

Inhaled Versus Systemic Corticosteroids for Acute Asthma in Children. A Systematic Review

Andrea A. Beckhaus, MD,¹ Maria C. Riutort, MD,¹ and Jose A. Castro-Rodriguez, MD, PhD^{2*}

Summary. Objective: To compare the effects of inhaled corticosteroids (ICS) against systemic corticosteroids (SC) in children consulting in emergency department (ED) or equivalent for asthma exacerbation. Methods: Electronic search in MEDLINE, CENTRAL, CINAHL, and LILACS databases and other sources. Study selection criteria: children 2–18 years of age, consulting in ED or equivalent for asthma exacerbation, comparison between ICS and SC, randomized controlled trials. Primary outcomes: hospital admission rate, unscheduled visits for asthma symptoms, need of additional course of SC. Secondary outcomes: improvement of lung function, length of stay in ED, clinical scores, and adverse effects. Results: Eight studies met inclusion criteria ($N = 797$), published between 1995 and 2006. All used prednisolone as SC and budesonide, fluticasone, dexamethasone, and flunisolide were administered as ICS. No significant difference between ICS versus SC was found in terms of hospital admission (RR: 1.02; 95% CI: 0.41–2.57), unscheduled visits for asthma symptoms (RR: 9.55; 95% CI: 0.53–170.52) nor for need of additional course of SC (RR: 1.45; 95% CI: 0.28–7.62). The change in % of predicted FEV₁ at fourth hour was significantly higher for SC group, but there was no significant difference between both groups after this time. There was insufficient data to perform meta-analysis of length of stay during first consult in ED and of symptom scores. Vomiting was similar among both groups. Conclusions: There is no evidence of a difference between ICS and SC in terms of hospital admission rates, unscheduled visits for asthma symptoms and need of additional course of SC in children consulting for asthma exacerbations. **Pediatr Pulmonol.** © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

Asthma exacerbations lead not only to a deterioration in the quality of life of asthmatics and their families, but also have a great impact in the utilization of health care

resources.^{1,2} In 2010 in the US, 4.3 million asthmatic children had an asthma attack in the previous year. Between 2007 and 2009, children had an emergency rate visit of 10.7 visits per 100 persons with asthma and the average hospital admission was 2.1 per 100 persons with

¹Department of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.

²Departments of Pediatrics and Family Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.

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*Correspondence to: Jose A. Castro Rodriguez, MD, PhD, Departments of Family Medicine and Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Lira 44, 1er Piso, casilla 114-D, Santiago, Chile. E-mail: jacastro17@hotmail.com

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asthma.³ In the US, between 2001 and 2009, asthma ED visits and hospitalizations per 100 persons with asthma remained stable.⁴ Moreover, exacerbations also have a role in the deterioration of the pulmonary function.⁵

Inhaled corticosteroids (ICS) are the most effective medicine in the long term management of asthma, both preschool and older children.^{6–9} ICS utility is given by gaining control of symptoms, reversal of airflow obstruction, improvement in quality of life, as well as reducing the number and severity of asthma exacerbations.¹⁰ On the other hand, the use of systemic corticosteroids (SC) during asthmatic exacerbations is widespread, being a standard tool in the management of asthmatic crisis.^{8,11} SC have been associated not only with a decrease in the hospital admission rate in patients consulting in an emergency department (ED), but have also been associated with improvement in lung function.¹²

Therapeutic effects of corticosteroids have been widely studied, having a classical genomic or anti-inflammatory response that takes hours to days, through changes in transcription of genes involved in the inflammatory response. This effect is common to both SC and ICS. However, more recently it has been reported a non-genomic response that takes minutes to occur through a process of vasoconstriction mediated by second messengers and it is a transient effect, dose dependent and occur only with ICS.^{8,12} Asthmatics have a significantly increased blood flow in the airway mucosa. ICS produce a decrease in this flow by a mechanism of vasoconstriction inhibiting the norepinephrine recapture in the synaptic cleft; hence increasing binding to its receptor in smooth muscle cells, causing contraction of it.^{12,13} Therefore, although traditionally reserved to maintenance therapy of asthma, its mechanism of action opens new therapeutic options for the management of exacerbations of the disease, as an alternative to SC and with the advantage of

having a likely better safety profile, with less probability to suppress adrenal axis.¹⁴

Three meta-analysis have been published in this topic,^{12,15} but those studies evaluated adults and children together, with a greater proportion of adults. Rodrigo¹² analyzed three studies that compared hospital admission rates, two of them with children participants, showing no difference between ICS and SC. Within the same meta-analysis, three studies compared hospital discharge, two of them with children population, reporting earlier discharge with use of ICS. Edmonds et al.¹⁵ evaluated ICS following ED discharge in adults (three studies) and children (four studies). They showed no differences in relapse rates, analyzing the four studies which reported this outcome, two of them with children participants. No hospital admissions were reported. Analysis where made with both populations, and unpublished data was used. More recently, a third meta-analysis was published by Edmonds et al.¹⁶ in 2012, which evaluates the early use of ICS in the ED in acute asthma, that compares ICS versus placebo and ICS versus SC, including both adult and pediatric population, concluding that there is insufficient evidence that ICS can replace SC therapy when treating acute asthma.

The objective of this systematic review is to evaluate the effects of ICS use compared with the use of SC only in children with acute asthma exacerbations, consulting on an ED or in an equivalent care setting.

METHODS

Search and Selection Criteria

We searched electronic databases (search June 2012) Medline, CENTRAL (Cochrane Collaboration clinical trials register), LILACS and CINAHL. The search process was conducted in conjunction with library electronic search specialists (using the keywords: budesonide OR ciclesonide OR mometasone OR beclomethasone OR flunisolide OR fluticasone OR triamcinolone AND prednisone OR prednisolone OR hydrocortisone OR methylprednisolone OR dexamethasone OR betamethasone, limited with the terms children OR child OR pediatric OR adolescents OR infants OR preschoolers). Also, we searched in other non-bibliographic data sources, as web searching, references of publications found and pharmaceutical industry web sites. If information was incomplete we attempted to contact the authors. The specific inclusion criteria were¹: children between 2 and 18 years of age who consulted in the ED or equivalent due to an acute asthma exacerbation²; compare the use of any ICS with any SC, administered by any route³; randomized (parallel group or cross-over) controlled trials (RCTs) without language restriction. The specific exclusion criteria were¹: infants <2 years of age or adults²; prior use of SC 2 weeks before enrollment³ letters

ABBREVIATIONS:

ACTH	Adrenocorticotrophic hormone
CI	Confidence interval
ED	Emergency department
FEV ₁	Flow expiratory volume in the first second
FMD	Fixed mean difference
HR	Heart rate
ICS	Inhaled corticosteroids
WMD	Weighted mean difference
NNT	Number needed to treat
pMDI	Pressurized metered-dose inhalers
PEF	Peak expiratory flow
RCT	Randomized controlled trial
RDA	Respiratory distress assessment
RR	Relative risk
SC	Systemic corticosteroids
SpO ₂	Pulse oximetry

or abstracts. The primary outcomes of the study were the need of hospital admission, unscheduled visits to the ED in the next 2 weeks following the intervention and need of additional course of SC. Secondary outcomes were the improvement of lung function (measured by FEV₁, PEF), length of stay during the first consult in the ED, symptom score and adverse effects.

Data Abstraction and Assessment of Risk of Bias

This systematic review was performed according to preferred reporting items for systematic reviews and meta-analyses guidelines.¹⁷ Titles, abstracts, and citations were independently analyzed by two independent investigators (AB, MR). From the full texts, the reviewers independently assessed all studies for inclusion based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. Disagreements were resolved through a mediator (JAC). Risk of bias of including studies was assessed according to recommendations of the Cochrane Handbook,¹⁸ with regards to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data addressed, selective reporting and if it was funded by the pharmaceutical industry.

Data Analysis

For the measurement of binary outcomes we used relative risk (RR) with 95% confidence interval (CI). For continuous outcomes we used the weighted mean difference (WMD) with 95% CI. For all outcomes measured, a random-effects meta-analysis was performed to address the variation across the included studies. Heterogeneity was assessed using the I² test and chi-square. We used a priori subgroup analysis to explore the influence of age (<5 years vs. >5 years), severity of asthma exacerbation (mild vs. moderate to severe), comparison of different types of ICS, route of administration, comparison of different SC and studies sponsored by pharmaceutical industry versus independent. A $P < 0.05$ using a 2-tailed test was considered to indicate significance. Meta-analysis was performed using ReviewManager 5.1.2 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, Copenhagen, Denmark).

Ethics Committee

The Research Ethics Committee of the *Pontificia Universidad Católica de Chile* took knowledge and approved the present study (registration number 11–252).

The trial has been registered with the international prospective register of systematic reviews (PROSPERO, #CRD42012002499).

RESULTS

A total of forty-three studies were initially identified in database and other sources. Thirty three studies were excluded, because they did not met inclusion criteria or had exclusion criteria, leaving 10 studies for which their eligibility was assessed. Two of these studies were excluded because they met exclusion criteria (Fig. 1).

Included Studies

Therefore, eight studies published from 1995 to 2006 were included^{19–26} (Table 1). Two were conducted in Canada,^{23,26} two in the U.S.,^{19,24} one in Israel,²⁰ one in India,²¹ one in the UK²¹ and one was conducted in Brazil.²⁵ A total of 797 patients were randomized, 62% of participants were male. Six of the studies were realized in the ED and two studies were conducted in an equivalent to an ED (one was in a clinic²² and one at a Pediatric walk-in clinic).²⁵

All studies used prednisolone (1–2 mg/kg per day) in the SC group. In the ICS group, four studies used budesonide, three administered by nebulization^{21,22,25} and one by turbohaler.²⁰ Two studies used fluticasone by pMDI,^{23,26} one used nebulized dexamethasone¹⁹ and one used flunisolide by pMDI.²⁴ Three studies used a single high dose of ICS^{19,22,23} and five studies used an initial high dose of ICS followed by a maintaining dose at home.^{20,21,23,24,26} Details of specific doses used are listed in Table 1. In six of the studies β_2 agonists were administered by protocol,^{19,21,23–26} in four studies β_2 agonists were also administered as needed,^{20,22,24,26} in three studies ipatropium bromide was given by protocol^{23,24,26} and in one study oxygen was administered by protocol.²¹ Scarfone et al.¹⁹ compared ICS and SC in the ER, but both groups received SC after discharge, so only the first phase of the study was used for analysis. The age range in the ICS group was 3.9–11 years and in the SC group 4.3–10.5 years and there was no statistical difference in age between both groups in any study. One study enrolled children with clinical mild to moderate acute exacerbation of asthma,²⁶ two studies compared clinical moderate acute exacerbation of asthma,^{19,25} two studies compared children with clinical moderate to severe asthma exacerbation,^{20,21} one study enrolled patients with clinical severe asthma exacerbation,²³ one study included children with PEF 45–75%²² and one with PEF 25–80%.²⁴ Therefore, the vast majority of the studies included moderate-severe acute asthma exacerbation.

Among all of the studies, six were sponsored by the pharmaceutical industry,^{20–24,26} the other two did not specify it.^{19,25} All studies were randomized, but no description of the allocation concealment was given in three of them. In every study the participants and personnel were blind to the intervention. All studies

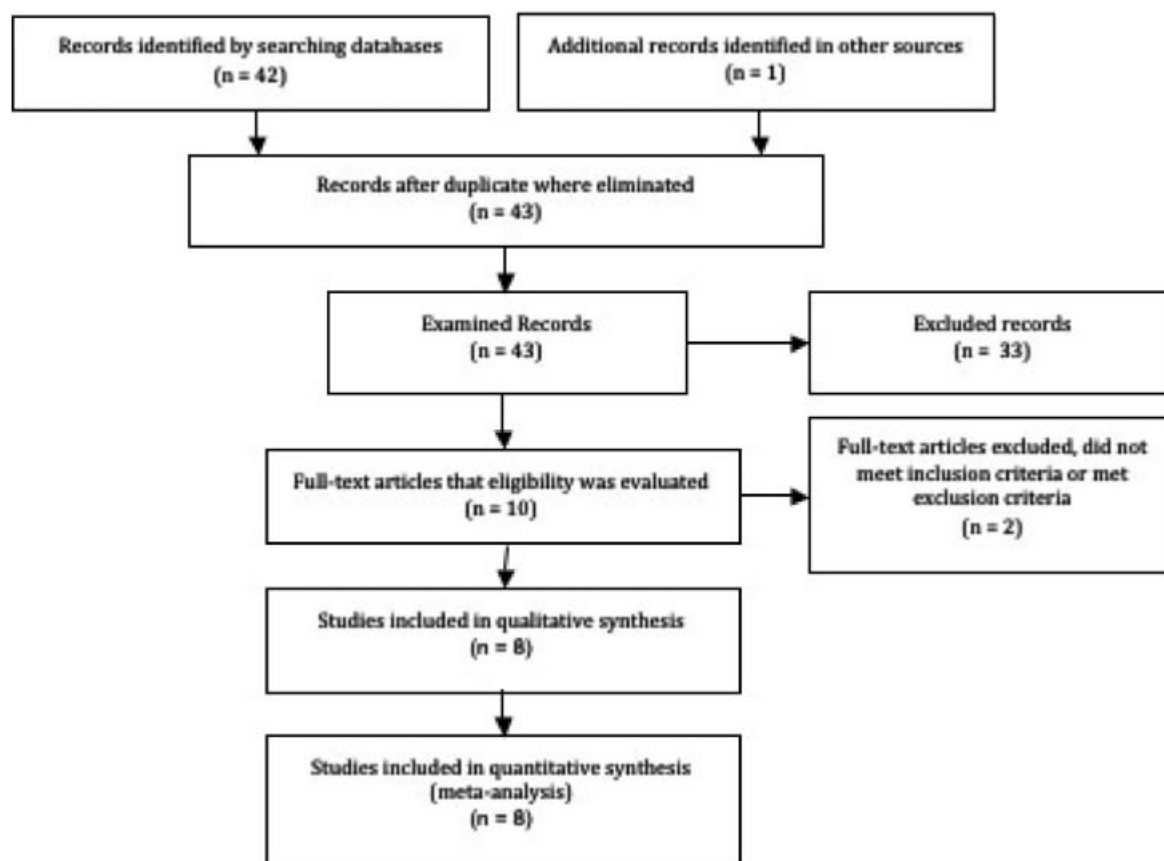


Fig. 1. Process of study selection.

used oral and inhaled or nebulized placebo comparing ICS with SC. High methodological quality was considered when there was an acceptable random sequence generation, allocation concealment, incomplete outcome data deal and blinding of participants, personnel and outcome assessor. Four studies were considered to have low risk of bias,^{21–23,26} whereas four had high risk of bias^{19,20,24,25} (Table 2).

Primary Outcome

For the hospital admission rate outcome, all studies reported this outcome (Fig. 2). There was no significant difference between ICS and SC (RR: 1.02; 95% CI: 0.41–2.57). We used a random effect model, and there was significant heterogeneity between studies ($I^2 = 53\%$, $P = 0.06$). Heterogeneity only diminished when comparing the route of administration. Including only the three studies which used nebulized ICS,^{19,21,22} there was still no significant difference (RR: 0.69; 95% CI: 0.24–1.95) with lower heterogeneity ($I^2 = 32\%$, $P = 0.23$). Analyzing the single study which used turbobaler²⁰ and the three studies which used pMDI,^{23,24,26} there was still no significant difference (RR: 2.18; 95% CI: 0.82–5.81), with low heterogeneity ($I^2 = 7\%$, $P = 0.34$). When

adjusting for type of ICS, one dose versus multiple doses, asthma severity and methodological quality, heterogeneity remained high and there was no significant difference between both studies. There was insufficient data to perform subgroup analyses divided by age (<5 years vs. >5 years) or sponsored by pharmaceutical industry or age, all studies used the same SC and all studies used high dose if ICS.

Studying the need of additional course of SC, four studies^{21,23,24,26} described this data (Fig. 3), showing no significant difference between both groups (RR: 1.45; 95% CI: 0.28–7.62). There was significant heterogeneity between studies ($I^2 = 66\%$, $P = 0.03$). Analyzing the single study with nebulized ICS,²¹ the difference became significant (RR: 0.12; 95% CI: 0.02–0.91), favoring the ICS group. On the contrary, when analyzing the other three studies which used pMDI,^{23,24,26} the difference also became significant favoring the SC group (RR: 3.35; 95% CI: 1.20–9.35), with low heterogeneity ($I^2 = 0\%$, $P = 0.99$). No difference was observed after adjusting for methodological quality.

Finally, when evaluating unscheduled visits for asthma symptoms, three studies reported this outcome,^{19,21,26} but Scarfone et al.¹⁹ was excluded for analysis because both groups received SC at home. There was no significant

TABLE 1—Characteristics of Included Studies

Study	Design	Location	Patients, <i>n</i> (% male)	Mean age ICS group, <i>y</i> (SD)	Mean age SC group, <i>y</i> (SD)	Selected comparisons
Scarfone et al. ¹⁹	R, DB, PG	Single center	111 (59)	5.3 (3.3)	4.6 (3)	ED: Neb DEX 1.5 mg/kg vs. PDN 2 mg/kg
Volovitz et al. ²⁰	R, DB, PG	Single center	22 (68%)	8.4 (3.3)	10.5 (2.7)	DT: PDN 2 mg/kg 5 days both groups ED: pMDI BUD 1,600 mcg vs. PDN 2 mg/kg DT: pMDI BUD 1,600 mcg 2 days, 1,200 mcg 2 days, 800 mcg 2 days, 400 mcg from day 6 to 24 vs. PDN 2 mg/kg 2 days, 1.5 mg/kg 2 days, 1 mg/kg 2 days, 0.5 mg/kg 2 days
Devidayal et al. ²¹	R, DB, PG	Single center	80 (75%)	7 (3.6)	6 (3)	ED: Neb BUD 800 mcg for three times vs. PDN 2 mg/kg single dose
Manjra et al. ²²	R, DB, PG	MC	321 (56%)	9 (3)	8 (2.8)	ED: Neb FLUT 1 mg BID 7 days vs. PDN 2 mg/kg 4 days, 1 mg/kg 3 days
Schuh et al. ²³	R, DB, PG	Single center	100 (59%)	9.3 (3.3)	9.5 (3.2)	ED: pMDI FLUT 2 mg vs. PDN 2 mg/kg DT: pMDI FLUT 500 mcg BID 7 days vs. PDN 1 mg/kg 7 d
Nakanishi et al. ²⁴	R, DB, PG	Single center	55 (64%)	11 (2.5)	10.4 (3.2)	ED: pMDI FLUN 1 mg BID 7 days vs. PDN 2 mg/kg 7 d
Milani et al. ²⁵	R, DB, PG	Single center	34 (47%)	3.9 (1.4)	4.3 (1.6)	ED: Neb BUD 2 mg vs. PDN 1 mg/kg
Schuh et al. ²⁶	R, DB, PG	Single center	69 (65%)	9 (2.6)	9.2 (3.4)	ED: pMDI FLUT 2 mg vs. PDN 2 mg/kg DT: pMDI FLUT 500 mcg BID 5 days vs. PDN 1 mg/kg 5 d

BID, twice daily; BUD, budesonide; DB, double-blind; DEX, dexamethasone; DT, discharge treatment; ED, emergency department; FLUN, flunisolide; FLUT, fluticasone; ICS, inhaled corticosteroids; MC, multicenter; Neb, nebulized; PDN, prednisolone; PG, parallel group; pMDI, pressurized metered-dose inhaler; R, randomized; SC, systemic corticosteroids; VS, versus.

statistical difference between ICS and SC (RR: 9.55; 95% CI: 0.53–170.52).

Secondary Outcome

Analyzing pulmonary function, there was only a significant difference favoring SC, when analyzing the change in % of predicted FEV1 at fourth hour. Only two studies^{23,26} showed this outcome, with a significant higher value for the SC group than the ICS group (WMD:

7.75; 95% CI: 2.93–12.57), with low heterogeneity ($I^2 = 0\%$, $P = 0.69$). When analyzing the change in % of predicted FEV1 at days 2 or 3, 6, or 7 or PEF at day 7, there was not a significant difference between both groups (Table 3).

There was insufficient data to perform meta-analysis of length of stay during the first consult in the ED and of symptom scores.

Among evaluated adverse effect, six studies reported the occurrence of vomiting^{19,21–23,25,26} (Fig. 4). There

TABLE 2—Risk of Bias of the Eligible Studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Funded by pharmaceutical industry
Scarfone et al. ¹⁹	Y	U	Y	Y	Y	N	U
Volovitz et al. ²⁰	Y	U	Y	Y	Y	Y	Y
Devidayal et al. ²¹	Y	Y	Y	Y	Y	Y	Y
Manjra et al. ²²	Y	Y	Y	Y	Y	N	Y
Schuh et al. ²³	Y	Y	Y	Y	Y	N	Y
Nakanishi et al. ²⁴	Y	Y	Y	Y	N	U	Y
Milani et al. ²⁵	Y	U	Y	Y	N	Y	U
Schuh et al. ²⁶	Y	Y	Y	Y	Y	N	Y

N, no; U, unknown; Y, yes.

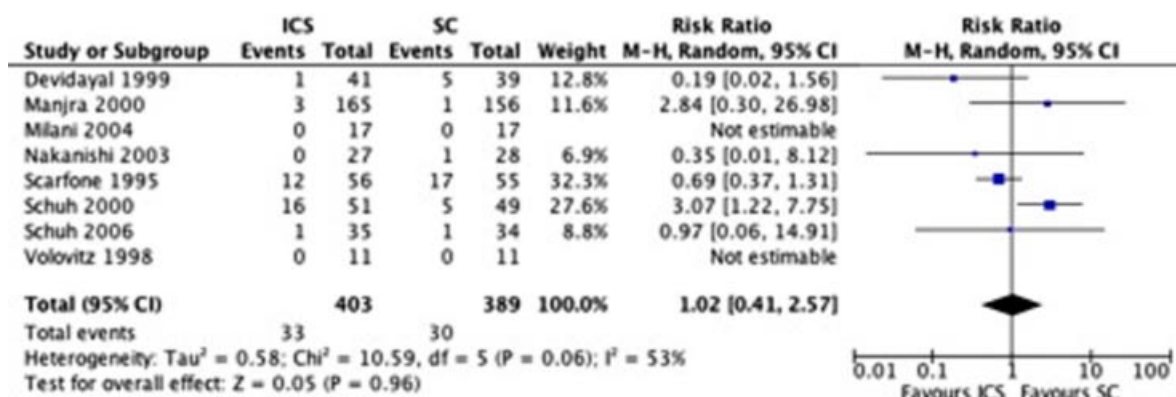


Fig. 2. Pooled RRs and 95% CIs for the number of hospital admitted patients comparing inhaled (ICS) versus systemic corticosteroids (SC).

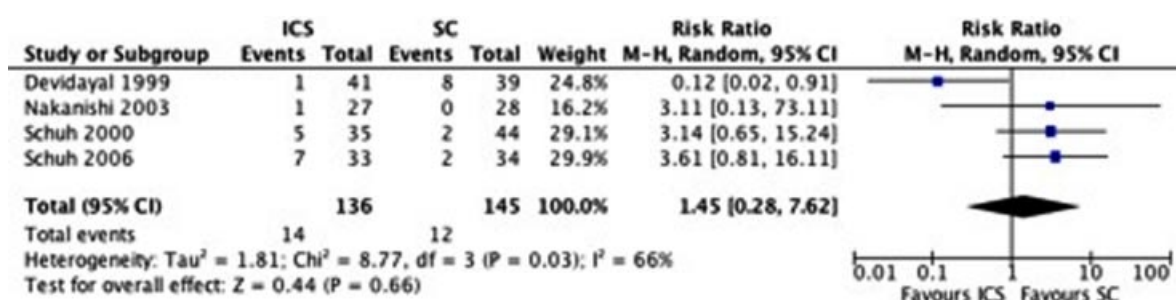


Fig. 3. Pooled RRs and 95% CIs for need of additional course of systemic corticosteroids comparing inhaled (ICS) versus systemic corticosteroids (SC).

was no significant difference between both groups (RR: 0.77; 95% CI: 0.25–2.40), with high heterogeneity ($I^2 = 73\%$, $P = 0.002$). There was insufficient data to perform meta-analysis of other adverse effects.

DISCUSSION

To our knowledge, this is the first meta-analysis performed of trials exclusively about child and adolescent

populations to explore the efficacy of ICS compared with SC for acute asthma exacerbation consulting in the ED or equivalent. Our study demonstrates that there was no statistically significant difference between ICS or SC in terms of hospital admission rate, need of additional course of SC, nor in less unscheduled visits to the ED for asthma symptoms. Our results are concordant to other prior publications with more heterogeneous participants, including children and adults,^{12,15,16} in which hospital

TABLE 3—Pulmonary Function

Outcome	Studies	Participants	Statistical method	Effect estimate	I^2	P -value ^a
Any ICS vs. any SC, % pred FEV1 fourth hour	2 ^{22,25}	160	Mean difference (IV, random, 95% CI)	7.75 [2.93, 12.57]	0%	0.69
Any ICS vs. any SC, % pred FEV1 days 2–3	2 ^{23,25}	121	Mean difference (IV, random, 95% CI)	7.26 [−2.50, 17.03]	67%	0.08
Any ICS vs. any SC, % pred FEV1 days 6–7	2 ^{23,25}	122	Mean difference (IV, random, 95% CI)	9.61 [−6.06, 25.29]	85%	0.009
Any ICS vs. any SC, PEF (L/min) day 7	1 ²¹	309	Mean difference (IV, random, 95% CI)	−16.00 [−34.75, 2.75]	NA	NA

FEV1, forced expiratory volume in the first second; ICS, inhaled corticosteroids; NA, not applicable; PEF, peak expiratory flow; SC, systemic corticosteroids.

^aHeterogeneity assessment.

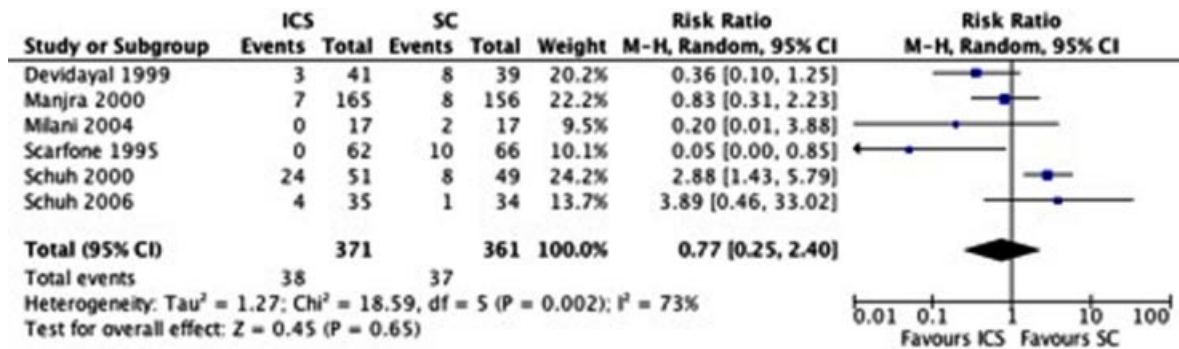


Fig. 4. Pooled RRs and 95% CIs for occurrence of vomiting comparing inhaled (ICS) versus systemic corticosteroids (SC).

admission rates, hospital discharge and relapse rates, were similar in both analyzed groups.

Moreover, in at least three studies^{23,24,26} we found that ICS delivered by pMDI may be inferior to SC in terms of the need of additional course of SC, with low heterogeneity. In contrast, when analysis was made with the single study that used ICS delivered via nebulizer, ICS were superior than SC in decreasing need of additional course of SC. This result needs to be considered with caution, because this result was obtained from a single study. To our knowledge, there are no studies comparing nebulized versus pMDI administration of ICS in acute asthma. A possible explanation for this is that nebulization is a delivery method that has less dependence on patient coordination compared to other methods.²⁷

However, SC are more likely to be more effective when analyzing pulmonary function, with a better improvement of FEV1 at 4 h. This can be explained by the fact that the genomic effect of ICS is faster and shorter than the anti-inflammatory response of SC that is more important from the fourth hour. Despite this, by days 2 or 3, 6, or 7, there was no significant difference between both groups. However, pulmonary function is not necessarily related with symptoms and as shown above there is no difference for outcomes that are clearly more relevant for the patients.

Furthermore, children treated with ICS seem to have shorter stays during the first consult and are more likely to be discharged within the first 2 h, with a faster improvement of asthma symptoms than those treated with SC, as shown in Scarfone et al.¹⁹ They reported a significantly greater proportion of the ICS treated patients who were discharged home within 2 h of enrollment, 23% compared to 7% in the SC group ($P = 0.02$). In Devidayal et al.²¹ more patients in the ICS group recovered fully from acute asthma episode at the end of third dose of budesonide nebulization, and at 1 and 2 h after completion of nebulization, compared to the SC group ($P < 0.01$). They also reported a significantly

higher decrease in mean RR, HR, pulmonary index and respiratory distress assessment in the ICS group ($P < 0.05$), and the change in the respiratory distress assessment occurred faster in this same group ($P < 0.01$). This may be attributable to the immediate initial response of ICS compared with the later anti-inflammatory response of SC, already reported.²⁸ Despite this, we could not analyze specific numeric effects of the first 2 h, because they were not reported. On the other hand, ICS effect is dose dependent, and most of the studies used high doses of ICS, at least four times the maintenance dose.²⁹ Different clinical scores were used that showed a reduction in the severity of asthma signs and symptoms, with no significant statistical difference between both groups.^{19,20,22–25} In addition, Volovitz et al.²⁰ showed an initial better clinical response in the ICS group ($P < 0.05$), but after day 2, coughing and wheezing was similar in both groups. Also, after day 4–5 symptoms were minimal in both groups.

Our findings, together with previous published data, suggest that ICS may have an important role treating children with asthma exacerbations and a reasonable scheme could be to use an increasing dose of ICS, which has been found useful in pediatric asthmatic population.³⁰ In the previous published meta-analysis, results are with both adult and pediatric population, with no analysis exclusively for pediatric population, including unpublished data.¹⁵ In the recent meta-analysis published by Edmonds et al.¹⁶ they did not include one of the studies included in this review,²⁴ though they included another study which was only available in abstract, not meeting our inclusion criteria.³¹

In respect to adverse effects, vomiting was the only we could assess in the meta-analysis, and was similar among children on ICS or SC. Serum cortisol concentration at the end of the first week was significantly decreased in almost all patients who received oral prednisolone at both 8 AM (mean, 121 vs. 300 nmol/L; $P = 0.0003$) and 1 h after stimulation with ACTH analogue (mean, 333 vs. 669 nmol/L; $P < 0.00001$).²⁰ Two weeks later both

groups showed similar normal concentrations. Manjra et al.²² showed no variations in morning serum cortisol concentration after a week of use of fluticasone. There was no data available to compare with the prednisolone group and the most common adverse event reported was candidiasis of mouth and throat (8% in fluticasone group, 3% in prednisolone group). In Devidayal et al.²¹ they reported transient facial irritation in two children of the nebulized budesonide group. In Schuh et al.²³ tremor was reported in 33% of patients in fluticasone group versus 12% in prednisolone group. They also reported an 18% in fluticasone group required intravenous hydration while none of the participants in the prednisolone group did. There is no description if it was a consequence of the use of fluticasone or secondary to other variable. The above shows that ICS may be an alternative to SC when treating an asthma exacerbation in children, particularly considering that SC have multiple known adverse systemic effects. They include alteration of adrenal function and bone metabolism,^{14,31} though adverse effects of short courses of SC are still controversial, as studied in a school-aged asthmatic population with four courses per year.³² Also, it must be considered that high doses of ICS are recommended for asthma exacerbations, and those doses may have a systemic effect, and therefore similar adverse effects than SC.³³ When comparing short courses of ICS and SC, there is evidence that suggests that SC have pronounced systemic effects, such as cortisol levels and bone metabolism markers alterations, while ICS have none or mild systemic effects.^{34,35} Despite all of this, ICS are more expensive and require more resources for their administration specially when nebulized, which must be also considered.

There are certain issues that are mentioned about the methodology of the studies included in the present meta-analysis. All studies are randomized, double blind, placebo controlled, but still in some of them the allocation concealment was unclear, and overall, four of them were defined as having low risk of bias. Additionally, in one study,¹⁹ children did not have previous asthma diagnosis, but they required one previous obstructive crisis to be included in the study. To diminish the risk of enrolling patients with bronchiolitis versus asthma, they increased the age of inclusion to the study. Also, up to a 70% of the patients had previous use of corticosteroids, which supports that the patients were potentially asthmatic. In another study²² a 2% of the patients included in each group where taking SC at time of randomization. It is important to consider that the heterogeneity was relatively high in most of the measured outcomes. This may be explained by the fact that most of the studies used different ICS and different dosage. As to the limitations of the present review, one of the main ones is the lack of more studies evaluating this topic, as many of our outcomes were measured with few studies and subjects,

and also because the sample is relatively small (N = 797). Also, most studies used different ICS, with different administration route. And children included in the present review had a small age range, without data for adolescents. The studies analyzed in this review included children from different countries, therefore we think these results are likely applicable to a generalized population.

In summary, when comparing ICS to SC in children with acute asthma, there is no evidence of a difference when comparing hospital admission rates, unscheduled visits to the ED for asthma symptoms and need of additional courses of SC. The evidence is insufficient to recommend the routine use of high doses of ICS as an alternative to SC in acute asthma exacerbation in children. More studies with big samples and good methodological quality are needed and also cost effectiveness studies must be performed in order to clear decision of most appropriate administration route of corticosteroids in acute asthma exacerbation in children.

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