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To cite this article: Scott W. Kirkland, Ben Vandermeer, Sandy Campbell, Cristina Villa-Roel, Amanda Newton, Francine M Ducharme & Brian H. Rowe (2018): Evaluating the effectiveness of systemic corticosteroids to mitigate relapse in children assessed and treated for acute asthma: A network meta-analysis, Journal of Asthma, DOI: [10.1080/02770903.2018.1467444](https://doi.org/10.1080/02770903.2018.1467444)

To link to this article: <https://doi.org/10.1080/02770903.2018.1467444>



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Accepted author version posted online: 25 Apr 2018.
Published online: 22 Jun 2018.



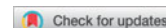
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Evaluating the effectiveness of systemic corticosteroids to mitigate relapse in children assessed and treated for acute asthma: A network meta-analysis

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ABSTRACT

Objective: The objective of this systematic review was to explore the effectiveness of various systemic corticosteroid (SCS) regimens to mitigate relapse in children with asthma discharged from an acute care setting. **Data Sources:** Medline, EMBASE, Global Health, International Pharmaceutical Abstracts, EMB ALL, CINAHL, SCOPUS, Proquest Dissertations and Theses Global, and LILACS were searched using controlled vocabulary and key words. Additional citations were searched via clinical trial registries, Google Scholar, bibliographies, a SCOPUS forward search of a sentinel paper, and hand searching conference abstracts. **Study Selection:** No limitations based on language, publication status, or year of publication were applied. Two independent reviewers searched to identify randomized controlled trials comparing the effectiveness of SCS regimens to prevent relapse in children following treatment for acute asthma. **Results:** Fifteen studies were included. In 3 studies comparing SCS to placebo, asthma relapse was significantly reduced (RR = 0.10; 95% CI: 0.01, 0.77; $I^2 = 0\%$). A network analysis identified a significant reduction in relapse in children treated with intramuscular corticosteroids (OR = 0.038; 95% CrI: 0.001, 0.397), short-course oral prednisone (OR = 0.054; 95% CrI: 0.002, 0.451), and oral dexamethasone (OR = 0.071; 95% CrI: 0.002, 0.733) compared to placebo. **Conclusion:** This review found evidence that SCS reduces relapse in children following treatment for acute asthma, albeit based on a limited number of studies. Additional studies are required to assess the differential effect of SCS doses and treatment duration to prevent relapse in children following discharge for acute asthma.

ARTICLE HISTORY

Received 26 February 2018
Accepted 15 April 2018

KEYWORDS

Dexamethasone; emergency department; prednisone; randomized controlled trials; systematic review

Introduction

Asthma is a common pediatric condition and exacerbations often require emergency department (ED) assessment. Most children with asthma are discharged after acute care treatment; however, relapse among children discharged from the ED is common, with estimates ranging from 10 (1) to 31% (2). While the effectiveness of systemic corticosteroids (SCS) to mitigate the risk of relapse in adult patients with asthma has been previously established (3,4) the evidence for children is less clear.

Guidelines on management of children with acute asthma recommends providing patients with SCS at discharge (most commonly oral prednisolone) to prevent relapse (5–7); these consensus recommendations stem primarily from 2 previous Cochrane reviews (3,4), which included studies with mixed populations of both adults

and children, with no subgroup analysis completed for the latter. In addition, the optimal regimen (preparation, administration route, and duration of treatment) of SCS to prevent relapse among children is unclear. Indeed, there is a recent debate as to whether single or several day doses of oral dexamethasone, a long-acting corticosteroid, is more effective than a 5-day course of short acting oral corticosteroids such as prednisone/prednisolone (8,9). Side-effects (10), suboptimal compliance (11,12), and palatability (13) particularly among children have resulted in some studies recommending a single dose of Intramuscular corticosteroids (IM) as an alternative to oral corticosteroids (14). Intramuscular corticosteroids have long-acting pharmacokinetic properties without the side effects common with oral preparations such as nausea and vomiting; however, discomfort and adverse

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events associated with the injection remain concerns (15). Importantly, the effectiveness of SCS to prevent hospital admission in preschoolers with wheezing has been raised with recent studies reaching conflicting conclusions (16,17) and recent systematic reviews failing to clarify the issue (18).

The objective of this systematic review was to explore the literature regarding the effectiveness of SCS compared to placebo to prevent relapse in children discharged from acute care settings following treatment for acute asthma and to identify the most effective regimen of SCS to reduce relapse using a Bayesian network analysis model.

Methods

Protocol

A study protocol was developed *a priori* to define the objective, outline the search strategy, establish explicit selection criteria, determine the primary outcome, guide the data collection process, and define the analysis. A meta-analysis was included after the initiation of the review to conduct a direct comparison of the effectiveness of SCS vs. placebo to prevent relapse. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for outcome reporting of a systematic review (19).

Study inclusion and exclusion

Eligible studies included randomized controlled trials (RCTs) or prospective controlled clinical trials (CCT) comparing the effectiveness of SCS to placebo or another SCS regimen in children (≤ 17 years) presenting to an acute care setting, such as an ED or similar setting, with acute asthma. Acute asthma was defined according to whatever criteria the authors used in the study, whether it was based on previous episodes of wheezing/dyspnea that responded to short-acting beta₂-agonists (SABA), established guideline criteria, or clinical gestalt of the attending physicians. Studies examining the efficacy of IM corticosteroids, oral dexamethasone, as well as either a short-course (1–6 days) or long-course (7–10 days) of other oral corticosteroids (e.g., prednisone/prednisolone, methylprednisolone, deflazacort), were eligible for inclusion regardless of route and duration of administration. While studies comparing dosages of corticosteroids were included, dosing was not formally analyzed in this review. Studies including infants in which the average age was less than 2 years were not eligible for inclusion due to the difficulty differentiating asthma from bronchiolitis in the toddler age group. Ineligible studies included those assessing solely the palatability of oral corticosteroids, comparing

tapered vs. fixed dose of oral corticosteroids, or studies comparing SCS to either intravenous or inhaled corticosteroids or those that included hospitalized children.

The primary outcome was relapse to additional care following discharge from the acute care setting, which had to be reported in the study for it to be included. Relapse was defined according to whatever criteria the authors used in the study; however, most often as an urgent visit relating to worsening asthma symptoms to an ED, primary care provider, or requiring hospitalization or supplemental corticosteroids within 4 weeks following the initial ED visit.

At least 2 independent reviewers (SWK, EC or TA) identified potentially relevant studies via titles and abstracts. Once identified, at least 2 reviewers independently reviewed the full text of selected studies using pre-defined inclusion/exclusion criteria. Disagreements were resolved by discussion with a third party adjudicator (CVR or BHR) until a consensus was reached.

Search strategy

A systematic search was executed by an expert health research librarian (SC) on the following databases: Medline, EMBASE, Global Health, International Pharmaceutical Abstracts, EMB ALL, CINAHL, SCOPUS, Proquest Dissertations and Theses Global, and LILACS, using controlled vocabulary and key words (see [Supplemental material 1](#)) which was last conducted in February 2017. No limits on patient age or language of publication were applied. An additional search was provided by the Cochrane Airways Group from the Airways Group Specialised Register (2002–2015). Additional citations were searched for within clinical trial registries, Google Scholar, bibliographies from included studies and reviews, and a SCOPUS forward search of a sentinel paper (20). Conference abstracts of the *Canadian Journal of Emergency Medicine* (2008–2017), *Annals of Emergency Medicine* (2008–2017), and *Academic Emergency Medicine* (2008–2017) were hand searched. Efforts were made to translate foreign language articles.

Quality assessment and data extraction

Quality assessment of included studies was completed by 2 of 3 independent reviewers (SWK, EC, or TA) using the Cochrane Risk of Bias tool (21). Two of 3 independent reviewers (SWK, EC, or TA) assessed risk of bias based on 6 different categories of bias including: 1) Sequence generation; 2) Allocation concealment; 3) Blinding of personnel, and patients; 4) Blinding of outcome assessors; 5) Incorporation of outcome data (attrition and exclusions); 6) Selective reporting; and 7) “Other” potential sources of bias. Disagreements were resolved and discussed by third

party adjudication (CVR or BHR) until a consensus was reached. Data were extracted by at least 2 independent reviewers (SWK, EC, or TA) onto standardized pre-tested forms and checked for reliability (SWK). Comparison of data extraction among reviewers was completed and any discrepancies were discussed and disagreements were resolved via third party adjudication (BHR). Authors were contacted for clarification if needed. Data were extracted into summary of findings tables prior to data synthesis.

Data synthesis

Comparing SCS vs. placebo (Traditional meta-analysis): Studies comparing SCS to placebo were included in a meta-analysis using Review Manager (RevMan; Version 5.3). Relapse events were calculated as risk ratios (RR) with 95% confidence intervals (CI) using a random-effects model. A random effects model was used because it was assumed that the study effect sizes would not be identical due to the inherent clinical heterogeneity among the included studies. The weights for each study in the pooled analysis were based on the Mantel-Haenszel method. Statistical heterogeneity was assessed with the I^2 statistic, in which a I^2 value of 25%, 50%, 75% represented low, moderate, and high heterogeneity, respectively (21). Sensitivity analysis included random vs. fixed effects. Publication bias was to be assessed using a funnel plot if 10 or more studies comparing SCS to placebo were found (21).

Comparing SCS regimens (Bayesian network analysis): The effectiveness of various SCS regimens to mitigate asthma relapse were assessed through an indirect study comparison using a Bayesian network model. This mixed treatment analysis allowed for the comparison of all eligible SCS regimens and their treatment effects simultaneously in a single analysis. The studies included in this analysis represented similar populations, outcomes, and designs, and the clinical heterogeneity was judged by the research team to be sufficiently low to justify pooling. Logarithmic odds ratio (OR) were modeled using non-informative prior distributions. Markov Chain Monte Carlo simulations using WinBUGS (22) software (MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, United Kingdom) Version 1.4 were carried out to obtain simultaneous estimates of all interventions compared with placebo, as well as estimates of which interventions performed the best (23). The simulations used a sample of 220,000 iterations, in which the results of the first 20,000 iterations were used as the burn in sample and ignored, while the following 200,000 iterations were used to compute estimates. A sample of the WinBUGS code is available in [Supplemental material 2](#). Results are reported with 95% credibility intervals (CrI) using a random effects model. The analyses were checked for consistency using cross validation of all contrasts that

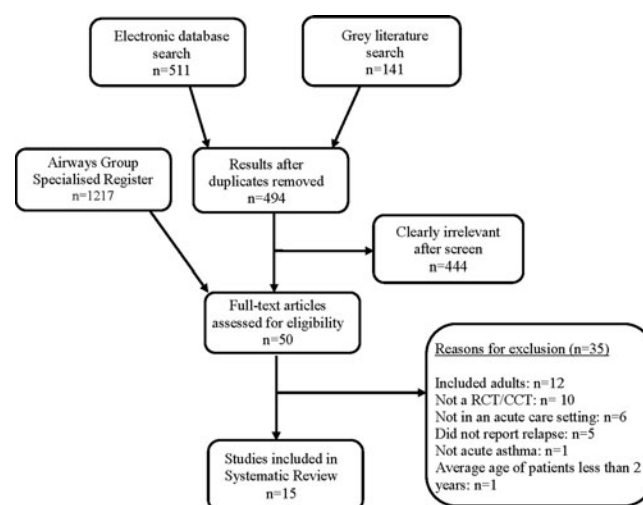


Figure 1. Systematic literature search overview.

had direct evidence (24). The effectiveness of various SCS regimens to placebo on relapse was assessed using any follow-up point. If a study assessed relapse at multiple days post-discharge, the last time-point was extracted for the analysis. A subgroup network analysis of relapse occurring within 10 days and after 10 days post-discharge was completed.

Results

Search results

The electronic and grey literature searches identified 534 and 141 articles, respectively (Figure 1). Removing duplicates resulted in 516 citations overall. A search of the Airways Group Specialized Register identified 1217 articles. Overall, a total of 51 studies were selected as potentially relevant and accessed for full-text review; 36 of which were excluded for irrelevancy. Consequently, 15 studies involving a total of 1786 patients were included in this review.

Description of the included studies

Table 1 provides a summary of study characteristics. Fourteen of the included studies were published in peer-reviewed journals, while one study was published as an abstract (25). The full text manuscript of a protocol identified in the search was provided by the study authors (26).

Design: All included studies were RCTs except one study, which was classified as a CCT due to a quasi-randomization method of allocation (27). The majority of studies recruited patients in acute care centers based in the United States (14,20,25,27–31), followed by the United Kingdom (32), Canada (33), Jordan (34), Australia (35), Ireland (26), Spain (36), and Israel (37).

Table 1. Characteristics of studies included in the pediatric systematic review.

Reference, year ages included	Location/setting	Comparison	Drug names	Corticosteroid doses and durations	Relapse assessment and definition	Relapse outcome
Systemic corticosteroids vs. placebo						
Deshpande 1986 Patient age: 5–15 years	United Kingdom, Pediatric chest clinic, ED	PO _{sc} vs. Placebo	Prednisolone (PO _{sc}) vs. Placebo	Prednisolone (PO _{sc}) 2 mg/kg on day 1, 1 mg/kg on day 2, 0.5 mg/kg on day 3 Three doses Placebo Placebo oral capsules for 3 days.	4 days post-discharge relapse was not clearly defined. Study reported return to hospital after discharge.	PO _{sc} group 0/23 (0%) Day 4 Placebo group 5/21 (24%) Day 4
Horowitz 1994 Patient age: 4–16 years	Israel, Pediatric community clinic	PO _{sc} vs. placebo	Prednisone (PO _{sc}) vs. Placebo	Prednisone (PO _{sc}) 20 mg for children under 5 yrs; 40 mg for children over 5 yrs Single dose Placebo Single dose of placebo oral capsules	3 days post-discharge relapse was not clearly defined. Study reported patients requiring additional corticosteroids following discharge for a period of 72 hours post-discharge.	PO _{sc} group 0/38 (0%) Day 3 Placebo group 3/32 (9%) Day 3
Shapiro 1982 Patient age: No age restrictions reported. Mean age 7.2 years (range 5.3–10.1 years)	United States, Allergy clinic and physicians private practice	PO _{lc} vs. placebo	Methylprednisolone (PO _{lc}) vs. placebo	Methylprednisolone (PO _{lc}) Tapered dosing over 8 days. 144 mg total Placebo Tapered dosing of placebo oral capsules over 8 days	14 days post-discharge relapse was not clearly defined. Study reported patients requiring additional emergency department (ED) visits or hospitalization.	PO _{lc} group 0/11 (0%) Day 14 Placebo group 0/15 (0%) Day 14
Oral dexamethasone vs. oral prednisone						
Altamimi 2006 Patient age: 2–16 years	Canada, Pediatric ED	DEX _{sc} vs. PO _{sc}	Dexamethasone (PO _{sc}) vs. Prednisolone (PO _{sc})	Dexamethasone (DEX _{sc}) 0.6 mg/kg (max 18 mg) Single dose of oral capsules. Provided additional placebo tablets for 5 days Prednisolone (PO _{sc}) 1 mg/kg (max 30 mg) twice daily for 5 days	5 days post-discharge relapse was not clearly defined. Study reported a secondary outcome of return to ED with worsening symptoms (shortness of breath, wheezing, or cough).	DEX _{sc} group 4/61 (7%) Day 5 PO _{sc} group 1/56 (2%) Day 5
Cronin 2016 Patient age: 2–16 years	Ireland, Pediatric ED	DEX _{sc} vs. PO _{sc}	Dexamethasone (PO _{sc}) vs. Prednisolone (PO _{sc})	Dexamethasone (PO _{sc}) 0.3 mg/kg (max 12 mg) Single dose Prednisolone (PO _{sc}) 1 mg/kg per day (max 40 mg) for 3 days	14 days post-discharge relapse defined as unscheduled return to a health care practitioner.	DEX _{sc} group 17/122 (14%) Day 14 PO _{sc} group 17/120 (14%) Day 14
Greenberg 2008 Patient age: 2–18 years	United States, Pediatric ED	DEX _{sc} vs. PO _{sc}	Dexamethasone (PO _{sc}) vs. Prednisone (PO _{sc})	Dexamethasone (PO _{sc}) 0.6 mg/kg a day for 2 days (max 16 mg) Prednisone (PO _{sc}) 2 mg/kg a day for 5 days (max 80 mg)	10 days post-discharge relapse defined as the need for subsequent hospitalization or an unscheduled visit with a medical provider (primary care doctor, urgent care, ED, etc.) due to continued or worsening asthma symptoms.	DEX _{sc} group 8/51 (16%) Day 10 PO _{sc} group 3/38 (8%) Day 10
Qureshi 2001 Patient age: 2–18 years	United States, Pediatric ED	DEX _{sc} vs. PO _{sc}	Dexamethasone (PO _{sc}) vs. Prednisone (PO _{sc})	Dexamethasone (PO _{sc}) 0.6 mg/kg (max 16 mg) a day for 2 days Prednisone (PO _{sc}) 2 mg/kg (max 60 mg) a day for 5 days	10 days post-discharge relapse defined as an unscheduled visit to a medical facility resulting from the patient's or parent's perception of persistent, worsening, or recurrent asthma symptoms in the 10 days after discharge from the ED.	DEX _{sc} group 20/272 (3.5%) Day 10 PO _{sc} group 18/261 (7%) Day 10

Intramuscular vs. oral corticosteroids

Al-wahadneh 2006 Patient age: 9 months–14 years	Jordon, ED	IM vs. PO _{sc}	Dexamethasone (IM) vs. Prednisolone (PO _{sc})	Dexamethasone (IM) 1.7 mg/kg Single dose Prednisolone (PO _{sc}) 2 mg/kg/day for 5 days	21 days post-discharge relapse defined as return visits to the ED with symptoms and signs requiring treatment with corticosteroids after initial clearance within 21 days of treatment.	IM group 1/16 (6%) Day 21 PO _{sc} group 3/14 (21%) Day 21
Gordon 2007 Patient age: 18 months–7 years	United States, Pediatric ED	IM vs. PO _{sc}	Dexamethasone (IM) vs. Prednisolone (PO _{sc})	Dexamethasone (IM) 0.6 mg/kg (max 16 mg) Single dose Prednisolone (PO _{sc}) 2 mg/kg (max 50mg) daily for 5 days	4 and 14 days post-discharge relapse not clearly defined. Study reported patients need for unplanned medical visits during the two weeks after enrollment.	IM group 8/69 (12%) Day 4 PO _{sc} group 11/73 (15%) Day 4 IM group 15/68 (22%) Day 14 PO _{sc} group 16/73 (22%) Day 14
Gries 2000 Patient age: 6 months–7 years	United States, Tertiary medical center	IM vs. PO _{sc}	Dexamethasone (IM) vs. Prednisone (PO _{sc})	Dexamethasone (IM) Patients 6–12 months old received 16 mg. Patients 13 to 35 months received 24 mg. Children ≥ 36 months received 36 mg. Single dose Prednisone (PO _{sc}) 2 mg/kg a day for 5 days	28 days post-discharge relapse defined as another exacerbation requiring treatment with corticosteroids within two weeks of the resolution of the initial asthma exacerbation.	IM group 1/15 (7%) Day 28 PO _{sc} group 3/17 (18%) Day 28
Klig 1997 Patient age: 3–16 years	United States, Pediatric ED	IM vs. PO _{sc}	Dexamethasone (IM) vs. Prednisone (PO _{sc})	Dexamethasone (IM) 0.3 mg/kg (max 15 mg) Single dose Prednisone (PO _{sc}) 2 mg/kg a day for 3 days (max 100 mg)	5 days post-discharge relapse was not clearly defined. Study reported patients who sought further medical treatment in a clinic, office, or ED during the follow-up period.	IM group 0/21 (0%) Day 5 PO _{sc} group 0/21 (0%) Day 5

(Continued on next page)

Table 1. (Continued)

Reference, year ages included	Location/setting	Comparison	Drug names	Corticosteroid doses and durations	Relapse assessment and definition	Relapse outcome
Comparing oral corticosteroid regimens						
Chang 2008 Patient age: 2–15 years	Australia, Three Pediatric EDs	PO _{sc} vs. PO _{lc}	Prednisolone (PO _{sc}) vs. Prednisolone (PO _{sc})	Group 1 Prednisolone (PO _{sc}) 1 mg/kg (max 50 mg/day) for 3 days, followed by two days of placebo capsules Group 2 Prednisolone (PO _{sc}) 1 mg/kg (max 50 mg/day) for 5 days	14 days post-discharge relapse was not clearly defined. Study reported recurrence of exacerbation and unscheduled re-presentation to a health facility. Study reported patients requiring additional corticosteroid treatment between day 4 and 14 following the initial event.	Group 1 PO _{sc} group 10/101 (10%) Day 14 Group 2 PO _{sc} group 5/100 (5%) Day 14
Gartner 2004 Patient age: 6–14 years	Spain, Two Pediatric EDs	PO _{lc} vs. PO _{lc}	Deflazocort (PO _{lc}) vs. Prednisolone (PO _{lc})	Group 1 Deflazocort (PO _{lc}) 1.5 mg/kg/day (max 60 mg) for 7 days Group 2 Prednisolone (PO _{lc}) 1 mg/kg/day (max 40 mg) for 7 days	7 days post-discharge relapse was not clearly defined. Study reported patients presenting to the ED for worsening symptoms.	Group 1 PO _{lc} group 1/28 (3.6%) Day 7 Group 2 PO _{lc} group 1/25 (4%) Day 7
Ghafari 2010 Patient age: 2–17 years	United States, ED	DEX _{sc} vs. DEX _{sc}	Dexamethasone (PO _{sc}) vs. Dexamethasone (PO _{sc})	Group 1 Dexamethasone (PO _{sc}) 0.6 mg/kg Single dose Group 2 Dexamethasone (PO _{sc}) 0.6 mg/kg (max 40) for 2 days	7 days post-discharge relapse defined as hospital admission after ED discharge, unscheduled follow-up visits, or additional corticosteroid prescriptions after 7 days of discharge.	Group 1 DEX _{sc} group 10/52 (19%) Day 7 Group 2 DEX _{sc} group 10/48 (21%) Day 7
Kayani 2002 Patient age: 2–18 years	United States, Unspecified hospital setting or outpatient asthma center	PO _{sc} vs. PO _{sc}	Prednisone (PO _{sc}) vs. Prednisone (PO _{sc})	Group 1 Prednisone (PO _{sc}) 1 mg/kg a day for 5 days Group 2 Prednisone (PO _{sc}) 2 mg/kg a day for 5 days	14 days post-discharge relapse defined as the presence or worsening of cough, wheezing, visits to the physician's office, or emergency department, or admission to the hospital.	Group 1 PO _{sc} group 0/43 (0%) Day 14 Group 2 PO _{sc} group 1/43 (2%) Day 14

Note. DEX_{sc} = short course of oral dexamethasone; IM = intramuscular; PO_{sc} = short course of oral corticosteroids; PO_{lc} = long course of oral corticosteroids; ED = emergency department.

Population: All studies enrolled children seeking treatment for acute asthma either in an ED (25–28,30–36) or other acute care settings (14,20,29,37). The ages of the children enrolled across the included studies ranged considerably (6 months–18 years) within the included trials. Some studies only included patients presenting with either mild (29) or moderate (28,34,36) exacerbations, while several studies included patients with mild and/or moderate exacerbations (14,25,30,33). No studies limited their inclusion criteria to patients with severe exacerbations. While the definitions of asthma used by the included studies to enroll patients varied, at least 2 prior episodes of wheezing or dyspnea responding to SABA was the most common definition provided (see [Supplemental material 3](#)). Only 3 studies did not report how asthma was defined (25,34,37).

Interventions/control: See [Table 1](#) for a description of the regimens of SCS utilized among the included studies. Briefly, IM corticosteroids were assessed in 4 studies, all of which provided patients with single-dose IM dexamethasone prior to discharge (14,28,30,34). All of these studies compared IM corticosteroids to a short-course of oral prednisone/prednisolone. Oral dexamethasone was examined in 5 studies, all of which provided patients with a short-course regimen (DEX_{sc}) (25–27,31,33). Oral prednisone was the only non-dexamethasone corticosteroid examined among the included studies; the regimen was always short-course; 12 studies assessed per os short-course (PO_{sc}) prednisone with treatment ranging from 1 (14,26–35,37), 3 (26,30,32,35) to 5 (14,27–29,31,33–35) days. Only 2 studies examined oral long-course (PO_{lc}) corticosteroids; one study compared an 8-day tapered dose of oral methylprednisolone to placebo (20), while another study compared 7 days of oral deflazocort to 7 days of oral prednisolone (36). No studies comparing the effectiveness of IM corticosteroids or oral dexamethasone vs. placebo in children were identified in the search.

The majority of studies reported providing additional co-interventions during the patient's ED presentation and/or after discharge. Co-interventions provided to patients during their ED visit consisted primarily of SABA (14,20,25–37), with some studies also providing patients with additional doses of ipratropium bromide (27,28,31). One study reported that all patients were treated with conventional bronchodilators as deemed necessary by their attending physician but did not specify which medications were provided (37). One study did not report whether patients were provided with any co-interventions as part of the study protocol during the patient's presentation (34). Regarding co-interventions provided to patients after discharge along with SCS, studies primarily

provided SABA (14,25–27,29–31,33,36). One study reported providing all patients with a course of SABA and theophylline after discharge (20). Four studies did not specify whether patients were provided with any co-interventions at discharge as part of the study protocol (28,32,34,35). Two studies reported to have permitted inclusion of patients who had been receiving inhaled corticosteroids prior to enrollment, and allowed for patients to continue taking inhaled corticosteroids post-discharge (29,36). Two studies asked patients to stop taking inhaled corticosteroids until after the study ended (25,33). Two studies reported to have provided patients with IV corticosteroids if they were randomized to receive oral corticosteroids and vomited after receiving their dose while in the ED (25,28). In both studies, the authors reported that patients who vomited still received their regimen of oral corticosteroids once they were discharged. The majority of studies (81%) reported excluding patients who were using SCS prior to study enrollment (14,20,26–31,33–37).

Outcomes: Ten studies assessed asthma relapse within 10 days or less following ED discharge (3 (37), 4 (28,32), 5 (30,33), 7 (25,36), and 10 (27,31) days). Seven studies assessed relapse at greater than 10 days (14 (20,26,28,29,35), 21 (34), and 28 (14) days) post-discharge. Only one study assessed relapse at 2 different time points (28). Overall, the median final assessment of relapse among the included studies was 10 days (Percentile₂₅, Percentile₇₅: 5, 14 days). While the definition of relapse varied considerably among studies (see [Table 1](#)); the most common concept was an unscheduled visit to a health setting or provider for perceived worsening symptoms. Eight studies did not specify a specific definition for relapse, and simply reported the number of patients who needed further medical assistance after discharge (20,28,30,32,33,35–37). Relapse events ranged from a low of none (0%) to a high of 24% (median = 7%; IQR: 3%, 15.5%).

Study quality

Overall, the majority of studies were assessed as either having a high (14, 25,27,28,30–32,34,36) or unclear (20,29,33,37) risk of bias ([Figure 2](#)). Only one study was assessed as having a low risk of bias (35). The majority of studies failed to provide detailed information on randomization, allocation concealment, blinding, and source of funding. Only 3 studies had published their protocol (25,26,35). Seven studies failed to provide appropriate blinding for patients and personnel [25,27,28,30,34,36], while 4 studies failed to blind outcome assessors (14,25,34,36).

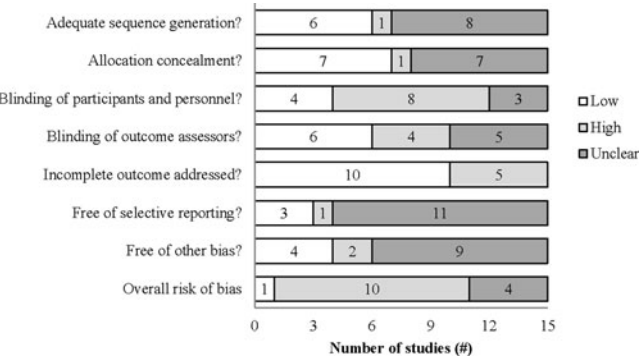


Figure 2. Risk of bias assessments for 15 RCTs included in a network analysis of SCS to prevent relapse in children following treatment for acute asthma.

The effectiveness of SCS vs. Placebo to mitigate relapse: A meta-analysis

Three studies involving 140 patients compared the effect of any SCS to placebo on relapse in children within 14 days of ED discharge for acute asthma (20,32,37). Relapse was reduced among children who received SCS treatment compared to placebo (RR = 0.10; 95% CI: 0.01, 0.77; $I^2 = 0\%$; Figure 3). Sensitivity analysis revealed a similar decrease in relapse after SCS treatment (RR = 0.10; 95% CI: 0.01, 0.75; $I^2 = 0\%$) using a fixed effects (see Supplemental material 4).

The effectiveness of various regimens of SCS to mitigate relapse: A bayesian network analysis

Eleven studies involving 1362 patients compared the effectiveness of SCS to other SCS regimens or placebo to reduce the odds of relapse at any time-point (14,20,26–28,30–34,37) (Figure 4). Compared to placebo, there was a decrease in the odds of relapse among children who received IM corticosteroids (OR = 0.038; 95% CrI: 0.001, 0.397), PO_{sc} corticosteroids (OR = 0.054; 95% CrI: 0.002, 0.451), or DEX_{sc} (OR = 0.071; 95% CrI: 0.002, 0.733). A visualization of the network geometry is available in Figure 5. The small number of studies precluded the assessment of PO_{lc} corticosteroids in the network meta-analysis as originally planned. A subgroup network analysis of studies assessing relapse within 10 days post-discharge revealed that only IM corticosteroids (OR =

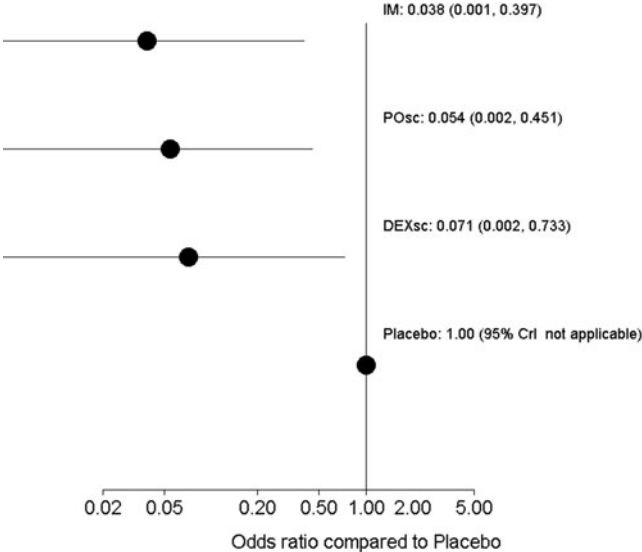


Figure 4. Forest plot of the odds of relapse of the differing regimens of SCS vs. placebo in children following treatment for acute asthma.

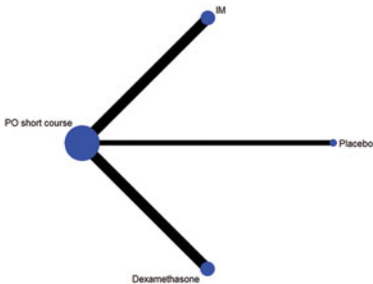


Figure 5. Network geometry of relapse at any time point. Note: Circle size reflects the number of patients included in the treatment groups. Line width reflects the number of direct comparisons included in the network meta-analysis.

0.037; 95% CrI: 0.001, 0.723) and PO_{sc} corticosteroids (OR = 0.051; 95% CrI: 0.001, 0.512) reduced relapse compared to placebo. No reduction in the odds of relapse within 10 days post-discharge was found among patients receiving DEX_{sc} (OR = 0.083; 95% CrI: 0.002, 1.277). A visualization of the network geometry for relapse occurring within 10 days post-discharge is available in Figure 6. A network analysis comparing the effectiveness of SCS to mitigate relapse 10 days post-discharge could not be completed as planned due to a lack of reporting.

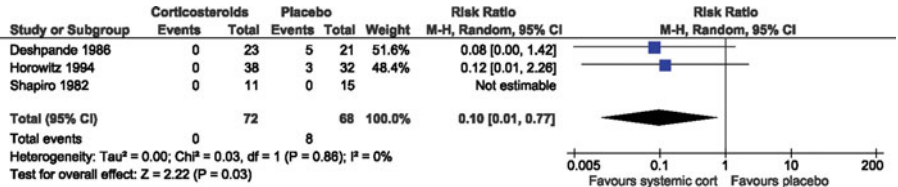


Figure 3. Forest plot of risk of relapse with SCS vs. placebo in children discharged from an acute care setting following treatment for an asthma exacerbation.

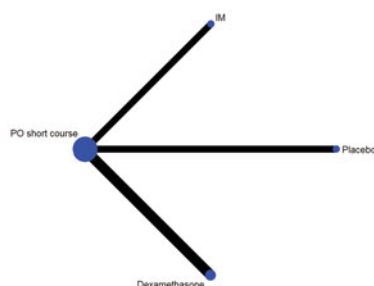


Figure 6. Network geometry of relapse occurring within 10 days post-discharge.

Note: Circle size reflects the number of patients included treatment groups. Line width reflects the number of direct comparisons were included in the network meta-analysis.

Discussion

This systematic review examined the effectiveness of SCS to mitigate relapses in children with acute asthma following treatment and discharge and attempted to identify an optimal regimen of SCS to prevent relapse. Employing a comprehensive literature search and efforts to avoid publication and selection biases, this review identified 15 relevant RCTs. Overall, the pooled analyses identified a significant reduction in relapse in pediatric patients following treatment with SCS compared to placebo. Moreover, evidence from a Bayesian network analysis suggested IM corticosteroids and oral short-course prednisone to be the most effective SCS regimens in reducing relapse within 10 days post-discharge. This review, however, also identified limited number of studies assessing the effectiveness of SCS vs. placebo, as well as a lack of evidence on the effectiveness of long-term SCS treatment to reduce relapse. Additional research on the use of SCS to mitigate asthma relapse in children, as well as on the comparative effectiveness of SCS regimens on long-term relapses are strongly recommended to provide further evidence clarity.

While this review did find evidence for SCS to prevent relapse in children, this finding should be interpreted with caution. First, the evidence for the effectiveness of SCS to prevent relapse vs. placebo in children arising from the meta-analysis is based on a limited number of small studies (3 studies; 140 patients published between 1982 and 1994) which were of unclear (20,37) or high risk of bias (32). All 3 studies compared oral corticosteroids (including prednisone or methylprednisolone) to placebo, and no studies comparing IM corticosteroids or oral dexamethasone to placebo in children with acute asthma could be found. In addition, of the 3 studies available for the meta-analysis, 2 of the studies examined the occurrence of early relapse (4 days post-discharge) (32,37), while one study assessed the occurrence of

long-term relapse (14 days post-discharge) (20), in which no relapse events were reported for either the corticosteroid or placebo groups. As such, the results of the meta-analysis report a 10% reduction in early relapse; however, the effectiveness of SCS to reduce late relapse is unclear. While clinicians in acute care settings frequently use these agents, and current clinical guidelines recommend the use of SCS to prevent relapse in children (5–7), these recommendations for the use of SCS appear to stem from widely cited systematic reviews combining pediatric and adult studies (3,4) and not from studies exclusively enrolling children. While additional studies examining the effectiveness of SCS to prevent relapse in children are strongly recommended, it is likely that many institutional review boards would find it unethical to withhold SCS from patients in a placebo controlled group.

In regards to the effectiveness of the SCS regimens, a Bayesian network analysis revealed that treatment with IM corticosteroids led to the largest decrease in the odds of relapse compared to placebo, followed by short-course oral prednisone and short-course oral dexamethasone. A subgroup analysis of early relapse (within 10 days post-discharge) reported similar results; however, there was no significant effect of short-course oral dexamethasone, which is likely due to the small number of studies included in the early relapse subgroup analysis. It is likely that additional studies assessing the effectiveness of oral dexamethasone to reduce early relapse in children with acute asthma would provide clinicians with sufficient clarity. In addition, a lack of available studies/comparisons impacted this review by excluding oral long-course corticosteroids in the Bayesian network analysis. Additional studies examining the various SCS regimens in children would increase the quantity of data included in the Bayesian network analysis, which could improve the ability of the network analysis to identify the optimal SCS regimen to prevent the short and long-term occurrence of relapse (38).

There are other factors which could have impacted the effectiveness of the various SCS regimens in the current review. First, there is evidence to suggest that the pathophysiology of asthma in children changes based on age, which may impact the effectiveness of SCS (39). Given that the age range of children enrolled among the included studies ranged from 6 months to 18 years, it is possible that the results of the studies could have been impacted by the varying effects of SCS among the children due to the evolving pathophysiology of asthma. Second, while statistical heterogeneity was low, it is possible that methodological heterogeneity among the studies including differences in patient populations, diagnosis, asthma severity, co-interventions, study settings, dosing of SCS, patient adherence to recommended treatment,

and individual response (effective dosage) could have impacted the results of this review. It is possible that issues of compliance with oral corticosteroids could have impacted the effectiveness of the oral corticosteroids, especially since poor palatability is often an important parental concern when children are receiving oral corticosteroids (13). Only 3 of the 16 included studies reported on adherence/compliance with oral corticosteroid treatment, of which, 18–29% of patients missed between 33 to 75% of their doses (14,27,34). It is vital that future research assess compliance/adherence, including access to medications and prescription claims, and parents/clinicians preferences.

Limitations

There are several limitations associated with this review that have not been discussed previously. The potential for publication and selection bias in all systematic reviews needs to be considered. Given the use of an extensive search of the published, unpublished, and foreign language trials should mitigate publication bias. By employing 2 independent reviewers with third party arbitration to identify all potential studies, the risk for selection bias should also have been minimized; however, despite these efforts, selection bias still may have occurred. Publication bias could not be assessed as planned using funnel plots due to a lack of studies comparing SCS to placebo, meaning that publication bias could be present.

In addition, this review strictly focused on the effectiveness of SCS to prevent relapse, and did not examine other outcomes such as pulmonary function, hospitalization, or adverse events. As such, while there is moderate evidence for SCS to prevent relapse in children after treatment and discharge from an ED or equivalent setting, we are unable to generalize the potential effects of SCS on other important clinical outcomes. Lastly, it is possible that pharmacological and non-pharmacological co-interventions provided in the majority of studies could have affected the results of this review. While the majority of studies reported providing all included patients with SABA at discharge, it is unlikely these agents could have a synergistic effect on relapse outcomes. Conversely, the failure to report on or use more effective preventive treatments (e.g., LKTRA, ICS, ICS/LABA agents) makes the results less generalizable to current practice. Finally, it is unclear as to whether any of the patients in the included studies received other effective interventions (i.e., asthma action plans, follow-up, etc.).

Conclusions

This review found moderate evidence for the effectiveness of SCS in reducing early relapse after discharge

in children with acute asthma compared to placebo treatment. This evidence, however, is based on a limited number of small low quality clinical trials. In regards to the effectiveness of various SCS regimens, IM corticosteroids seem to be more effective in reducing the odds of relapse, followed by short-course oral prednisone, and oral dexamethasone. A subgroup analysis revealed that short-course oral dexamethasone did not significantly reduce the odds of relapse within 10 days post-discharge; however, future studies may provide additional clarity.

Given the high risk of bias and small number of trials, additional research on SCS in children with acute asthma is urgently needed in order to clarify the comparative effectiveness of SCS to prevent relapse, and to identify the optimal SCS regimens to reduce early and long-term relapse. There is insufficient evidence from this review to make any recommendations for practice on the optimal regimen of administering systematic corticosteroids. Given these results, current practices, and the limited available evidence, this review does not justify a change in the current consensus-based guidelines regarding SCS use in post-discharge care for children with acute asthma. The results of this review do, however, highlight the importance of recognizing when the evidence supporting guideline recommendations has important limitations.

Acknowledgements

The authors would like to thank Drs. Chang, Cronin, Ghafouri, Grant, Klig, Greenberg, and Shariëff for responding to their requests for additional information. We would also like to thank Drs. Elfriede Cross (EC) and Tariq AlShawabkeh (TA) (Department of Emergency Medicine, University of Alberta) for their assistance with screening, study quality assessment, and data extraction. We would also like to thank Lynette Krebs (Department of Emergency Medicine, University of Alberta) for her feedback on the manuscript. Finally, we would like to thank Elizabeth Stovold for providing the search from the Cochrane Airways Group.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding

This review was supported by a grant from the Canadian Institutes of Health Research (CIHR; 250480). In-kind resources were provided by the Emergency Medicine Research Group (EMERG) affiliated with the Department of Emergency Medicine, University of Alberta. SWK is supported by the Emergency Strategic Clinical Network. At the time of the research, CVR was supported by CIHR in partnership with the Knowledge Translation branch. AN is supported by the CIHR as a CIHR New Investigator. FMD's research is supported by the Fonds de la Recherche en Santé du Québec which

provides infrastructure support to the Research Institutes of the Sainte-Justine University Health Centre. BHR's research is supported by a Tier I Canada Research Chair in Evidence-based Emergency Medicine from CIHR through the Government of Canada (Ottawa, Ontario). The funders take no responsibility for the conduct, results, and conclusions of this review.

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Supplemental material 1. Full search strings

Table AI - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to present>

	String terms
1	asthma*.mp. or exp Asthma/
2	exp Acute Disease/ or acute*.mp. or exacerbat*.mp.
3	1 and 2
4	exp Emergency Service, Hospital/ or emergenc*.mp.
5	ER.mp.
6	exp Emergency Medicine/
7	emergency nursing.mp. or exp Emergency Nursing/
8	4 or 5 or 6 or 7
9	1 and 8
10	3 or 9
11	exp Adrenal Cortex Hormones/ or exp Glucocorticoids/ or corticosteroid*.mp. or exp Prednisone/ or exp Methylprednisolone/
12	glucocortico*.mp.
13	cortico-steroid*.mp.
14	(prednis* or (deltason or prelone or orapred or pediapred or deltasone or betamethasone)).mp.
15	(solumedrol or medrol or dexamethasone or methylpred* or solucortef or decadron).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
16	(triamcinolone or kenalog* or trivaris).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
17	11 or 12 or 13 or 14 or 15 or 16
18	10 and 17
19	Injections, Intramuscular/
20	(intramuscul* or IM or repository).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
21	19 or 20
22	19 or 21
23	18 and 22
24	oral administration.mp. or exp Administration, Oral/ or ((drug administration route.mp. or exp Drug Administration Routes/) and po.mp.)
25	23 and 24
26	18 and 24
27	23 or 26
28	limit 27 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial)
29	27
30	limit 29 to randomized controlled trial
31	27
32	limit 31 to comparative study
33	27
34	randomized controlled trial.pt.
35	clinical trial.pt.
36	randomi?ed.ti,ab.
37	placebo.ti,ab.
38	dt.fs.
39	randomly.ti,ab.
40	trial.ti,ab.
41	groups.ti,ab.
42	or/34-41

43 animals/
44 humans/
45 43 not (43 and 44)
46 42 not 45
47 27 and 46
48 28 or 30 or 32 or 47
49 [post-discharge.mp.](#)
50 [relapse.mp.](#) or exp Recurrence/
51 exp Follow-Up Studies/ or [follow-up.mp.](#)
52 ((return* or revisit* or recur* or recrudescen*) adj3 (emerg* or ED or ER or acute*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
53 49 or 50 or 51 or 52
54 Treatment Outcome"/
55 53 or 54
56 48 and 55
57 21 or 24
58 18 and 57

Table AII – Ovid Embase, <1974 to 2015 Week 35>

	String terms
1	asthma*.mp. or exp Asthma/
2	exp Acute Disease/ or acute*.mp. or exacerbat*.mp.
3	1 and 2
4	exp Emergency Service, Hospital/ or emergenc*.mp.
5	ER.mp.
6	exp Emergency Medicine/
7	emergency nursing.mp. or exp Emergency Nursing/
8	4 or 5 or 6 or 7
9	1 and 8
10	3 or 9
11	exp Adrenal Cortex Hormones/ or exp Glucocorticoids/ or corticosteroid*.mp. or exp Prednisone/ or exp Methylprednisolone/
12	glucocortico*.mp.
13	cortico-steroid*.mp.
14	(prednis* or (deltason or prelone or orapred or pediaped or deltasone or betamethasone)).mp.
15	(solumedrol or medrol or dexamethasone or methylpred* or solucortef or decadron).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
16	(triamcinolone or kenalog* or trivaris).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
17	11 or 12 or 13 or 14 or 15 or 16
18	10 and 17
19	Injections, Intramuscular/
20	(intramuscul* or IM).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
21	19 or 20
22	oral administration.mp. or exp Administration, Oral/ or (po.mp. and exp drug administration route/)
23	18 and 21 and 22
24	post-discharge.mp.
25	relapse.mp. or exp Recurrence/
26	exp Follow-Up Studies/ or follow-up.mp.
27	((return* or revisit* or recur* or recrudescen*) adj3 (emerg* or ED or ER or acute*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
28	24 or 25 or 26 or 27

- 29 "Treatment Outcome"/
- 30 28 or 29
- 31 exp clinical trial/
- 32 randomi?ed.ti,ab.
- 33 placebo.ti,ab.
- 34 dt.fs.
- 35 randomly.ti,ab.
- 36 trial.ti,ab.
- 37 groups.ti,ab.
- 38 or/31-37
- 39 animal/
- 40 human/
- 41 39 not (39 and 40)
- 42 38 not 41
- 43 23 and 30
- 44 limit 43 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
- 45 42 and 43
- 46 44 or 45
- 47 21 or 22
- 48 18 and 30 and 42 and 47

Table AIII Ovid All EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 2015>, EBM Reviews - ACP Journal Club <1991 to August 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2015>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <3rd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>

String terms	
1	asthma*.mp. or exp Asthma/
2	exp Acute Disease/ or acute*.mp. or exacerbat*.mp.
3	1 and 2
4	exp Emergency Service, Hospital/ or emergenc*.mp.
5	ER.mp.
6	exp Emergency Medicine/
7	emergency nursing.mp. or exp Emergency Nursing/
8	4 or 5 or 6 or 7
9	1 and 8
10	exp Adrenal Cortex Hormones/ or exp Glucocorticoids/ or corticosteroid*.mp. or exp Prednisone/ or exp Methylprednisolone/
11	glucocortico*.mp.
12	cortico-steroid*.mp.
13	(prednis* or (deltason or prelone or orapred or pediaped or deltasone or betamethasone)).mp.
14	(solumedrol or medrol or dexamethasone or methylpred* or solucortef or decadron).mp. [mp=ti, ab, tx, kw, ct, ot,sh, hw]
15	(triamcinolone or kenalog* or trivaris).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
16	10 or 11 or 12 or 13 or 14 or 15
17	Injections, Intramuscular/
18	(intramuscul* or IM).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
19	17 or 18
20	oral administration.mp. or exp Administration, Oral/ or ((drug administration route.mp. or exp Drug Administration Routes/) and po.mp.)
21	randomized controlled trial.pt.
22	clinical trial.pt.
23	randomi?ed.ti,ab.
24	placebo.ti,ab.
25	dt.fs.

26 randomly.ti,ab.
 27 trial.ti,ab.
 28 groups.ti,ab.
 29 or/21-28
 30 animals/
 31 humans/
 32 30 not (30 and 31)
 33 29 not 32
 34 [post-discharge.mp.](#)
 35 [relapse.mp.](#) or exp Recurrence/
 36 exp Follow-Up Studies/ or [follow-up.mp.](#)
 37 ((return* or revisit* or recur* or recrudescen*) adj3 (emerg* or ED or ER or acute*)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]
 38 34 or 35 or 36 or 37
 39 Treatment Outcome"/
 40 38 or 39
 41 19 and 20
 42 [rct.mp.](#) [mp=ti, ab, tx, kw, ct, ot, sh, hw]
 43 33 or 42
 44 9 and 16 and 40 and 41 and 43

Table AIV - International Pharmaceutical Abstracts <1970 to August 2013>

	String terms
1	asthma*.mp.
2	Acute Disease/ or acute*.mp. or exacerbat*.mp.
3	1 and 2
4	Emergency Service, Hospital/ or emergenc*.mp.
5	ER.mp.
6	Adrenal Cortex Hormones/ or Glucocorticoids/ or corticosteroid*.mp. or Prednisone/ or Methylprednisolone/
7	(glucocortico* or "steroids, cortico*").mp.
8	cortico-steroid*.mp.
9	(prednis* or (deltason or prelone or orapred or pediaped or deltasone or betamethasone)).mp.
10	(solumedrol or medrol or dexamethasone or methylpred* or solucortef or decadron).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
11	(triamcinolone or kenalog* or trivaris).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
12	6 or 7 or 8 or 9 or 10 or 11
13	Injections, Intramuscular/
14	(intramuscul* or IM).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
15	13 or 14
16	oral administration.mp. or Administration, Oral/ or ((drug administration route.mp. or Drug Administration Routes/) and po.mp.)
17	("randomized controlled trial" or "drug comparison*").mp.
18	clinical trial.mp.
19	randomi?ed.ti,ab.
20	placebo.ti,ab.
21	randomly.ti,ab.
22	trial.ti,ab.
23	groups.ti,ab.
24	animals/
25	post-discharge.mp.
26	relapse.mp. or Recurrence/
27	Follow-Up Studies/ or follow-up.mp.
28	((return* or revisit* or recur* or recrudescen*) adj3 (emerg* or ED or ER or acute*)).mp. [mp=title, subject

	heading word, registry word, abstract, trade name/generic name]
29	25 or 26 or 27 or 28
30	"Outcomes (clinical)".sh.
31	29 or 30
32	14 or 16
33	17 or 18 or 19 or 20 or 21 or 22 or 23
34	33 not 24
35	4 or 5
36	3 and 32 and 34 and 35

Table AV - Global Health <1973 to 2015 Week 34>, Global Health Archive <1910 to 1972>

	String terms
1	(random* or trial* or placebo* or rct or comparative or outcome*).mp. [mp=abstract, title, original title, broad terms, heading words]
2	animal studies.mp. or laboratory animals.sh. or rats.od.
3	intramuscular.mp. [mp=abstract, title, original title, broad terms, heading words]
4	"oral administration".mp. [mp=abstract, title, original title, broad terms, heading words]
5	(corticosteroid* or "steroids, cortico*" or corticosteroid* or prelone or orapred or pediapred or deltasone or solumedrol or medrol or betamethasone or dexamethasone or methylpred or solucortef or decahedron or triamcinolone or kenalog* or trivaris).mp. [mp=abstract, title, original title, broad terms, heading words]
6	(asthma* and (acute or exacerbat*or emerg*).mp. [mp=abstract, title, original title, broad terms, heading words]
7	exp corticoids/
8	(oral or ((im or po) and (drug* or delivery or administration or route*)) or intravenous*).mp. [mp=abstract, title, original title, broad terms, heading words]
9	3 or 4 or 8
10	5 or 7
11	1 and 9 and 10
12	6 and 11
13	12 not 2

Table AVI – CINAHL Plus <searched Sept 2015>

	String terms
1	(asthma* AND (emergency OR emergent OR emergencies OR acute* OR exacerbate*)) AND (corticosteroid* OR "steroids, cortico*" OR corticosteroid* OR prelone OR orapred OR pediapred OR deltasone OR solumedrol OR medrol OR betamethasone OR dexamethasone OR methylpred OR solucortef OR decahedron OR triamcinolone OR kenalog* OR trivaris) AND (oral OR ((im OR po) AND (drug* OR delivery OR administration OR route*)) OR intravenous*)
2	(MH "Adrenal Cortex Hormones+")
3	asthma
4	intramuscular injection*
5	(MH "Injections, Intramuscular+")
6	(MH "Administration, Oral+")
7	(MH "Emergency Medical Services+") OR "emergency services"
8	(MH "Asthma+")
9	(MH "Randomized Controlled Trials") OR (MH "Clinical Trials+")
10	((MH "Randomized Controlled Trials") OR (MH "Clinical Trials+")) AND (S4 or S5 or S6)
11	((((MH "Randomized Controlled Trials") OR (MH "Clinical Trials+")) AND (S4 or S5 or S6)) AND (S9 and S10)
12	(((((MH "Randomized Controlled Trials") OR (MH "Clinical Trials+")) AND (S4 or S5 or S6)) AND (S9 and S10)) AND (S2 and S7 and S8 and S10)
13	((((((MH "Randomized Controlled Trials") OR (MH "Clinical Trials+")) AND (S4 or S5 or S6)) AND (S9 and S10)) AND (S2 and S7 and S8 and S10)) AND (S1 or S12)

Box AI – Other search strings <searched Sept 2015>

String terms

SCOPUS

(TITLE-ABS-KEY(asthma* AND (acute OR exacerbat*))) AND (TITLE-ABS-KEY((po AND drug*) OR "oral drug delivery" OR (im AND drug*) OR intramuscular*)) AND (TITLE-ABS-KEY(emergenc*)) AND (TITLE-ABS-KEY(random* OR "clinical trial*" OR comparative OR outcome* OR RCT OR placebo))

LILACS

asthma* AND (acute OR exacerbat* AND emerg*) [Words] AND oral OR ((po OR Im) AND (drug* OR administration OR route* OR delivery) OR intramuscular OR intra-muscular [Words] AND (corticosteroid* OR "steroids, cortico*" OR corticosteroid* OR predlone OR orapred OR pediaped OR daltasone OR solumedrol OR medrol OR betamethasone OR dexamethasone OR methylpred OR solucortef OR decahedron OR triamcinolone OR kenalog* OR trivaris) [Words]

ProQuest Dissertations and Theses

all(asthma* AND (emergency OR emergent OR emergencies OR acute* OR exacerbate*)) AND all(moral OR (im AND drug*) OR (po AND drug*) OR intramuscular*) AND all((random* OR trial* OR placebo* OR rct OR comparative OR outcome*))

Box AII – Cochrane Airways Register 2002-2008

String terms

2002-2003

A search of this ARG registry was completed using the following terms:

- a) Asthma OR Wheez*
- b) Glucocorticoid OR Steroid* AND
- c) Exacerbate* OR Relapse* OR Emerg*

2004-2005

(glucocorticoid* OR steroid* OR corticosteroid* OR cortico-steroid* OR prednis* OR solumedrol OR medrol OR dexamethasone OR methylpred* OR solucortef OR decadron) AND (emerg* OR relaps* OR exacerb* OR discharg*) (this search was limited to records coded as 'asthma')

2006

(glucocorticoid* OR steroid* OR corticosteroid* OR cortico-steroid* OR prednis* OR solumedrol OR medrol OR dexamethasone OR methylpred* OR solucortef OR decadron) AND (acute* OR emerg* OR relaps* OR exacerb* OR discharg*)

(this search was limited to records coded as 'asthma')

2007-2008

(glucocorticoid* OR steroid* OR corticosteroid* OR cortico-steroid* OR prednis* OR solumedrol OR medrol OR dexamethasone OR methylpred* OR solucortef OR decadron) AND (acute* OR emerg* OR relaps* OR exacerb* OR discharge OR admi* OR hospit*)

(this search was limited to records coded as 'asthma')

Table AVII – Cochrane Airways Register 2009-2015

	String terms
1	AST:MISC1
2	MeSH DESCRIPTOR Asthma Explode All
3	asthma*:ti,ab
4	#1 OR #2 OR #3
5	acute*
6	emergenc*
7	relaps*

8 exacerb*

9 discharg*

10 #5 or #6 or #7 or #8 or #9

11 MeSH DESCRIPTOR Adrenal Cortex Hormones

12 glucocorticoid*

13 steroid*

14 corticosteroid*

15 cortico-steroid*

16 prednis*

17 solumedrol

18 medrol

19 dexamethasone

20 methylpred*

21 solucortef

22 decadron

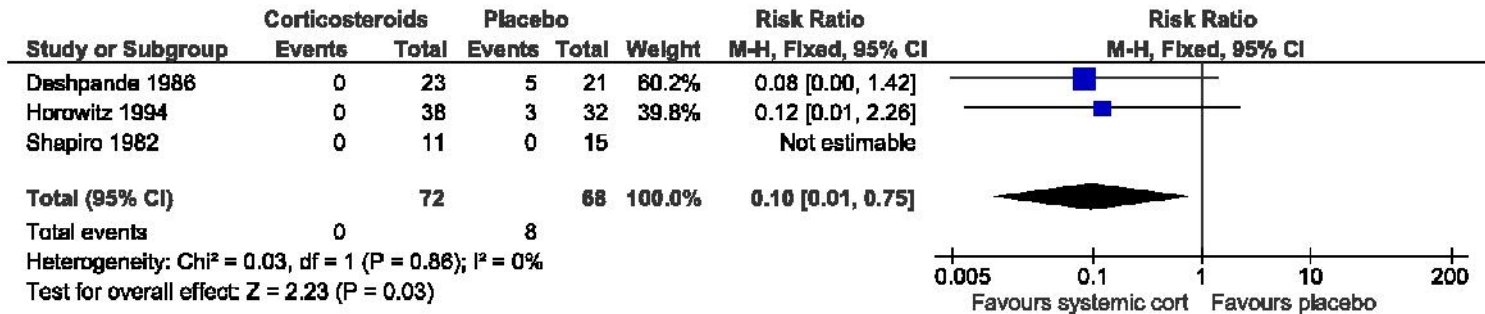
23 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 #21 or #22

24 #4 and #10 and #23

Supplemental material 3. Definition of asthma reported among the included studies

Reference year	Patient age range	Asthma definition
Altamimi 2006	2-16 yrs	Presenting to the ED with an acute exacerbation of mild/moderate asthma with a history of at least one prior episode suggestive of “asthma-like” acute shortness of breath or wheezing that was treated with salbutamol. Mild to moderate asthma defined as a Pulmonary Index score of less than nine or a PEF > 60% predicted value for height.
Al-Wahadneh 2006	9 months-14 yrs	Presenting with moderate exacerbation of asthma. Asthma not otherwise defined.
Chang 2008	2-15 yrs	Presenting with acute exacerbation of asthma. Asthma defined as recurrent (> two) episodes of wheeze and/or dyspnea with a clinical response (decreased respiratory rate and work of breathing) to salbutamol. Asthma exacerbation was defined as acute deterioration of asthma control requiring treatment with more than a single dose (>600 µg via metered dose inhaler and spacer or > 2.5 mg nebulized) of salbutamol in an hour.
Cronin 2016	2-16 yrs	Presenting with acute asthma exacerbation with a history of asthma, which was defined as at least one previous episode of wheeze responsive to SABA therapy or a previous physician diagnosis of asthma (pediatrician or clinician of comparable experience). Exacerbation of asthma defined as acute asthma that prompts ED assessment, with any or all of the following clinical features: dyspnea, wheeze, acute cough, increased work of breathing, increased requirement for SABA from baseline or SaO ₂ < 95%.
Deshpande 1986	5-15 yrs	Presented with an acute wheezy episode and with a PEF of 15-80% of a baseline value obtained when they were well.
Gartner 2004	6-14 yrs	Presenting with moderate asthma exacerbation. Asthma defined as per the American Thoracic Society.
Ghafouri 2010	2-17 yrs	Presented with mild to moderate asthma exacerbations. Asthma not otherwise defined.
Gordon 2007	18 months-7 yrs	Patients who required treatment for wheezing if they had a history of asthma, defined by at least two prior episodes of respiratory illness treated with SABA.
Greenberg 2008	2-18 yrs	Presenting to an ED with an acute exacerbation of asthma with a history of asthma (two or more episodes of wheezing treated with SABA).
Gries 2000	6 months-7 yrs	Presenting with mild/moderate exacerbations of asthma. Diagnosis of asthma defined as recurrent coughing, wheezing, or shortness of breath response to corticosteroids or SABA agents, and an asthma exacerbation was defined as increased asthma signs and symptoms (coughing, wheezing, or shortness of breath) unresponsive to the patients routine asthma medications and additional SABA therapy.
Horowitz 1994	4-16 yrs	Presented with an acute asthma attack. Asthma not otherwise defined.
Kayani 2002	2-18 yrs	Presenting with mild persistent asthma based on National Institutes of Health guidelines (cough, shortness of breath, or wheeze more than twice a week but less than once a day and similar nighttime symptoms more than twice a month but less than once a week), were receiving inhaled corticosteroids daily and were using an albuterol metered-dose inhaler as needed.
Klig 1997	3-16 yrs	Presenting with mild to moderate wheezing episodes. Patients must have had two prior episodes of wheezing treated with SABA agents.
Qureshi 2001	2-18 yrs	Presenting with an acute exacerbation with a known history of asthma (two or more episodes of wheezing treated with SABA, with or without corticosteroids). Acute exacerbation of asthma defined as a worsening of their asthmatic symptoms or increased difficulty in breathing with worsening of their PEF.
Shapiro 1982	No age restrictions listed. Mean age 7.2 yrs (range 5.3 – 10.1 yrs)	Acute asthma exacerbation that required three consecutive treatments of SABA treatments. If the patient responded well yet had a persistent FEV ₁ < 80% of a previous baseline determination when well.

Note: ED = emergency department; FEV₁ = forced expiratory volume in one second; PEF = peak expiratory flow; SABA = short-acting beta-agonists; SaO₂ = oxygen saturation; yrs = years.



```

Supplmental_material_2._Sample_winbugs_code.txt
#Random effects model for multi-arm trials (any number of arms)
model{
  for(i in 1:NS){
    w[i,1] <-0
    delta[i,1]<-0
    mu[i] ~ dnorm(0,.0001)
    # vague priors for 24 trial baselines
    for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])
      # binomial likelihood
      logit(p[i,t[i,k]])<-mu[i] + delta[i,k] }
      # model
      for (k in 2:na[i]) {
        delta[i,k] ~ dnorm(md[i,k],taud[i,k]) #
      }
    }
    trial-specific LOR distributions
    md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
    # mean of LOR distributions
    taud[i,k] <- tau *2*(k-1)/k
    #precision of LOR distributions
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
    #adjustment, multi-arm RCTs
    sw[i,k] <-sum(w[i,1:k-1])/(k-1) } # cumulative
  }
  adjustment for multi-arm trials

  d[1]<-0
  for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors
  for basic parameters

  sd~dunif(0,2) # vague prior for
  random effects standard deviation
  tau<-1/pow(sd,2)

  # ranking
  for (k in 1:NT) { rk[k]<-rank(T[,k])
    best[k]<-equals(rk[k],1)}

  # pairwise ORs
  for (c in 1:(NT-1))
    { for (k in (c+1):NT)
      { lor[c,k] <- d[k] - d[c]
        log(or[c,k]) <- lor[c,k]
      }
    }
  }

  # NT=no. treatments, NS=no. studies;
  # NB : set up M vectors each r[,]. n[,], and t[,], where M is the Maximum number
  of treatments
  # per trial in the dataset. In this dataset M is 3.

  list(NT=4,NS=7)

  r[,1]   n[,1]   r[,2]   n[,2]   t[,1]   t[,2]   na[]
0.5      22      0.5      22      2        3        2
5.5      22      0.5      24      1        3        2
8        69      11       73      2        3        2
1        56      4        61      3        4        2
3        38      8        51      3        4        2
18       261     20       272     3        4        2
3.5      33      0.5      39      1        3        2

```

END

Supplemental_material_2._Sample_winbugs_code.txt

```
list(  
d=c(NA,0,0,0),  
sd=1,  
mu=c(0,0,0,0,0, 0,0)  
)
```