

Role of Inhaled Corticosteroids for Asthma Exacerbation in Children: An Updated Meta-Analysis

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Abstract

Background: Several studies showed that inhaled corticosteroids (ICS) may be a potential treatment in acute asthma exacerbation in children. This study was an update meta-analysis on the roles of ICS in the management of acute asthma exacerbation in children presenting to the hospital. **Materials and Methods:** Published articles with key words of ICS for asthma exacerbation, asthma attacks, and acute asthma in children aged under 18 years in the hospital setting with outcome of hospital admission between 2009 and 2018 were enrolled. The databases used in this study were Medline, Scopus, and Web of Science. Odds ratio of comparison between ICS and other treatments on hospital admissions was calculated. **Results:** There were 311 eligible studies met the searching criteria; seven eligible studies for the analysis; comprised of three meta-analysis and four added studies. The ICS had a significant reduction in hospital admission compared with placebo in overall with odds ratio of 0.63 (95% confidence interval [CI]: 0.41–0.96) and in moderate-to-severe group with odds ratio of 0.17 (95% CI: 0.05–0.51). Comparing with systemic corticosteroid (SC), ICS had significantly lower hospital admissions overall and in mild-to-moderate group with odds ratios of 0.63 and 0.26, respectively. The combination of ICS and SC had odds ratio of 0.75 (95% CI: 0.57–0.99) over SC in moderate-to-severe asthma exacerbation. **Conclusions:** ICS significantly reduced hospital admission in asthma exacerbation in children. It may be used alone for mild-to-moderate asthma exacerbation and combination with SC for moderate-to-severe asthma exacerbation.

Keywords: Admission, hospitalization, systemic corticosteroids

INTRODUCTION

Asthma is a common chronic disease in children, ranked among the top 10 conditions worldwide in terms of disability-adjusted life years for children aged 5–14 years.^[1] During 2001–2013, its prevalence in children aged <17 years in the US was 8.91%.^[2] Although its global mortality rate is low (0.7/100 000), acute asthma attacks and uncontrolled asthma can cause disability, affecting both the patients and their parents or caregivers.^[1] A US study found that school-aged children with asthma missed 1.54 times more school days than those without asthma, with their caregivers missing 1.16 times more working days than those of children without asthma.^[3]

Children with asthma often experience an exacerbation of the condition, with a US survey reporting that 52% of patients experienced at least one exacerbation requiring an emergency department visit.^[4] A study reported that the quality of life

score of children with asthma decreased from 6.2 to 4.2 during hospitalizations.^[5] Systemic corticosteroids (SC) are effective in the treatment of acute asthma exacerbation. A review concluded that treatment with SC within 1 h of exacerbation significantly reduced admission rates by 60% (95% confidence interval [CI]: 0.21–0.78) compared with that without corticosteroid treatment.^[6] The first-line therapy for chronic asthma is inhaled corticosteroids (ICS); however, their effect on asthma exacerbation remains under debate.^[7]

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Reported benefits of using ICS compared with oral prednisolone include a greater likelihood of discharge from the emergency department within 2 h (23% vs. 7%), a greater proportion of patients without respiratory distress (34% vs. 15%), and less vomiting (0% vs. 15%).^[8,9] However, in another study, children with asthma exacerbation had a higher admission rate if treated with inhaled fluticasone compared with oral prednisone (31% vs. 10%).^[10] The 2018 Global Initiative for Asthma Report stated that ICS can be used for asthma exacerbation in children;^[7] in contrast, the Japanese guidelines for childhood asthma do not mention the use of ICS for asthma exacerbation.^[11] A meta-analysis on the use of ICS at the emergency department concluded that ICS may reduce the admission rate by 56% (95% CI: 0.31–0.62).^[12] It is still controversial on using ICS in acute asthma exacerbation in children. The last meta-analysis on roles of ICS in children with acute asthma exacerbation in hospital setting was in 2014. This study aimed to update the meta-analysis on the roles of ICS in the management of acute asthma exacerbation in children presenting to the hospital.

MATERIALS AND METHODS

This updated meta-analysis was conducted on articles published between 2009 and 2018, only in English language. The databases used in this study were Medline, Scopus, and Web of Science. The 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.

All eligible articles were included only if involved with children age under 18 years, conducted at a hospital setting, compared ICS with or without SC versus other treatments such as placebo or SC, and had hospital admission as the outcome. The ICS was ICS in any form, while SC includes oral prednisolone, intravenous dexamethasone, or intravenous methylprednisolone. Previous meta-analysis studies were reviewed and extracted eligible studies. Other randomized controlled trials (RCT), not included in the previous meta-analysis, were added to this update meta-analysis. The Preferred Reporting Items for Systematic review and meta-analysis criteria were used for the review process. Titles and abstracts were independently analyzed by two researchers (KaS, KS). Full texts of potential articles were also independently reviewed by both researchers. Disagreements between the two reviewers were evaluated by the third person (PL).

Statistical analysis

The main primary outcome was hospital admission. There were three comparisons; ICS versus placebo, ICS versus SC, and ICS plus SC versus SC. Odds ratios with 95% CI were executed for the three comparisons with a subgroup analysis by the severity of asthma exacerbation. A homogeneity was

also calculated using Chi-square test. Fixed-effect models were used due to small included studies in each analysis. All meta-analysis calculations were executed by Review Manager 5.3.5 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

There were 311 eligible studies met the searching criteria and checked for duplication. Of those, 282 studies were not relevant to the topic. In total, 29 potential studies were reviewed; 22 studies excluded mainly due to non-ICS studies ($n = 11$), as shown in Figure 1. There were 7 studies remaining for the analysis; comprised of three meta-analysis and four added studies.^[12-18] The three meta-analysis included Edmonds *et al.*, in 2012; Su *et al.*, in 2014; and Beckhaus *et al.*, in 2014.^[12-14] The other four RCT studies were added and shown in Table 1.^[15-18]

There were 14 studies conducted in children with the ICS treatment from the Edmonds study, while there were 10 and 8 studies from the study by Su and Beckhaus, respectively [Table 1]. There were four studies included in all three meta-analysis; Scarfone 1995, Devidayal 1999, Schuh 2000, and Milani 2004. An unpublished study, Razi 2012, by the Edmonds meta-analysis, was excluded due to a duplication with the Razi 2017 study. In total, there were 19 studies included in the final analysis.^[8-10,15-30] These 19 studies had 20 comparisons between ICS and other treatments; Milani 2004 study had two comparisons; ICS versus placebo and ICS versus SC. The 20 comparisons categorized as ICS versus placebo (5 comparisons), ICS versus SC (11 comparisons), and ICS plus SC versus SC (4 comparisons).

Inhaled corticosteroids versus placebo

There were five studies comparing ICS with placebo in acute asthma exacerbation; Chen 2013, Eastrada-Reyes 2005, Milani 2004, Sekerel 2005, and Singhi 1999. Only the Sekerel 2005 study conducted in mild-to-moderate asthma exacerbation, while the other studies conducted in either moderate or moderate-to-severe asthma exacerbation. In overall, the odds ratio for hospital admission by ICS over placebo was 0.17 (95% CI: 0.05–0.51), as shown in Figure 2a. The odds ratio for mild-to-moderate asthma exacerbation was not calculated due to no outcome in the Sekerel study in both arms. For moderate or moderate-to-severe asthma exacerbation, the ICS also had significantly lower hospital admission rate than placebo with an odds ratio of 0.17 (95% CI: 0.05–0.51), as shown in Figure 2b. Both analyses had an I^2 of 0%.

Inhaled corticosteroids versus systemic corticosteroid

There were 11 studies comparing ICS versus SC [Figure 3a-d]; two studies (Nikanishi and Manjra) did not define asthma exacerbation severity. Therefore, nine studies included in the subgroup analyses; two studies for mild-to-moderate asthma exacerbation [Figure 3b], four studies for moderate or moderate-to-severe asthma exacerbation [Figure 3c], and three studies for severe asthma exacerbation [Figure 3d]. ICS had significant odds ratios compared with SC in

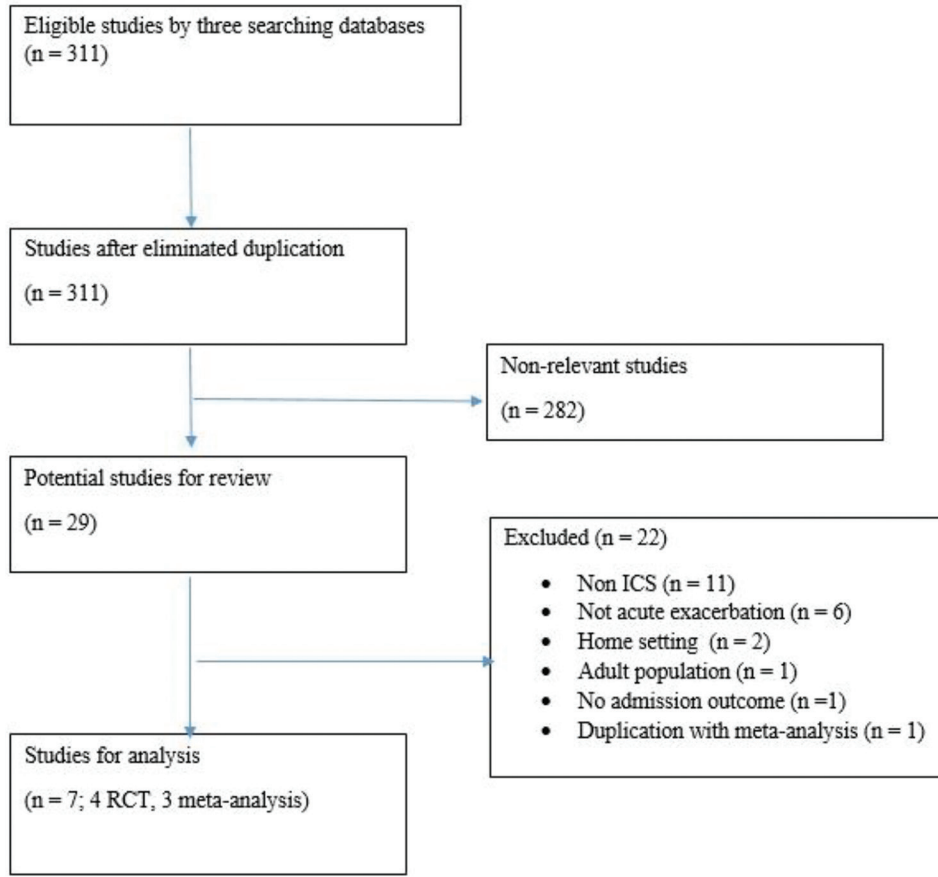


Figure 1: Flow chart for study selection

Table 1: Included studies in the previous meta-analysis studies or added randomized controlled trials comparing inhaled corticosteroid versus other treatments in children with acute asthma exacerbation presenting to the hospitals (n=20)

Number	Edmonds 2012	Su 2014	Beckhaus 2014	Added studies
1	Scarfone 1995	Scarfone 1995	Scarfone 1995	
2	Sung 1998	Sung 1998		
3	Volovitz 1998		Volovitz 1998	
4	Devidayal 1999	Devidayal 1999	Devidayal 1999	
5	Singhi 1999	Singhi 1999		
6	Schuh 2000	Schuh 2000	Schuh 2000	
7	Macias 2003			
8	Milani 2004	Milani 2004	Milani 2004	
9	Estrada-Reyes 2005	Estrada-Reyes 2005		
10	Sekerel 2005	Sekerel 2005		
11	Schuh 2006		Schuh 2006	
12	Ancheta 2008			
13	Upham 2011	Upham 2011		
14	Razi 2012			
15		Nakanishi 2003	Nakanishi 2003	
16			Manjra 2000	
17				Chen 2013
18				Alangari 2014
19				Arulparithi 2014
20				Razi 2017

overall (0.63; 95% CI: 0.41–0.96) and mild-to-moderate asthma exacerbation (0.26; 95% CI: 0.08–0.79), as shown in

Figure 3a and b, respectively. The I^2 for both analyses was 59% and 0%.

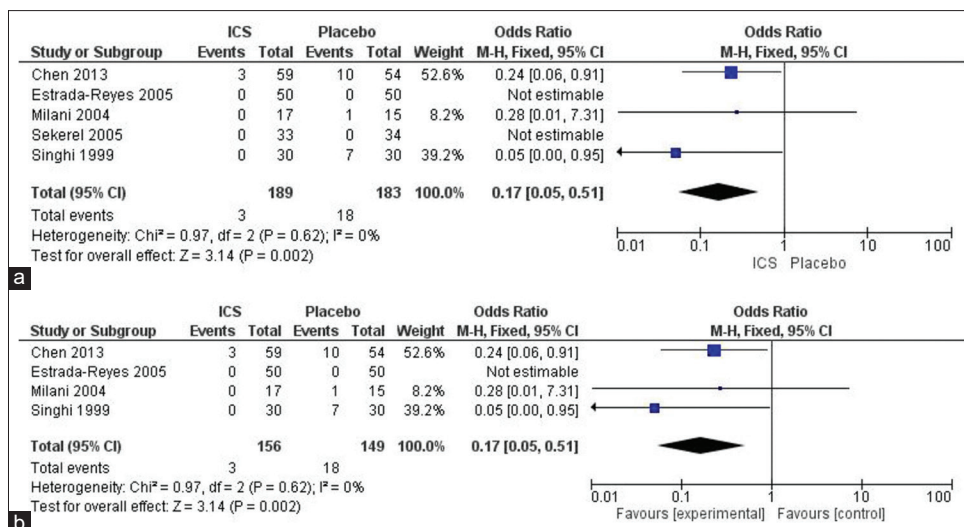


Figure 2: Comparisons between inhaled corticosteroid versus placebo (a) and subgroup analysis in moderate or moderate-to-severe asthma exacerbation (b)

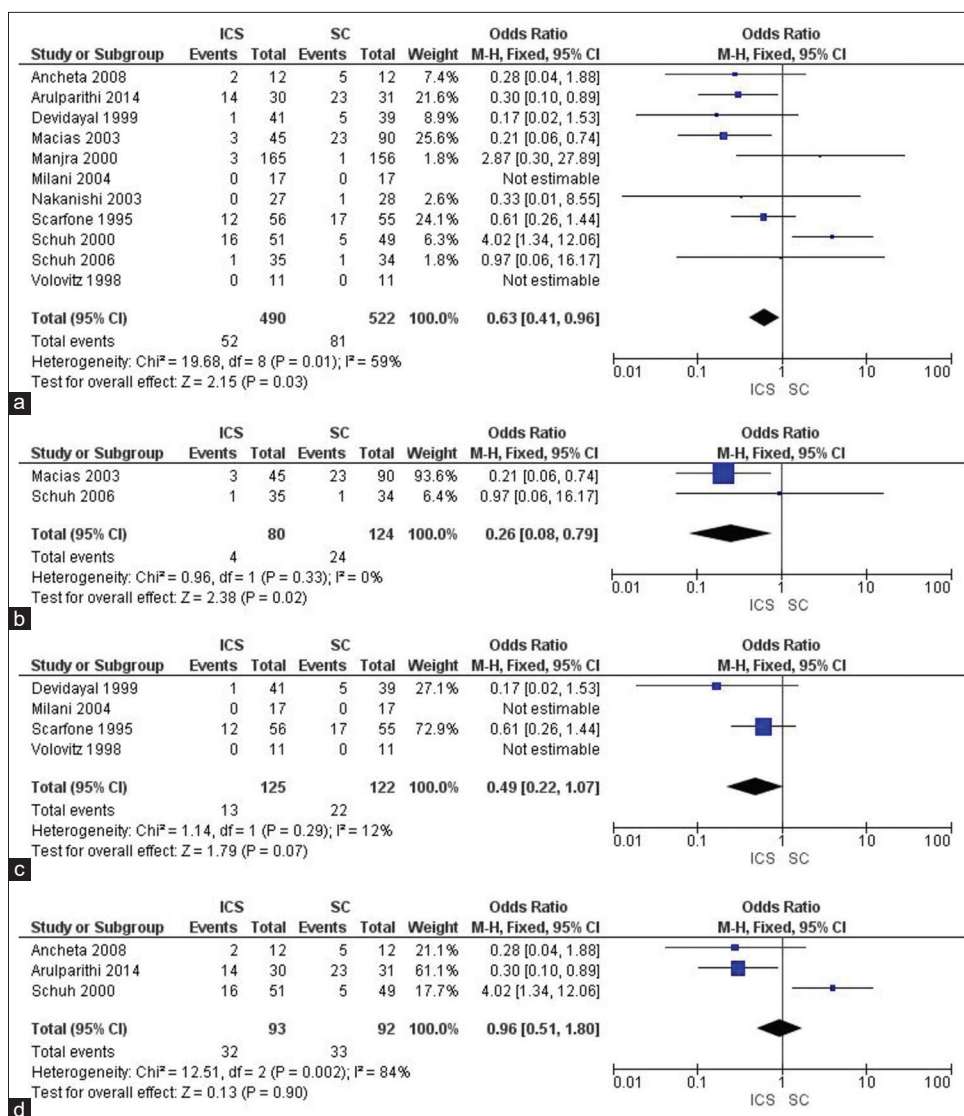


Figure 3: Comparisons between inhaled corticosteroid versus systemic corticosteroid in overall (a) and subgroup analysis by severity; mild-to-moderate asthma exacerbation (b), moderate or moderate-to-severe asthma exacerbation (c), severe asthma exacerbation (d)

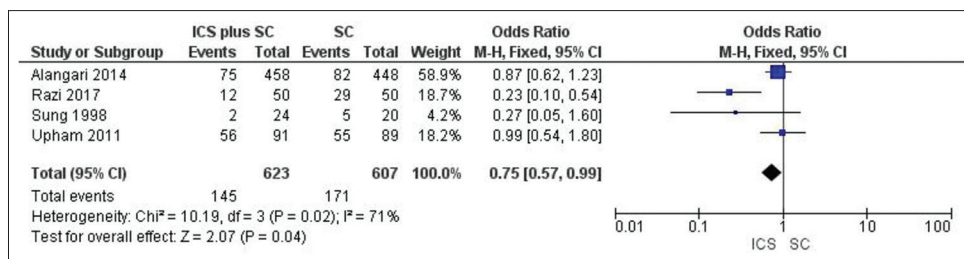


Figure 4: Comparison between inhaled corticosteroid plus systemic corticosteroid versus systemic corticosteroid in moderate or moderate-to-severe asthma exacerbation

Inhaled corticosteroids plus systemic corticosteroid versus systemic corticosteroid

There were four studies comparing ICS plus SC versus SC; Anagari 2014, Razi 2017, Sung 1998, and Upham 2011 [Figure 4]. All studies conducted in moderate or moderate-to-severe asthma exacerbation. The odds ratio for ICS plus SC over SC was 0.75 (95% CI: 0.57–0.99) with the I^2 of 71%.

DISCUSSION

Asthma hospitalizations can be a stigma for children causing poor quality of life.^[5] In addition, it may cause substantial costs during hospital admissions. A report showed that the admission costs for asthma might be high as \$3,102.53 for the average stay of 3.8 days in adult patient.^[31] The results of this study showed that ICS is effective in the reduction of asthma hospitalizations significantly in all three comparisons.

The ICS reduced hospital admission by 83% in moderate or moderate-to-severe asthma exacerbation when compared with placebo [Figure 2a and b], and 27% when compared with SC in overall [Figure 3a]. The ICS had beneficial effects only in mild-to-moderate asthma exacerbation but not moderate-to-severe group when compared with SC [Figure 3b-d]. When adding to SC, this combination reduced hospitalization by 25% when compared with SC alone in moderate-to-severe asthma exacerbation. Therefore, ICS may be more effective than SC in mild-to-moderate asthma exacerbation. For moderate-to-severe asthma exacerbation, ICS may be equivalent or nonsignificant superior to SC from odds ratio of lower 1 (0.49 for moderate and 0.96 for severe group). Adding ICS to SC in moderate-to-severe asthma exacerbation may be beneficial. To the best of our knowledge, this is the first meta-analysis to demonstrate roles of ICS on asthma exacerbation based on the severity of the exacerbation. All three previous meta-analysis studies have not explored this issue.^[12-14]

There is sufficient evidence to use ICS for asthma exacerbation of moderate severity. It can be used immediately in the emergency setting in combination with a nebulized bronchodilator.^[15] The rapid action of ICS is crucial in an emergency setting. Several articles have reported that SC is slow acting, taking at least 3–4 h after administration.^[6,32] In contrast, ICS acts faster, showing topical effects in reducing airway hyperresponsiveness within 2 h.^[33,34] Compared with

prednisolone, inhaled fluticasone significantly reduced sputum eosinophils at 2 and 6 h after treatment.

In addition to reduction of asthma hospitalizations, several studies showed that ICS improved clinical scores^[15,35] and pulmonary function test, particularly FEV115; reduced uses of bronchodilators;^[36] and shorter length of hospital stay.^[37] No serious adverse events associated with nebulized the use of ICS for asthma exacerbation were reported in any study, although one study found a nonsignificant higher risk for tremor by 1.29 times (95% CI: 0.58–2.88).^[24] Another benefit of ICS is that they may be less invasive than intravenous methylprednisolone. Disadvantages of ICS include higher cost, less accessibility in developing countries, and reduced effectiveness in individuals with a high respiratory rate. ICS has very low side effects. The suppression of the pituitary adrenal axis was low compared with that by SC.^[36] In 1998, Shapiro *et al.* showed that budesonide inhalation (0.5–2 mg/day) for 12 weeks had no effect on basal and adrenocorticotrophic hormone-stimulated cortisol responses compared with the placebo.^[38] In patients experiencing repeated asthma exacerbation and receiving SC, there may be a reduction in the osteocalcin level and in the response of cortisol hormone to hypoglycemia.^[39,40] However, the long-term side effects of ICS in asthma exacerbation have not yet been evaluated.

There were some limitations in this study. First, there was no estimated odds ratio or no data for some comparisons such as ICS versus placebo or ICS plus SC versus SC in mild-to-moderate asthma exacerbation. This limitation may effect on generalizable of ICS on various severities. Second, the I^2 was high in some comparisons such as ICS plus SC versus SC comparison ($I^2 = 71$), but it was not as extremely high (over 75%). Finally, other outcomes of ICS were not evaluated such as clinical asthma score or side effects of ICS.

CONCLUSIONS

ICS significantly reduced hospital admission in asthma exacerbation in children. It may be used alone for mild-to-moderate asthma exacerbation and combination with SC for moderate-to-severe asthma exacerbation.

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Conflicts of interest

There are no conflicts of interest.

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