Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Inhaled Corticosteroids During Hospitalization

Specific Care Question

For pediatric patients hospitalized with acute asthma exacerbation and receiving systemic corticosteroids (SC), does the addition of inhaled corticosteroids (ICS) during the hospital stay versus no ICS result in improved outcomes?

Rationale for Question Asked

Patients who are hospitalized with acute asthma exacerbations generally receive systemic corticosteroids as part of routine care. In addition, they are often provided inhaled corticosteroids during their hospital stay, either as a continuation of their home regimen, or as a new therapy. In some cases, the inhalers administered in the hospital may be different from the inhalers prescribed for home use (due to re-evaluation of asthma severity, patient/family preferences, insurance coverage issues, etc.) resulting in additional healthcare costs such as wasted drug at discharge and wasted time spent ordering, dispensing, and teaching families on the wrong inhalation device.

The Global Initiative for Asthma (GINA) 2024 report notes that although add-on ICS are generally well-tolerated, the added cost and lack of clear guidance on agent, dose, route, and duration are important considerations. The document further recommends that "patients admitted to the hospital for asthma exacerbation should continue on, or be prescribed, ICS-containing therapy" (GINA, 2024, p. 174), though it is unclear if this recommendation applies to children receiving concurrent SC.

The intent of this review is not to provide a clinical recommendation but to give a summary of evidence to inform clinical decisions. Such decisions should consider not only this evidence but also benefits, harms, value, feasibility, and acceptability.

Overview and Certainty of Evidence

There was very limited data regarding the addition of ICS to SC during hospitalization; however, three systematic reviews (SR) compared similar treatment groups predominantly in the Emergency Department (ED) (Kearns et al., 2020; Li & Liu, 2021; Sawanyawisuth et al., 2020). For the outcome of patients requiring hospitalization, nebulized budesonide in combination with SC resulted in fewer admissions than SC alone (*RR* = 0.67, 95% CI [0.46, 0.98], $p < 0.01$ [Li & Liu, 2021]); (*OR* = 0.75, 95% CI [0.57, 0.99], $p = 0.04$ [Kearns et al., 2020; Sawanyawisuth et al., 2020]). For the outcome of length of stay, no significant differences were found between groups (*WMD* = −1.86; 95% CI [−4.72, 0.99], [Li & Liu, 2021]).

While the pooled analyses in these SRs focused primarily on patients in the ED setting, two single studies were identified that reported length of stay in the inpatient setting. High dose nebulized budesonide given twice daily to patients receiving SC resulted in a significantly shorter length of stay than placebo ($p = 0.01$, [Razi et al., 2015]); ($p < 0.001$, [Bahrami et al., 2020]).

Certainty Of The Evidence The certainty of the body of evidence was very low due to serious inconsistency and serious indirectness, with variability in the settings, populations studied, and treatment strategies employed. Additionally, one study included in both SRs (Razi et al., 2015) allowed patients to be randomized multiple times and reported cumulative visit data, which was then combined with single patient visit data in the pooled analysis. This may have introduced bias in the reported results.

Date Developed: 10/30/2024 If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu

Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Inhaled Corticosteroids During Hospitalization

Table 1
Included Studies

Author (year)	Study Type	Population	Participants / visits	Intervention	Control	Results *(note only comparisons in which both groups received SC in addition to the intervention or control are summarized)*
Li & Liu, (2021)	SR/MA of RCTs	Hospitalization (5 studies): • Patients aged 6 months – 18 years with moderate to severe acute asthma Length of Stay (3 studies): • Patients aged 6 months – 12 years with moderate to severe acute asthma	Hospitalization: *N* = 1285 Length of stay: *N* = 1106	ICS (nebulized budesonide) + SC (IV/IM methylprednisolone or oral prednisolone)	Placebo + SC	• For the outcome of hospitalization, the use of budesonide reduced admission rates versus placebo (*RR* = 0.67, 95% CI [0.46, 0.98], $p < 0.01$) • For the outcome of length of stay (2 ED studies and 1 inpatient study), there were no differences between patients receiving nebulized budesonide versus placebo in the pooled analysis (*WMD* = −1.86; 95% CI [−4.72, 0.99]) ○ The single study (Razi et al., 2015) reporting on inpatient length of stay found a significant difference between treatment groups favoring budesonide (44 hours in the budesonide group versus 80 hours in the placebo group [$p = 0.01$])
Sawanyawisuth et al., (2020)	SR/MA of RCTs	Hospitalization (4 studies): • Patients aged < 18 years with moderate to severe asthma exacerbation	*N* = 1150	ICS (any form) + SC (oral prednisolone, IV dexamethasone or IV methylprednisolone)	Placebo + SC	• For the outcome of hospitalization, ICS + SC was more effective than SC alone (*OR* = 0.75, 95% CI [0.57, 0.99], $p = 0.04$)*

Date Developed: 10/30/2024 If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu

Bahrami et al., (2020)	RCT	Patients aged 2 – 12 years hospitalized with acute asthma exacerbation	*N* = 80	ICS (nebulized budesonide 0.25 mg q 6hr) + SC (IV hydrocortisone 40 mg/kg/day)	Placebo + SC	• For the outcome of length of stay, ICS + SC was more effective than SC alone ($p < 0.001$) Budesonide ○ 1 day: n = 29 (72.5%) ○ 2 days: n = 10 (25%) ○ 3 days: n = 1 (2.5%) Placebo ○ 1 day: n = 3 (7%) ○ 2 days: n = 19 (42.5%) ○ 3 days: n = 13 (32.5%) ○ 4 days: n = 5 (12.5%)

*Note the systematic review published by Kearns et al., (2020) reported the same results as Sawanyawisuth et al., (2020) using the same four studies.

Identification of Studies
Search Strategy and Results

12) #11 AND ('Article'/it OR 'Article in Press'/it OR 'Editorial'/it OR 'Letter'/it OR 'Note'/it OR 'Review'/it)
11) #10 AND ('clinical trial'/de OR 'comparative effectiveness'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'evidence based practice'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'systematic review'/de)
10) #8 AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim) AND [humans]/lim AND [english]/lim AND [2018-2024]/py
9) #8 AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)
8) #3 AND #7
7) #4 OR #5 OR #6
6) 'ciclesonide'/exp OR 'mometasone furoate'/exp OR 'beclometasone'/exp OR 'flunisolide'/exp OR 'fluticasone'/exp OR 'triamcinolone'/exp OR 'prednisone'/exp OR 'prednisolone'/exp OR 'hydrocortisone'/exp OR 'methylprednisolone'/exp OR 'dexamethasone'/exp OR 'betamethasone'/exp
5) 'inhaled corticosteroid':ti,ab,kw OR 'inhaled steroid':ti,ab,kw
4) 'steroid'/exp OR steroid:ti,ab,kw OR 'corticosteroid'/exp OR corticosteroid:ti,ab,kw OR 'budesonide'/exp
3) #1 OR #2
2) 'asthma'/exp/mj AND 'acute exacerbation':ti,ab,kw
1) 'asthma exacerbation'/exp OR 'asthma exacerbation':ti,ab,kw OR 'asthmatic state'/exp OR 'status asthmaticus' OR 'acute asthma'/exp OR 'acute asthma':ti,ab,kw OR 'acute asthma exacerbation':ti,ab,kw OR 'asthma attack'/exp OR 'asthma attack':ti,ab,kw

Date Developed: 10/30/2024 If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu

Critically Appraised Topic (CAT): Inhaled Corticosteroids During Hospitalization

Search Dates: 2018-Current
Records identified through database searching *n* = 404
Additional records identified through other sources *n* = 0
Records excluded due to not answering PICOT question *n* = 400

Question Originator
J. Tam-Williams, MD
Findings from this review were presented with the question originator on November 8, 2024.
Medical Librarian Responsible for the Search Strategy
K. Swaggart, MLIS, AHIP
EBP Team or EBP Scholars Responsible for Analyzing the Literature
G. Stephens, BSN, RN
R. Rhodes, MHA, RRT, RRT-ACCS, RRT-NPS, C-NPT, CPPS
EBP Medical Director Responsible for Reviewing the Literature
K. Berg, MD, FAAP
EBP Team Member Responsible for Reviewing, Synthesizing, and Developing this Document
J. Dusin, MS, RD, LD, CPHQ
K. Hess, PharmD

Date Developed: 10/30/2024

If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu

Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Inhaled Corticosteroids During Hospitalization

Characteristics of Systematic Reviews of Intervention
Li & Liu (2021)

Design	Quantitative Synthesis (meta-analysis)
Objective	This study aimed to evaluate hospital admission rates, need for use of SC, length of hospital stay and adverse events when inhaled budesonide is added to standard pediatric management of moderate-to-severe acute exacerbations of asthma.

Methods	**Criteria for considering studies for this review**
	• **Types of studies:**
	  ○ Randomized controlled trials (RCTs)
	• **Participants:**
	  ○ Children with acute moderate-to-severe asthma
	• **Target Condition(s):**
	  ○ Acute asthma exacerbations occurring in patients with moderate-to-severe asthma
	
	Search methods for identification of studies
	• **Electronic databases searched:**
	  ○ PubMed, Scopus, CENTRAL (Cochrane Central Register of Controlled Trials), and Google Scholar databases
	• **Search strategy employed:**
	  ○ English as well as non-English language papers published until November 31, 2019.
	  ○ For non-English language papers, Google Translator was used for translation to English prior to the extraction of relevant information.
	  ○ Details of the search strategy have been provided in Supplemental Table 1.
	  ○ Studies that reported relevant outcome measures of interest to this meta-analysis were potentially considered for inclusion.
	• **Searching other resources (such as reference list):**
	  ○ The bibliographic list of the identified studies and relevant reviews on the subject were examined for additional possible studies.
	
	Data collection and analysis
	• **Inclusion criteria:**
	  ○ RCT conducted among children with acute moderate-to-severe asthma who attended the pediatric ED
	  ○ Compared the efficacy of budesonide against a placebo or control
	  ○ Outcomes of the study should have been at least one of the following:
	  ▪ Length of hospital stay
	  ▪ Hospitalization rate
	  ▪ Need for SC
	  ▪ Adverse events
	• **Exclusion criteria:**
	  ○ Studies that were done in children with mild or persistent asthma
	  ○ Studies on adults
	  ○ Non-randomized studies (i.e., case reports, observational studies, case-control, cohort studies) or review articles
	• **Setting:**
	  ○ Pediatric ED/inpatient
	• **Data collection process:**

	○ Using a data extraction sheet, two authors independently extracted information from the included studies. ○ The following data were extracted from all eligible studies: ▪ Surname of the first author, year in which the study was published, geographical location where the study was done, design of the study, characteristics of the study subjects, study groups, and key findings of the study. • **Assessment of the certainty of the evidence** ○ Methodological assessment was done independently by two authors using the Cochrane Risk of Bias Tool ○ See supplemental Table 2 • **Data Synthesis** (what statistical plan/tools do the authors establish a priori): ○ **Overall Effect Size** ▪ Effect sizes were reported as weighted mean differences (*WMD*) for continuous outcomes. ▪ For categorical outcomes, pooled relative risks (*RR*) were reported. ▪ All estimates were reported with 95% confidence intervals (CI). ○ **Heterogeneity** ▪ Heterogeneity of effects was assessed and quantified by the I^2 statistic. An I^2 value greater than 50% was considered to represent substantial heterogeneity. In cases with substantial heterogeneity, random-effects modeling was used.
Results	**Study Selection** **Number of articles identified:** *N* = 1656 **Full-text articles assessed for eligibility:** *n* = 25 **Studies included in qualitative synthesis:** *n* = 16 **Synthesis of quality of evidence:** • All of the included studies were randomized, double-blinded, placebo-controlled trials. • Four studies were conducted in Turkey, two in China, and one each in India, Bangladesh, Canada, Brazil, Belgium, USA, France, Denmark, and Saudi Arabia. • Supplemental Table 2 presents the authors' judgment of the risk of bias in included studies. • All the studies adopted random sequence generation, blinding of participants, blinding of study personnel, and blinding of outcome assessment. • Allocation concealment was reported in 14 studies. • Attrition bias did not occur in 11 studies. • There was no evidence of publication bias for any of the outcomes considered. • Overall, the quality of the included studies was judged to be good. **Synthesis of quantitative evidence:** • There were no differences in length of stay in the pooled analysis (*Hedges' g standardized mean difference (SMD)* = −1.53, 95% CI [−3.64, 0.58]) and risk of adverse events (*RR* = 0.87, 95% CI [0.65, 1.17]) between the two groups. ○ In a subgroup analysis where SC were used as a co-intervention, there were also no differences in the length of stay (two ED studies and one inpatient) (*WMD* = −1.86, 95% CI [−4.72, 0.99], I^2 = 99.4%). ▪ When inpatient results were isolated, the authors reported a reduction in length of stay with ICS + SC (44 hours in the budesonide group versus 80 hours in the placebo group [*p* = 0.01])

	• The pooled *RR* suggested a significant effect of nebulized budesonide in reducing hospitalization rates. Compared to placebo, children receiving budesonide had a 43% lower risk of being hospitalized (*RR* = 0.57, 95% CI [0.39, 0.85], I^2=70.3%, *p* = 0.01)
	  ○ No evidence of publication bias (*p* = 0.754)
	  ○ See funnel plot in Supplemental Fig. 1
	  ○ In a subgroup analysis where SC were used as a co-intervention, budesonide resulted in fewer admissions both in studies that did not use SC (*RR* = 0.24, 95% CI [0.09, 0.63], I^2 = 0.0%, *p*=0.82) and those that did (*RR* = 0.67, 95% CI [0.46, 0.98], I^2 = 77.6%, *p* < 0.01)
	• Children receiving nebulized budesonide had a lower need for SC compared to children receiving a placebo
	  ○ *RR* = 0.34, 95% CI [0.21, 0.22], I^2 = 0.0%, *p* < 0.01
	  ○ There was no evidence of publication bias (*p* = 0.462)
	  ○ A funnel plot is presented in Supplemental Fig. 2
	• The use of nebulized budesonide was not associated with an increased risk of adverse events
	  ○ *RR* = 0.87, 95% CI [0.65, 1.17], I^2= 27.9, *p*=0.37
	  ○ There was no evidence of publication bias (*p* = 0.602)
	  ○ A funnel plot is presented in Supplemental Fig. 4
	
	Heterogeneity
	• For the outcomes of risk of hospitalization and length of stay, the degree of heterogeneity was high. The high inter-study heterogeneity may be attributed to the methodological differences between the included studies.
	• Risk of hospitalization
	  ○ I^2 = 70.30%
	• Length of stay
	  ○ I^2= 99.17%

Discussion	**Summary of evidence** • The use of nebulized budesonide was beneficial in terms of reducing length of hospital stay, hospitalization rates and the need for the use of SC. • The use of budesonide was not associated with increased occurrence of adverse events. • These findings agree with previously published reviews of ICS in acute asthmatic exacerbations. **Limitations** • Small sample size in some studies could have affected the overall pooled estimates and reduced the statistical power of the analysis. • Pooled effect sizes could not be calculated for all clinical outcomes due to limited data and non-coherent reporting. ○ Findings of these outcomes were only presented in a narrative manner • Heterogeneity was high due to differences in methodology. • The review was restricted to studies of patients with moderate to severe asthma . Therefore, the findings of the meta-analysis may not be applicable to children with mild and/or persistent asthma.
Funding	**Funding** • No benefit has been received or will be received from any party related directly or indirectly to the subject of this article.

Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): Inhaled Corticosteroids During Hospitalization

Sawanyawisuth et al. (2020)

Design	Quantitative Synthesis (meta-analysis)
Objective	This study aimed to update a previous meta-analysis on the roles of ICS in the management of acute asthma exacerbation in children presenting to the hospital*.

Methods	**Criteria for considering studies for this review**
	• **Types of studies:** RCTs/meta-analysis
	• **Participants:** Children under age 18
	• **Target Condition(s):** Asthma exacerbations occurring in patients with moderate or moderate-to-severe asthma
	
	Search methods for identification of studies
	• **Electronic databases searched:**
	  ○ Medline
	  ○ Scopus
	  ○ Web of Science
	• **Search strategy employed:**
	  ○ English-only articles published between 2009 and 2018
	  ○ Search terms included asthma, acute asthma, acute exacerbation, acute asthma exacerbation, asthma attack, steroid, corticosteroid, inhaled corticosteroid, inhaled steroid, budesonide, ciclesonide, mometasone, beclomethasone, flunisolide, fluticasone, triamcinolone, prednisone, prednisolone, hydrocortisone, methylprednisolone, dexamethasone, or betamethasone.
	• **Searching other resources (such as reference list):**
	  ○ No references made to other sources.
	
	Data collection and analysis
	• **Inclusion criteria:**
	  ○ Children age under 18 years
	  ○ Conducted in a hospital setting*
	  ○ Compared ICS with or without SC versus other treatments such as placebo or SC
	  ○ Had hospital admission as the outcome
	  ○ The ICS was ICS in any form, while SC included oral prednisolone, intravenous dexamethasone, or intravenous methylprednisolone.
	• **Exclusion criteria:**
	  ○ None specifically listed
	• **Setting:**
	  ○ Hospital*
	• **Data collection process:**
	  ○ Previous meta-analysis studies were reviewed, and eligible studies were extracted. Other RCTs not included in the previous meta-analysis were added to this update.
	  ○ Titles and abstracts were independently analyzed by two researchers.
	  ○ Both researchers independently reviewed the full texts of potential articles. Disagreements between the two reviewers were evaluated by the third person.
	  ○ The method for extracting data from individual studies was not discussed.
	• **Assessment of the certainty of the evidence:**
	  ○ The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) criteria were used for the review process.

Date Developed: 10/30/2024 If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu

	○ Specific tools for assessing the risk of bias or certainty of evidence were not described. • **Data Synthesis** (what statistical plan/tools do the authors establish a priori): ○ **Overall Effect Size** ▪ Odds ratios with 95% CI were executed for the three comparisons with subgroup analysis by the severity of asthma exacerbation. ▪ Fixed effect models were used due to the small number of included studies in each analysis. ▪ All meta-analysis calculations were executed by Review Manager 5.3.5 software. ○ **Heterogeneity** ▪ Heterogeneity of effects was quantified by the I^2 statistic.
Results	**Study Selection (actual results/data)** **Number of articles identified:** *N* = 311 **Full-text articles assessed for eligibility:** *n* = 29 ○ **Studies included in qualitative synthesis:** *n* = 7 (3 meta-analyses and 4 added studies) **Synthesis of quality of evidence** (strength of evidence): • Not reported **Synthesis of quantitative evidence:** (provide reported data here) • Four studies compared ICS plus SC to SC alone ○ For the outcome of hospitalization, ICS plus SC was more effective than SC alone (*OR* = 0.75, 95% CI [0.57, 0.99], I^2 = 71%, *p* = 0.04)
Discussion	**Summary of evidence** • ICS significantly reduced hospital admission for asthma exacerbation, both in children receiving SC and those without. • The authors recommend that ICS may be used alone for mild-to-moderate asthma exacerbation and in combination with SC for moderate-to-severe asthma exacerbation. **Limitations:** • The hospital setting was not clearly defined. • Data were not reported for some comparisons in mild-to-moderate asthma exacerbation. This limitation may affect the generalizability of ICS on various asthma exacerbation severities. • I^2 was high in some comparisons, such as ICS plus SC versus SC alone. • Other outcomes of ICS were not evaluated, such as clinical asthma score or side effects of ICS.
Funding	**Funding:** • No funding reported.

*****The hospital setting is assumed to be the ED based on context unless otherwise stated.

Critically Appraised Topic (CAT): Inhaled Corticosteroids During Hospitalization

References

Bahrami, A., Jafarnejad, S., Khoshnezhad Ebrahimi, H., Mahmoudinezhad, S. M., & Dezfouli, R. P. (2020). Evaluating the effect of pulmicort inhalation on children with acute asthma attack. *Systematic Reviews in Pharmacy, 11*(9), 905-912.

Global Initiative for Asthma. (2024, May). *Global Strategy for Asthma Management and Prevention*. https://ginasthma.org/2024-report/

Kearns, N., Maijers, I., Harper, J., Beasley, R., & Weatherall, M. (2020). Inhaled corticosteroids in acute asthma: A systemic review and meta-analysis. *J Allergy Clin Immunol Pract*, *8*(2), 605-617.e606. https://doi.org/10.1016/j.jaip.2019.08.051

Li, C. Y., & Liu, Z. (2021). Effect of budesonide on hospitalization rates among children with acute asthma attending pediatric emergency department: A systematic review and meta-analysis. *World J Pediatr*, *17*(2), 152-163. https://doi.org/10.1007/s12519-020-00403-y

Razi, C. H., Akelma, A. Z., Harmanci, K., Kocak, M., & Kuras Can, Y. (2015). The addition of inhaled budesonide to standard therapy shortens the length of stay in hospital for asthmatic preschool children: A randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol*, *166*(4), 297-303. https://doi.org/10.1159/000430443

Sawanyawisuth, K., Chattakul, P., Khamsai, S., Boonsawat, W., Ladla, A., Chotmongkol, V., Limpawattana, P., Chindaprasirt, J., Senthong, V., Phitsanuwong, C., & Sawanyawisuth, K. (2020). Role of inhaled corticosteroids for asthma exacerbation in children: An updated meta-analysis. *J Emerg Trauma Shock*, *13*(2), 161-166. https://doi.org/10.4103/jets.Jets_116_19

Date Developed: 10/30/2024 If you have questions regarding this CAT – please contact evidencebasedpractice@cmh.edu