantial deficits in important quality domains and are limited and inconsistent due to different interpretations of weak evidence to inform the management of severe or critical asthma.

How this study might affect research, practice or policy.

The current development of hospital-specific, region-specific or even national guidance risks considerable duplication of effort, inefficiency, and production of guidelines which are not of high quality.

Large, well-designed, multi-centre randomised controlled trials are needed to provide a solid foundation for future clinical practice guidelines, which should be developed through a rigorous global collaborative process to ensure high-quality robust guidance.

Introduction

Clinical practice guidelines guide management of paediatric asthma exacerbations in hospital settings. These documents may have been developed by international asthma bodies,[1] by experts in individual countries or regions,[2-9] or created at specific hospitals.[10]

Most children attending Emergency Departments (EDs) have mild or moderate exacerbations, and quickly respond to first-line therapy (usually inhaled bronchodilators and oral steroids) for which there is general consensus and considerable research support.[11-13] In contrast, the management of severe asthma exacerbations is less clear due to a lack of robust evidence. [14, 15]

Previous studies have documented significant practice variation in acute asthma, particularly for severe exacerbations.[16-18] It has not been determined whether this is due to differences in clinical guidelines. Further, it is unknown whether there is variation in guidelines within or between geographic regions/countries.

The Pediatric Emergency Research Networks (PERN) asthma working group was formed in 2017, with the aims of developing consensus evidence-based asthma outcome measures and international consensus guidelines for the conduct and reporting of clinical trials of therapies for acute asthma exacerbations. Currently, the group comprises members from seventeen countries.[19]

The aims of this study were to assess current clinical practice guidelines used in EDs associated with PERN. We aimed to:

1) Describe and compare **recommendations for the management** of acute exacerbations of asthma in children between geographic regions.

2) Assess **guideline quality**.

Methods.

This was an observational study of acute paediatric asthma guidelines from institutions belonging to a global emergency research network. Approval was provided from Monash Health Human Research Ethics Committee (Melbourne, Australia) as a Quality Assurance project exempt from full ethical review (RES-18-0000-525Q). The project results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

Setting and guideline collection.

Physicians and hospitals were invited to participate in the study by email (October 2018) via the eight partner networks that belong to PERN, and to the members of the PERN asthma working group. The PERN comprises the following networks: Research in European Paediatric Emergency Medicine (REPEM); Pediatric Emergency Care Applied Research Network (PECARN) and Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics (PEM CRC) from the USA; Pediatric Emergency Research Canada (PERC); Paediatric Research in Emergency Departments International Collaborative (PREDICT) from Australia and New Zealand; Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI); Red de Investigación de la Sociedad Española de Urgencias de Pediatría/Spanish Pediatric Emergency Research Group (RISEUP / SPERG); and Red de Investigacion y Desarrollo de la Emergencia Pediatrica en Latinoamerica (RIDEPLA).[21]

The email recipients were invited to forward the email to other physicians and hospitals within their local geographic region and/or research network. The request for participation was also shared on social media. This snowball approach aimed to encourage sampling within countries without formal organised research networks.

Each participating hospital was asked to provide a copy of their current acute asthma guideline. This could include local, regional, or national guidelines for management of acute onset of wheezing or asthma.

Data abstraction: guideline content.

To reduce the risk of bias, each clinical guideline was independently abstracted by two trained reviewers, who were provided with clear definitions, rules for interpretation of clinical guidelines, and instructions for data extraction. Abstracted data were recorded on a paper-based form and then entered into a specifically designed Research Electronic Data Capture (REDCap) database hosted at Monash University.[22, 23]

Any discrepancies between reviewers resulted in a discussion; if the discrepancy remained unresolved, a senior author (SC) was consulted about a final decision.

We planned for guidelines written in languages other than English to be abstracted by two investigators fluent in both English and the non-English language in which the guideline was written. While this was possible for guidelines written in Spanish and Catalan, we were unable to achieve this goal for those written in Dutch and French. An online translator (Google Translate) was therefore used to extract guideline content from Dutch and French guidelines.

For each guideline, specific data were obtained on the definition of asthma (including age range); assessment of acute asthma severity (according to the criteria used within each

guideline); and recommendations and severity thresholds for initiating various treatments, including: (a) inhaled beta-agonist therapy; (b) systemic corticosteroids; (c) adjunctive therapy, such as inhaled ipratropium and magnesium; (d) parenteral bronchodilator medications, including intravenous magnesium and adrenaline; (e) oxygen therapy (including devices and flow rates); (f) non-invasive and invasive ventilation; (g) Heliox™; and (h) ketamine.

A copy of the data extraction sheet is provided in Appendix One.

Guideline quality assessment

Each clinical practice guideline was assessed using the Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument, an international best-practice tool for the assessment of clinical practice guidelines.[24] Two raters were used, in accordance with recommendations from AGREE-II, to increase the reliability of the instrument.[24] All raters had specific training and were provided with an AGREE-II instruction manual. 23 items across six quality domains were assessed (scope and purpose; stakeholder involvement; rigour of development; clarity of presentation; applicability; and editorial independence), as well as overall quality, and whether each reviewer would (a) recommend the guideline, (b) recommend use of the guideline with modifications, or (c) not recommend the guideline.

Quality domain scores were determined by summing up all scores of the individual items in a domain and scaling the total as a percentage of the maximum possible score.[25] The AGREE-II instrument does not provide specific advice on how to interpret domain scores and notes that “there are no empirical data to link specific quality scores with specific implementation outcomes”, but provides examples using a threshold of >70% as evidence

of “high quality”. [25] We considered domain scores >70% as a high rating, while those <40% reflected a poor rating.

The process of online translation was deemed insufficient to assess guideline quality. Therefore, for the four guidelines written in Dutch or French, guideline content was extracted, but an assessment of guideline quality was not performed.

Statistical methods.

Guideline content was extracted and analysed descriptively. Guidelines were collated into the following six groups, based upon established PERN networks: United Kingdom and Ireland (PERUKI network); Spain (RISEUP-SPERG network); United States of America (PEM-CRC and PECARN networks); Australia and New Zealand (PREDICT network); Canada (PERC network) and “Other” (single guidelines from Netherlands, Romania, Switzerland, France, Zimbabwe, Singapore, India, Costa Rica, and two guidelines from South Africa). We did not pre-specify a sample size, as we aimed to obtain as many guidelines as possible throughout the participating networks.

Descriptive statistics were used to summarise guideline characteristics, treatment recommendations and guideline quality. Non-parametric data are reported using median and interquartile range (IQR), while categorical data are presented as count and percentage. We did not impute any missing data. Differences in proportions of categorical and non-parametric data are compared using the Chi-square and Kruskal-Wallis test, respectively. All analyses were performed using SPSS for Windows (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

Patient and public involvement

Patients were not involved in the design of this study.

Results

There were 158 clinical guidelines identified. The majority (95.6%) were from hospitals participating in national or regional PERN-associated networks, with the greatest number submitted from the United Kingdom and Ireland (PERUKI network), Spain (RISEUP-SPERG network) and the United States (PECARN and PEM-CRC networks). (Table 1)

Most guidelines were written in English; the most common non-English language used was Spanish. The majority did not provide a specific age range for inclusion; 60/158 (38%) provided a minimum age, and 29/158 (18%) provided a maximum age. Half of the guidelines provided separate management guidance for specific age groups. Of these, 62/79 (78%) had recommendations for two age groups, while 17/79 (22%) provided advice for three age groups.

Most guidelines provided distinct treatment recommendations according to asthma severity, although this varied by region (Table 2). Mild asthma was addressed in over two-thirds, while 28 (18%) guidelines focused on asthma of moderate severity or worse, and 5 (3%) guidelines focused only on severe asthma. Recommendations on treatment for critical/life-threatening asthma were provided in 105 (66%), while 53 (34%) provided recommendations on severe (but not critical/life-threatening) asthma.

A summary of region-specific guidelines for each severity of asthma exacerbation is provided in Supplementary Appendix Two. There were consistent recommendations for the

use of inhaled short-acting beta-agonists at all levels of severity, and for systemic corticosteroids for moderate, severe, and critical asthma (Figure 1). Inhaled anticholinergic therapy was recommended in most guidelines for severe and critical asthma, with a few guidelines also recommending this therapy for mild and moderate asthma. There was considerable variation in inhaled anticholinergic recommendations for moderate asthma with over 90% of US and Spanish guidelines recommending use compared to <30% of UK & Ireland. Some guidelines from the USA did not recommend inhaled beta-agonists or systemic corticosteroids for critical asthma; however, these guidelines focused on ventilatory support rather than pharmacological therapy.

Recommendations for oxygen therapy were less clearly articulated (Figure 2). In general, supplemental oxygen delivered via low-flow nasal or face-mask route was the first-line treatment, while high-flow nasal cannulae and non-invasive ventilation were reserved for severe and critical illness. Other inhaled therapies such as helium-oxygen mixture (Heliox™) and nebulised magnesium were inconsistently recommended for severe and critical illness.

Parenteral bronchodilator therapy (Figure 3) and adrenaline (Figure 4) were mostly reserved for severe and critical asthma. Intravenous magnesium was most recommended, however, there were some differences in the choice of specific therapies between regions. In nine guidelines, intramuscular adrenaline was also specifically advised in cases where anaphylaxis was suspected.

With respect to guideline quality (Table 3), clarity of guideline presentation and scope and purpose of the guideline were rated highly. In contrast, stakeholder involvement, rigour of development, applicability and editorial independence received poor ratings. Only one guideline (the Global Strategy for Asthma Management and Prevention,[26] provided as the guideline used in a Romanian hospital) was recommended for use without modification.

Ninety-eight (63.6%) guidelines were recommended for use with modification, and 53 (34.4%) were not recommended.

Discussion

Although clinical practice guidelines for the management of acute paediatric asthma provide consistent recommendations for management of mild and moderate exacerbations, there is considerable variation in treatment recommendations for severe and critical presentations. The guidelines have deficits in quality domains and are limited by a lack of robust evidence for the management of severe or critical asthma.

The use of inhaled bronchodilators and systemic corticosteroids for acute asthma exacerbations is supported by decades of practice and robust evidence.[26] This is reflected in consistent guideline recommendations. However, recommendations are inconsistent for children with severe or critical exacerbations, who require treatment beyond first-line therapies.

Cochrane reviews of escalated pharmacologic treatment (beyond inhaled bronchodilators and systemic corticosteroids) of children with acute asthma exacerbations highlight a number of knowledge gaps.[27] The evidence supporting intravenous magnesium is extremely limited (including only five small randomized studies with disparate results from a total of 182 children)[28], while only one study (showing no significant benefit) was identified addressing intravenous ketamine.[29] Despite a meta-analysis of nearly 3,000 patients enrolled in trials of inhaled magnesium, review authors noted that large, well-conducted trials had not shown clinically meaningful benefits.[30] This finding has been reinforced by a recent Canada-wide randomized trial of over 800 children demonstrating no

difference in hospitalization when nebulized magnesium was added to nebulized albuterol.[31]

Meta-analyses of studies on intravenous beta$_2$-agonists[32, 33] and/or intravenous aminophylline[34] have not demonstrated clinically significant benefit. There is no available Cochrane review on the utility of parenteral adrenaline for acute severe asthma in children.[27]

A recent Overview of Cochrane reviews of clinical trials on escalated therapy for asthma[35] assessed the evidence for parenteral bronchodilators, Heliox™, respiratory support and inhaled magnesium. The review found that the majority of comparisons involved between one and three trials and fewer than 100 participants, making it difficult to assess the balance between benefits and potential harms. The authors were unable to make firm practice recommendations.[35]

A large multicentre study comparing high-flow nasal oxygen to low-flow oxygen for children aged 1-4 years with hypoxic respiratory failure (including a subgroup of children diagnosed with “obstructive” lung disease, such as wheezing, asthma), did not find any overall benefits.[36] A Cochrane review of the use of non-invasive ventilation in paediatric asthma identified two trials, with a total of 40 children.[37] The authors concluded that current evidence did not permit confirmation or rejection of the effects of non-invasive ventilation for acute asthma in children, and recommended large, well-designed randomised controlled trials.

It is therefore apparent, that existing recommendations for the best management of severe acute paediatric asthma are currently based on suboptimal evidence with inconsistent, inconclusive or absent results and a paucity of adequately powered randomized controlled trials. Large observational studies have identified that some outcomes (such as intubation)

are likely too rare to be used as primary outcome measures, and practice-changing studies will require collaboration between a large number of centres.[38] There remains an urgent need for a global agreement regarding optimized trial designs with the most relevant core outcome measures to provide better evidence to inform future clinical practice.[19]

The overall guideline quality was moderate in our study, with high ratings for clarity of presentation, scope and purpose. A 2013 review of asthma guidelines providing recommendations for treatment of both children and adults identified significant deficits in guideline quality.[38] The proportion of guidelines rated as adequate was low for assessed categories including: scope and purpose, 44.1% (range: 10.0%-79.0%); stakeholder involvement, 33.8% (range: 4.0%-66.0%); rigour of development, 32.4% (range: 8.0%-64.0%); clarity and presentation, 52.1% (range: 17.0%-85.0%); applicability, 21.1% (range: 3%-55%); and editorial independence, 25% (range: 0%-58%).[39] Our study has demonstrated improvements in some areas (scope and purpose, clarity and presentation), but highlights ongoing deficits in other important domains such as stakeholder involvement, rigour of development, applicability and editorial independence. Development of comprehensive, rigorous clinical guidance is a resource-intensive undertaking. The current development of hospital-specific, region-specific or even national guidance risks considerable duplication of effort and inefficiency. However, the current 246-page comprehensive Global Initiative for Asthma (GINA) Management and Prevention does not provide easily accessible, stand-alone guidance for acute severe exacerbations and provides little guidance beyond initial parenteral magnesium.[26]

Collaboration between GINA and the PERN Asthma working group could enable development of a focused living guideline based on the best available evidence, updated

with emerging research, and relevant to the emergency care of children globally. Such a guideline could then be readily adapted for local implementation.

The strengths of our study include solicitation of guidelines from a geographically wide representation by leveraging multiple research networks in pediatric emergency medicine and the appraisal of guidelines using a validated tool. [25]

Despite this, there are limitations in our study. We did not extract data on methods of assessment of severity. Differences in severity assessment between countries / regions may explain differences in the use of inhaled anticholinergics for moderate exacerbations of asthma.

Although we attempted to obtain clinical guidelines from hospitals from many countries, a large proportion of the analysed guidelines were from the United Kingdom, Spain, and the USA. Hospitals providing guidelines were members of active research networks, which may have introduced some bias. In addition, there were more guidelines from the UK than USA, despite a much larger number of hospitals and greater population size in the USA. Although this may have introduced some bias, we made comparisons across geographic regions, thereby reducing the impact of different numbers of guidelines from each network. We had relatively few guidelines from Europe, Asia, South America, or Africa, and did not have the capacity to fully translate guidelines from languages other than Spanish and Catalan.

Overall, around one third of guidelines were not recommended by reviewers. The AGREE-II instrument requires appraisers to make an overall judgement as to whether or not they would recommend use of a particular guideline, however, does not require any explanation as to why this assessment was made.[25] We did not ask appraisers to provide specific reasons for their assessment, so are unable to comment on the main reasons why these guidelines were not recommended.

In conclusion, current guidelines for the management of acute paediatric asthma exacerbations have substantial deficits in important quality domains and are limited due to a lack of robust evidence for the management of severe or critical asthma. Large, well-designed, multi-centre randomised controlled trials are needed to provide a solid foundation for future clinical practice guidelines.

Table 1. Overview of clinical guidelines for acute asthma management in children.

Country / region (Research Network)	n (%)
United Kingdom & Ireland (PERUKI)	59 (37.3)
Spain (RISEUP-SPERG)	31 (19.6)
USA (PECARN, PEM-CRC)	27 (17.1)
Australia / New Zealand (PREDICT)	21 (13.3)
Canada (PERC)	9 (5.7)
Other (Singapore, India, Costa Rica, Africa and Europe)	11 (6.9)
Language	
English	122 (77.2)
Spanish	27 (17.1)
Catalan	5 (3.2)
Other (French =3, Dutch=1)	4 (2.5)
Minimum age	
<12 months	2 (1.3)
12 months	28 (17.7)
12 to <24 months	1 (0.6)
24 months	29 (18.4)
Not specified	98 (62)
Maximum age	
11 years	2 (1.3)
14 years	5 (3.2)
16 years	10 (6.3)
17 years	2 (1.3)
18 years	9 (5.7)
21 years	1 (0.6)
Not specified	129 (81.6)
Age groups	
Two age groups	62 (39.2)
Three age groups	17 (10.8)
Oldest age group >5 years	13 (8.2)
Oldest age group >11 years	4 (2.5)
Not specified	79 (50)
Lowest classification of severity described within guideline	
Mild	107 (67.7)
Mild/moderate	18 (11.4)
Moderate	28 (17.7)
Severe	5 (3.2)
Highest classification of severity described within guideline	
Critical / life-threatening	105 (66.5)
Severe	53 (33.5)
Number of guidelines which distinguish severe and critical / life-threatening	
Separate guidance for severe and critical / life-threatening	95 (60.1)
Guidance for severe, but not for critical / life-threatening	53 (33.5)
Guidance for critical / life-threatening but not severe	10 (6.3)

Table 2. Proportion (number and percentage) of guidelines providing treatment recommendations according to each severity of illness, by region.

	Mild	Mild-moderate	Moderate	Moderate-severe	Severe	Critical
United Kingdom & Ireland	16 (27.1)	12 (20.3)	42 (71.2)	2 (3.4)	57 (96.6)	58 (98.3)
Spain	31 (100)	0 (0)	31 (100)	2 (6.5)	31 (100)	6 (19.4)
United States of America	26 (96.3)	3 (11.1)	24 (88.9)	2 (7.4)	22 (81.5)	12 (44.4)
Australia / New Zealand	20 (95.2)	2 (9.5)	18 (85.7)	1 (4.8)	18 (85.7)	21 (100)
Canada	9 (100)	0 (0)	9 (100)	1 (11.1)	9 (100)	2 (22.2)
Other	5 (45.5)	4 (36.4)	6 (54.5)	1 (9.1)	11 (100)	6 (54.5)

Table 3. Guideline quality assessment (according to AGREE II domains). Results are expressed as the median (interquartile range) score from a maximum of 100. Each score represents the percentage of the maximum possible score for that domain.

	Canada (n=9)	UK / Ireland (n=59)	Australia / New Zealand (n=21)	Spain (n=31)	USA (n=27)	Other (n=6)	Total (n=153)	P value
Scope and Purpose†	56 (29 – 83.5)	97 (76.5 – 100)	86 (74.25 – 100)	14 (0 – 56)	98 (77.5 – 100)	91.5 (81.75 – 97.75)	83 (44 – 100)	0.04
Stakeholder involvement†	14 (0.5 – 36.5)	17 (4.5 – 32)	40.5 (8 – 59)	6 (0 – 22)	29 (6 – 67)	0 (0 – 0)	17 (3 – 33)	0.08
Rigour of development†	0 (0 – 0)	13 (1.5 – 27.5)	17.5 (3.5 – 24.5)	8 (3.5 – 13)	7 (1.5 – 31.5)	0 (0 – 0)	10 (1 – 23)	0.10
Clarity of presentation†	94 (90.5 – 97)	92 (69.5 – 97)	89 (78.75 – 93.5)	75 (59.75 – 83)	86 (72 – 94)	82 (65.5 – 97.75)	87 (67 – 94)	0.36
Applicability†	10 (0 – 32.5)	31 (20 – 51.5)	45 (17 – 57.5)	0 (0 – 4)	27 (7 – 43)	41 (18 – 49)	21 (4 – 44)	0.01
Editorial independence†	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	33 (0 – 42)	0 (0 – 0)	0 (0 – 31.25)	0 (0 – 0)	0.37
Overall quality (rated from 0-7)	3 (2.5 – 4)	4 (3 – 5)	4 (3.25 – 5)	3 (2 – 4)	4 (3 – 5)	3 (2.75 – 3.25)	4 (3 – 5)	0.04
Reviewer recommends guideline for use?								
Yes	0	0	0	0	0	1	1	<0.001
Yes, with modifications	5	44	17	11	18	3	98	
No	4	15	3	20	9	2	53	

Green shading indicates a domain quality score of >70%; yellow shading indicates a domain quality score of 40-70%; red shading indicates a domain quality score of <40%.

Figure 1. Guideline recommendations for inhaled bronchodilators and systemic corticosteroids, by region and exacerbation severity

Figure 2. Guideline recommendations for respiratory support and additional inhaled therapy, by region and exacerbation severity

NIV = non-invasive ventilation (continuous positive airway pressure or bi-level positive airway pressure)

Figure 3. Guideline recommendations for parenteral bronchodilators, by region and exacerbation severity

Figure 4. Guideline recommendations for adrenaline, by region and exacerbation severity

Contributorship statement

SC, FEB, CVEP, SRD and AG identified the research question. SC was responsible for the study design and research protocol, with input from all authors. JB, RV, MC and SC obtained data supervised data extraction and analysis. SC was responsible for statistical analysis. SC drafted the initial manuscript. All authors contributed equally to writing, reviewing and editing the manuscript.

All authors provided comments on the drafts and have read and approved the final version of the article. All authors had full access to all of the data (including statistical reports and tables) at the conclusion of the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

SC is the guarantor for the paper, accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Competing interests

There are no competing interests for any author.

Funding

This work is supported by the NHMRC Centre of Research Excellence in Paediatric Emergency Medicine (GNT1171228), Canberra, Australia. SC's contribution was funded by the Thoracic Society of Australia and New Zealand and National Asthma Council Fellowship, 2020 and the Australasian College for Emergency Medicine

Foundation Al Spilman Early Career Research Grant 2017. SRDs time was in part funded by Cure Kids New Zealand. FEB's time was funded by an NHMRC Investigator Leadership grant (GNT2017605) and the Royal Children's Hospital Foundation, Parkville, Australia.

Data sharing statement

Data are available on reasonable request. De-identified data will be available for sharing from 1 January 2025. Any data access requests should be sent to SC (simon.craig@monash.edu) and should include a proposal from the individual or organisation regarding their plan for use of the data.

The study team will review the request and consider the scientific merit of the proposed use of the data, and the legal, regulatory and ethical issues pertinent to the request. Presuming all constraints are addressed, the data will be shared using a secure file transfer platform.

Ethical statement.

Approval was provided from Monash Health Human Research Ethics Committee (Melbourne, Australia) as a Quality Assurance project exempt from full ethical review (RES-18-0000-525Q).

Acknowledgements

The authors would like to acknowledge Annie Rice, Anysha Walia, Caitlin Falloon, Claire Thomas, Emma Walker, Evita Lie, Jia Tan, Kang Hui Teow, Lauren Clementson, Lorna Pellegrino, Nam Gupta, Sarah Tan, Suma Sreedhar, Timothy Nguyen, Jessica Waghorn and Emma Ramage for assistance in data extraction, guideline assessment and data entry. We also thank members of all participating networks for contributing clinical guidelines for analysis.

The authors wish to acknowledge the Pediatric Emergency Research Networks (PERN) executive committee at the time of study approval: Nathan Kupperman (Chair, PECARN), Stuart Dalziel (Vice Chair, PREDICT), Franz Babl (PREDICT), Jim Chamberlain (PECARN), David Johnson (PERC), Mark Lyttle (PERUKI), Santiago Minteg (REPEM), Rakesh Mistry (PEMCRC), Lise Nigrovic (PEMCRC), Amy Plint (PERC), Damian Roland (PERUKI), and Patrick Van de Voorde (REPEM).

On behalf of the Pediatric Emergency Research Networks (PERN). Participating networks include: the Pediatric Research in Emergency Departments International Collaborative (PREDICT), the Pediatric Emergency Care Applied Research Network (PECARN), the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics (PEMCRC), Pediatric Emergency Research Canada (PERC), Pediatric Emergency Research in the United Kingdom and Ireland (PERUKI), Research in European Pediatric Emergency Medicine (REPEM), the Red de Investigación SEUP (Sociedad Española de Urgencias Pediátricas – Spanish Pediatric Emergency Research Group (RISeuP SPERG) network, and the Red de Investigación y Desarrollo de la Emergencia Pediatrica Latinoamericana (RIDEPLA) network.

References

1. *GINA (Global Initative for Asthma) Report, Global Strategy for Asthma Management and Prevention. 2018. Accesed from www.ginasthma.org on March 25th 2018.*
2. *National Asthma Council Australia. Australian Asthma Handbook, Version 1.1. National Asthma Council Australia, Melbourne, 2015. Website. Available from: http://www.asthmahandbook.org.au.*
3. *National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7232/.*
4. *British Thoracic Society and Scottish intercollegiate guidelines Network (2016). British Guideline On The Management of Asthma. London: British Thoracic Society.*
5. Al-Moamary, M.S., et al., *The Saudi Initiative for Asthma - 2016 update: Guidelines for the diagnosis and management of asthma in adults and children.* Ann Thorac Med, 2016. **11**(1): p. 3-42.
6. Arakawa, H., et al., *Japanese guidelines for childhood asthma 2017.* Allergol Int, 2017. **66**(2): p. 190-204.
7. Kim, D.K., et al., *Korean Asthma Guideline 2014: Summary of Major Updates to the Korean Asthma Guideline 2014.* Tuberc Respir Dis (Seoul), 2016. **79**(3): p. 111-20.
8. Kling, S., et al., *Guideline for the management of acute asthma in children: 2013 update.* S Afr Med J, 2013. **103**(3 Pt 3): p. 199-207.
9. Lougheed, M.D., et al., *Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults.* Can Respir J, 2012. **19**(2): p. 127-64.
10. *Royal Children's Hospital, Melbourne, Australia, Clinical Practice Guideline on Asthma, Acute. [Internet, last updated May 2015]* 2015; Available from: http://www.rch.org.au/clinicalguide/index.cfm.
11. Giordano, K., et al., *Pulmonary function tests in emergency department pediatric patients with acute wheezing/asthma exacerbation.* Pulm Med, 2012. **2012**: p. 724139.
12. Kelly, A.M., D. Kerr, and C. Powell, *Is severity assessment after one hour of treatment better for predicting the need for admission in acute asthma?* Respir Med, 2004. **98**(8): p. 777-81.
13. Powell, C.V., A.M. Kelly, and D. Kerr, *Lack of agreement in classification of the severity of acute asthma between emergency physician assessment and classification using the National Asthma Council Australia guidelines (1998).* Emerg Med (Fremantle), 2003. **15**(1): p. 49-53.
14. Neame, M., et al., *Salbutamol or aminophylline for acute severe asthma: how to choose which one, when and why?* Arch Dis Child Educ Pract Ed, 2015. **100**(4): p. 215-22.

15. Pollock, M., et al., *Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews.* Allergy, 2017. **72**(2): p. 183-200.
16. Babl, F.E., et al., *Paediatric acute asthma management in Australia and New Zealand: practice patterns in the context of clinical practice guidelines.* Arch Dis Child, 2008. **93**(4): p. 307-12.
17. Morris, I., et al., *Which intravenous bronchodilators are being administered to children presenting with acute severe wheeze in the UK and Ireland?* Thorax, 2015. **70**(1): p. 88-91.
18. Biagini Myers, J.M., et al., *Heterogeneity in asthma care in a statewide collaborative: the Ohio Pediatric Asthma Repository.* Pediatrics, 2015. **135**(2): p. 271-9.
19. Craig, S., et al., *Acute severe paediatric asthma: study protocol for the development of a core outcome set, a Pediatric Emergency Reserarch Networks (PERN) study.* Trials, 2020. **21**(1): p. 72.
20. von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.* Ann Intern Med, 2007. **147**(8): p. 573-7.
21. Klassen, T.P., et al., *The Pediatric Emergency Research Network (PERN): A decade of global research cooperation in paediatric emergency care.* Emerg Med Australas, 2021. **33**(5): p. 900-910.
22. Harris, P.A., 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): p. 377-81.
23. Harris, P.A., et al., *The REDCap consortium: Building an international community of software platform partners.* J Biomed Inform, 2019. **95**: p. 103208.
24. Brouwers, M.C., et al., *AGREE II: advancing guideline development, reporting and evaluation in health care.* Cmaj, 2010. **182**(18): p. E839-42.
25. *AGREE Next Steps Consortium (2017). The AGREE II Instrument [Electronic version]. Retrieved 28/04/2023 from http://www.agreetrust.org.*
26. *Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Available from www.ginasthma.org*
27. Craig, S.S., 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): p. Cd012977.
28. Griffiths, B. and K.M. Kew, *Intravenous magnesium sulfate for treating children with acute asthma in the emergency department.* Cochrane Database Syst Rev, 2016. **4**(4): p. Cd011050.
29. Jat, K.R. and D. Chawla, *Ketamine for management of acute exacerbations of asthma in children.* Cochrane Database Syst Rev, 2012. **11**(11): p. Cd009293.
30. Knightly, R., et al., *Inhaled magnesium sulfate in the treatment of acute asthma.* Cochrane Database Syst Rev, 2017. **11**(11): p. Cd003898.
31. Schuh, S., et al., *Effect of Nebulized Magnesium vs Placebo Added to Albuterol on Hospitalization Among Children With Refractory Acute Asthma Treated in the Emergency Department: A Randomized Clinical Trial.* Jama, 2020. **324**(20): p. 2038-2047.

32. Travers, A.H., et al., *Intravenous beta(2)-agonists versus intravenous aminophylline for acute asthma.* Cochrane Database Syst Rev, 2012. **12**: p. Cd010256.
33. Travers, A.H., et al., *Addition of intravenous beta(2)-agonists to inhaled beta(2)-agonists for acute asthma.* Cochrane Database Syst Rev, 2012. **12**: p. Cd010179.
34. Nair, P., S.J. Milan, and B.H. Rowe, *Addition of intravenous aminophylline to inhaled beta(2)-agonists in adults with acute asthma.* Cochrane Database Syst Rev, 2012. **12**(12): p. Cd002742.
35. Craig, S.S., 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**: p. Cd012977.
36. Franklin, D., 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: The PARIS-2 Randomized Clinical Trial.* Jama, 2023. **329**(3): p. 224-234.
37. Korang, S.K., et al., *Non-invasive positive pressure ventilation for acute asthma in children.* Cochrane Database Syst Rev, 2016. **9**(9): p. Cd012067.
38. Craig, S., 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).
39. Acuña-Izcaray, A., et al., *Quality assessment of asthma clinical practice guidelines: a systematic appraisal.* Chest, 2013. **144**(2): p. 390-397.