Inhaled steroids for acute asthma following emergency department discharge (Review)

Edmonds ML, Milan SJ, Brenner BE, Camargo Jr CA, Rowe BH

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 12

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[Intervention Review]

Inhaled steroids for acute asthma following emergency department discharge

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Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2012.
Review content assessed as up-to-date: 28 September 2012.

Citation: Edmonds ML, Milan SJ, Brenner BE, Camargo Jr CA, Rowe BH. Inhaled steroids for acute asthma following emergency department discharge. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD002316. DOI: 10.1002/14651858.CD002316.pub2.

ABSTRACT

Background

Patients with acute asthma treated in the emergency department (ED) are frequently treated with inhaled beta$_2$-agonists and systemic corticosteroids after discharge. The use of inhaled corticosteroids (ICS) following discharge may also be beneficial in improving patient outcomes after acute asthma.

Objectives

To determine the effectiveness of ICS on outcomes in the treatment of acute asthma following discharge from the ED. To quantify the effectiveness of ICS therapy on acute asthma following ED discharge, when used in addition to, or as a substitute for, systemic corticosteroids.

Search methods

Controlled clinical trials (CCTs) were identified from the Cochrane Airways Review Group register, which consists of systematic searches of EMBASE, MEDLINE and CINAHL databases supplemented by handsearching of respiratory journals and conference proceedings. In addition, primary authors and pharmaceutical companies were contacted to identify eligible studies. Bibliographies from included studies, known reviews and texts also were searched. The searches have been conducted up to September 2012

Selection criteria

We included both randomised controlled trials (RCTs) and quasi-RCTs. Studies were included if patients were treated for acute asthma in the ED or its equivalent, and following ED discharge were treated with ICS therapy either in addition to, or as a substitute for, oral corticosteroids. Two review authors independently assessed articles for potential relevance, final inclusion and methodological quality.

Data collection and analysis

Data were extracted independently by two review authors, or confirmed by the study authors. Several authors and pharmaceutical companies provided unpublished data. The data were analysed using the Cochrane Review Manager software. Where appropriate, individual and pooled dichotomous outcomes were reported as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CIs). Where appropriate, individual and pooled continuous outcomes were reported as mean differences (MD) or standardized mean differences (SMD) with 95% CIs. The primary analysis employed a fixed effect model and heterogeneity is reported using I-squared (I^2) statistics.

Main results

Twelve trials were eligible for inclusion. Three of these trials, involving a total of 909 patients, compared ICS plus systemic corticosteroids versus oral corticosteroid therapy alone. There was no demonstrated benefit of ICS therapy when used in addition to oral corticosteroid therapy in the trials. Relapses were reduced; however, this was not statistically significant with the addition of ICS therapy (OR 0.68; 95% CI 0.46 to 1.02; 3 studies; N = 909). In addition, no statistically significant differences were demonstrated between the two groups for relapses requiring admission, quality of life, symptom scores or adverse effects.

Nine trials, involving a total of 1296 patients compared high-dose ICS therapy alone versus oral corticosteroid therapy alone after ED discharge. There were no significant differences demonstrated between ICS therapy alone versus oral corticosteroid therapy alone for relapse rates (OR 1.00; 95% CI 0.66 to 1.52; 4 studies; N = 684), admissions to hospital, or in the secondary outcomes of $beta_2$-agonist use, symptoms or adverse events. However, the sample size was not adequate to exclude the possibility of either treatment being significantly inferior and people with severe asthma were excluded from these trials.

Authors' conclusions

There is insufficient evidence that ICS therapy provides additional benefit when used in combination with standard systemic corticosteroid therapy upon ED discharge for acute asthma. There is some evidence that high-dose ICS therapy alone may be as effective as oral corticosteroid therapy when used in mild asthmatics upon ED discharge; however, the confidence intervals were too wide to be confident of equal effectiveness. Further research is needed to clarify whether ICS therapy should be employed in acute asthma treatment following ED discharge. The review does not suggest any reason to stop usual treatment with ICS following ED discharge, even if a course of oral corticosteroids are prescribed.

PLAIN LANGUAGE SUMMARY

Inhaled corticosteroids for acute asthma following emergency department discharge

Acute asthma is a common cause of visits to emergency departments (ED) and the majority of patients are treated and discharged home. Some people will have a relapse of acute asthma within two weeks of being discharged after apparently successful treatment. $Beta_2$-agonist drugs are used to open the muscles in the airways and corticosteroids drugs are used to reduce inflammation of the swollen airways. Corticosteroids can be inhaled (ICS) or swallowed as a tablet (so-called oral corticosteroids). ICS may reduce adverse effects and get to the airways more directly than oral corticosteroids. This review of trials found that there was insufficient evidence that inhaling corticosteroids as well as taking the drugs orally is better than oral use alone, after emergency department treatment for an asthma attack. There is also insufficient evidence that taking ICS alone is as good as taking them orally, although there is some evidence to support using ICS alone for mild asthma attacks after emergency department discharge. More research is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Any ICS plus oral corticosteroid versus oral corticosteroid for acute asthma following emergency department discharge

Patient or population: predominantly adults with acute asthma following emergency department discharge
Settings: community following emergency department discharge
Intervention: any ICS plus oral corticosteroid versus oral corticosteroid
Comparison: oral corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Any ICS plus oral corticosteroid versus oral corticosteroid				
Asthma relapse[1] **at 20 to 24 days**	**141 per 1000**	**100 per 1000** (70 to 143)	**OR 0.68** (0.46 to 1.02)	909 (3 studies)	⊕⊕⊕⊕ **high**[2]	Predominantly adult patients in Camargo 2000 and adults in Brenner 2000 and Rowe 1999
Hospital admission mean follow-up period 21 days	**22 per 1000**	**22 per 1000** (9 to 55)	**OR 0.99** (0.39 to 2.52)	805 (2 studies)	⊕⊕⊕◯ **moderate**[3]	Predominantly adult patients in Camargo 2000 and adult patients in Rowe 1999
Hoarseness at 20 to 24 days	**149 per 1000**	**95 per 1000** (59 to 150)	**OR 0.6** (0.36 to 1.01)	596 (2 studies)	⊕⊕⊕◯ **moderate**[4]	Predominantly adult patients in Camargo 2000 and adult patients in Rowe 1999

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI confidence interval; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] relapse was defined as ' ' an unscheduled visit for worsening asthma symptoms".
[2] No point deducted for imprecision as OR = 1.02 was not regarded as a clinically significant increase in risk of admission.
[3] Point deducted for imprecision due to wide confidence intervals.
[4] Point deducted for hoarseness at 20 to 24 days as $I^2 = 55\%$.

BACKGROUND

Description of the condition

Acute asthma is a common presenting complaint to the emergency department (ED). In the US, acute asthma accounts for nearly two million ED visits per year (Mannino 1998). Approximately 10% to 20% of these patients will require admission to the hospital, and for those discharged from the ED after apparently successful treatment, approximately 10% to 20% will relapse within the subsequent two weeks (Griswold 2005; Rowe 2008b; Rowe 2010;). The enormity of the asthma problem overall has led to the creation of several national (NAEPP 1997; Boulet 1998; BTS/SIGN 2011; EPR3 2007) and international (GINA 2011) asthma guidelines.

Description of the intervention

There is general agreement that $beta_2$-agonists (e.g. salbutamol, albuterol) and systemic corticosteroids (e.g. delivered by oral or intramuscular (IM) routes) are first-line agents for acute asthma. $Beta_2$-agonists are bronchodilators and are used to provide rapid symptom relief, whereas corticosteroids are used to counter airway inflammation and hasten resolution of the asthma exacerbation. However, there remain numerous controversies regarding the optimal dose, frequency and route of delivery of these medications. Current practice for patients discharged after assessment and treatment in the ED usually involves the use of short-acting $beta_2$-agonists and oral corticosteroids prescribed for five to 10 days after discharge in a majority of cases (Rowe 2003). Oral corticosteroids may be prescribed as fixed-dose treatments (Verbeek 1995); however, complicated tapering regimens have also been described. While the evidence for oral corticosteroids is strong, the evidence and recommendations for the role of inhaled corticosteroids (ICS) in the management of acute asthma after discharge are inconsistent. This is also reflected in practice. For example, in Canadian EDs, use is as high as 69% at discharge, whereas in US centres use is lower (< 15%) (Rowe 1998). When ICS agents are prescribed, they may either be used with (Rowe 1998; Rowe 1999; Brenner 2000) or as a replacement for (Levy 1996) oral corticosteroids. Given the practice variation with respect to ICS treatment in acute asthma care (Griswold 2005; Rowe 1998), the update for this systematic review in this area has been carried out to provide direction for treatment and further research.

How the intervention might work

ICS have the potential to be of benefit in the acute setting. Potential advantages of ICS in acute asthma therapy might include their reduced systemic side effects, direct delivery to the airways and a greater efficacy in reducing airway reactivity and oedema either alone or in addition to systemic corticosteroids (Rodrigo 1998). Furthermore, ancillary evidence from studies of other airway diseases suggests that ICS agents may act over the short term to improve outcomes (Ausejo Segura 1999). They have been shown to be effective alternatives to oral corticosteroids in long-term asthma therapy, where they can reduce or even eliminate oral corticosteroid requirements (Barnes 1995)

Why it is important to do this review

Several trials have examined the use of ICS in acute asthma upon ED discharge and they have yielded conflicting results (Levy 1996; Rowe 1999; Brenner 2000); however, systematic literature searching and meta-analytic techniques should generate stronger conclusions and recommendations. One cost effectiveness analysis Andrews 2012 suggested that ICS may lead to a decreased number of admissions and ED visits as well as providing substantial cost savings. The previous version of this review (Edmonds 2000) concluded "there is insufficient evidence that ICS therapy provides additional benefit when used in combination with standard oral corticosteroid therapy upon ED discharge for acute asthma. There is some evidence that high-dose ICS therapy alone may be as effective as oral corticosteroid therapy when used in mild asthmatics upon ED discharge; however, there is a significant possibility of a type II error in drawing this conclusion. Further research is needed to clarify whether ICS therapy should be employed in acute asthma treatment in the ED or following ED discharge." The 2012 update of this review will examine these conclusions in relation to evidence from relevant randomised controlled trials (RCTs) published since 2000.

Separate reviews are available on *The Cochrane Library* for: Early use of inhaled corticosteroids in the emergency department treatment of acute asthma (Edmonds 2003), Early emergency department treatment of acute asthma with systemic corticosteroids (Rowe 2008) and corticosteroids for preventing relapse following acute exacerbations of asthma (Rowe 2008a).

OBJECTIVES

To determine the effectiveness of ICS therapy on outcomes in the treatment of acute asthma following discharge from the ED.

To quantify the effectiveness of ICS therapy on acute asthma following ED discharge, when used in addition to, or as a substitute for, oral corticosteroids.

METHODS

Criteria for considering studies for this review

Types of studies

To be considered, clinical studies had to be RCTs or quasi-RCTs (e.g. allocation on days of the week/flipping a coin).

Types of participants

Studies involving adults or children discharged from an ED, or equivalent, following assessment and treatment for acute asthma were considered for inclusion in this systematic review. We considered data form trials where patients from other settings could be removed easily from the study (e.g., if stratified randomisation was employed). Studies recruiting paediatric or adult participants were reviewed; however, studies of young children (< 2 years of age) with bronchiolitis were excluded.

Types of interventions

Patients must have been randomised to receive ICS treatment following discharge from the ED, either in addition to, or as a substitute for, standard oral corticosteroid therapy. ICS administration was defined as any corticosteroid agent administered by metered-dose inhaler (MDI), other inhaler, or nebuliser after ED discharge. Asthmatic patients also may have received additional asthma medications (such as IM corticosteroids, beta$_2$agonists, ipratropium bromide, theophylline compounds, antibiotics, and/or anti-histamines). Data for these co-interventions were recorded or requested from the authors directly when this information was incompletely reported.

There were two distinct types of studies in this systematic review, which form two separate parts of the review. In the first type of study, the treatment groups compared ICS combined with oral corticosteroid versus oral corticosteroid alone. In the second type of study, the treatment groups compared ICS alone versus oral corticosteroid alone. It is anticipated that this review may be divided into two separate systematic reviews in the future, when more studies in each topic area are completed.

Types of outcome measures

Primary outcomes

Acute asthma relapse (defined as an unscheduled visit for worsening asthma symptoms).

Secondary outcomes

1. Asthma-related quality of life.
2. Pulmonary function tests.
3. Beta$_2$-agonist use.
4. Relapse resulting in hospitalisation.
5. Any report of adverse side effects.
6. Symptoms.

Search methods for identification of studies

Electronic searches

For the previous version of this review, searches were conducted up to February 2003. For this version, the search strategy was updated and run from 2003 up to September 2012. Trials were identified from the following sources:

- Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases and handsearching of respiratory journals and meeting abstracts (see Appendix 1 for full details of sources and search methods);
- ClinicalTrials.gov.

The databases were searched from their inception and there was no restriction on the language of publication. See Appendix 2 for the full search strategies. See Appendix 3 for search methods prior to 2003.

Searching other resources

For the 2003 version, additional efforts to locate potential trials were as follows:

- reference lists of all available primary studies and review articles were reviewed;
- inquiries were made regarding other published or unpublished trials known or supported by the authors of the primary studies so that these results could be included in this review;
- the scientific advisors of the various pharmaceutical industries that manufacture known ICS agents (Astra: budesonide; Glaxo Wellcome: fluticasone and beclomethasone; Forest: flunisolide) were contacted for any unpublished or interim results on relevant research;
- handsearching of abstracts, from 1997 to 1999 of the Society for Academic Emergency Medicine meetings (published in *Academic Emergency Medicine*), and from 1995 to 1999 of the American College of Chest Physicians (published in *Chest*) and the British Thoracic Society (published in *Thorax*) was completed. Abstracts from the 1997 to 1999 abstracts-on-disk from the American Thoracic Society (published in *American Journal of Respiratory and Critical Care Medicine*) meetings also were searched;
- personal contact with colleagues, collaborators and other trialists working in the field of asthma was made to identify potentially relevant studies.

In 2012, in addition to the database searches, we checked bibliographies of new included papers for additional RCTs.

Data collection and analysis

Selection of studies

On the basis of a search of title, abstract, key words and MeSH headings, two review authors (MLE, BHR) independently examined the output generated from the computer search to identify potentially relevant trials for full review. No specific blinding techniques were used (Jadad 1996). In the 2012 update this process was completed by SJM and MLE.

Data extraction and management

Data extraction from published papers was performed independently by two review authors (MLE, BHR). Authors of trials were contacted to provide missing data where possible. As many of these trials were unpublished, a large amount of data was obtained directly from the primary investigators or the pharmaceutical companies in a specified format. The data were checked and entered onto the computer by one review author. In the 2012 update, data extraction was performed by SJM and checked by MLE, and entered into RevMan 2011 by SJM and checked by MLE.

Assessment of risk of bias in included studies

In the original version of this review methodological quality assessment was performed independently by two review authors (MLE, BHR) using the Jadad tool and the Cochrane concealment of allocation approach. In 2012, the risk of bias of included studies was assessed using the Collaboration's risk of bias (RoB) methodology (see Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011). Two review authors (MLE and SJM) assessed the (RoB) for all included studies with regard to random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each item was assessed as high, low or unclear risk of bias along with relevant information reported in the RCT.

Measures of treatment effect

In the 2012 update of this review data were entered into RevMan 2011 by a single review author (SJM).

For dichotomous variables, we presented data as odds ratios (OR) with 95% confidence intervals (CI). Data for continuous variables were reported as mean differences (MD) or standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

The unit of analysis was the patient.

Dealing with missing data

If outcome data or information on trial design was missing, authors were contacted where possible for the original version of the review; however, this was not necessary for the 2012 update. All the authors for the ICS plus oral corticosteroid versus oral corticosteroid alone comparison were contacted and provided data from their studies for the review (two were unpublished at the time of the initial review; Brenner 2000; Camargo 2000). For the ICS versus oral corticosteroid comparison, several drug companies provided information about studies that were unpublished at the time of their inclusion in the review: Julia Earnshaw of Glaxo Wellcome UK provided additional information about three studies (Francis 1997; Verona 1998; Manjra 2000), Dr Elisabeth Stahl of Astra Draco AB provided information about Nana 1998 and Jennifer Haddon of AstraPharma Canada provided information about Fitzgerald 2000. Toni Maslen of Glaxo Wellcome UK provided information about the published study Levy 1996. In addition, Dr Benjamin Volovitz provided further information about his study (Volovitz 1998).

Intention-to-treat analyses were calculated for the primary outcome, asthma relapse.

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of forest plots. The Chi^2 test was similarly considered ($P < 0.10$) but interpreted with caution owing to the low power associated with this test. We considered the I^2 test and interpreted values in relation to the following guidance:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

Examination of publication bias was planned, using funnel plots, if there was an adequate number of trials aggregated in the analyses. However, it is recognised that an asymmetrical funnel plot can reflect heterogeneity, outcome reporting bias and small study effects, and is therefore not necessarily a reflection of publication bias.

Data synthesis

Trials were combined using RevMan 2011. For continuous variables, an MD or SMD and 95% CI was calculated for each study. For dichotomous variables, an OR with 95% CI was calculated for individual studies. All similar studies were pooled using a fixed-

effect model, but a random effects model was used if heterogeneity was found.

Subgroup analysis and investigation of heterogeneity

Two separate comparisons were performed as described above. Within these comparisons, the following three specific subgroup analyses were planned a priori:

1. adults versus children;
2. severe asthma versus less severe asthma (categorised by % predicted peak expiratory flow (PEF), and by the placebo group admission rate);
3. males versus females (relapse rates only).

Due to the small number of studies, however, only subgroup analysis comparing males and females was performed.

Sensitivity analysis

In the original version of this review asthma relapse rates in the primary analyses were calculated as intention to treat. Because of marked differences in the rate of follow-up between the trials, the analyses were repeated excluding all patients who were lost to follow-up.

RESULTS

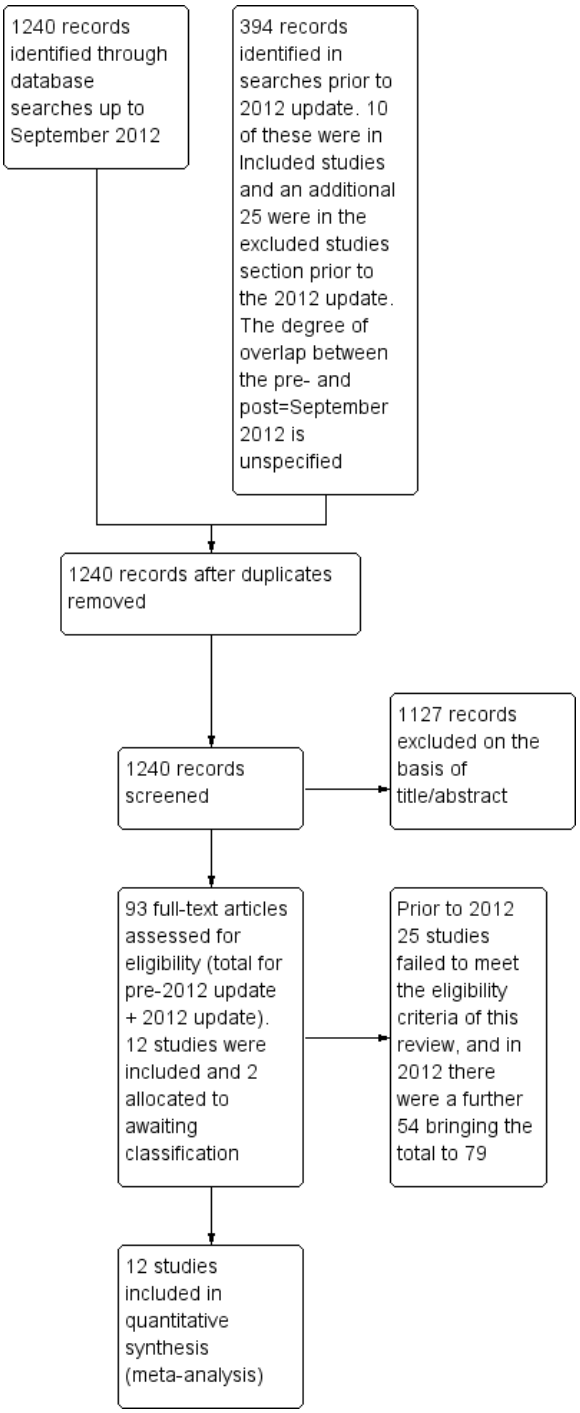
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

In the original version of this review 187 citations were identified in the computerised CARG register search. A total of 12 articles were identified as being potentially relevant, with moderate agreement (kappa = 0.57) between the two review authors. An additional 19 studies were identified from handsearching, review of the reference lists, contact with authors and contact with the pharmaceutical industry. Thirty-one full articles were reviewed for inclusion. Full texts were obtained for published articles; further information was sought about unpublished studies from the authors. From these 31 studies, nine were identified by both review authors for inclusion, with excellent agreement (kappa = 1.0). In the update search in April 1999, 42 further articles were identified. One of these articles was selected for inclusion (Volovitz 1998), giving a total of 10 included articles. Further update searches conducted in February 2002 and February 2003 did not yield any new studies for inclusion in the review. In the 2012 update, searches were re-run and 1240 records were identified through database searching; these searches covered the period addressed by previous searches and the additional period up to September 2012 (Figure 1). These extensive searches added a further two trials to the included studies (Di Franco 2006 (N = 37); Nakanishi 2003 (N = 55)); they were both relevant to the ICS versus oral corticosteroid comparison. No new studies were identified relating to the ICS plus oral corticosteroid to oral corticosteroid alone comparison.

Figure 1. Study flow diagram.



Included studies

The first published study was reported in 1996, and three of the 12 studies were unpublished at the time of this writing. Three were performed in the US (Brenner 2000; Camargo 2000; Nakanishi 2003), two were from Canada (Rowe 1999; Fitzgerald 2000), and one was from each of the UK (Levy 1996), Thailand (Nana 1998), Israel (Volovitz 1998), and Italy (Di Franco 2006). Three were multicentre studies based in the UK (Francis 1997; Verona 1998; Manjra 2000). Seven studies involved adults and five studies involved children. Full details of included studies can be found in the Characteristics of included studies table and the key features are summarised in Table 1; Table 2).

ICS plus oral corticosteroid to oral corticosteroid alone

Three studies compared ICS plus oral corticosteroids to oral corticosteroids alone (Rowe 1999; Brenner 2000; Camargo 2000). All three studies were from North America, and all three involved adolescents or adults (aged 12 to 60 years overall). Earliest mean PEFs in the ED were 40% to 55% predicted in all of these trials, suggesting moderate to severe disease at presentation.

ICS were administered in the intervention group for 20 to 24 days. Different drugs were administered, in doses ranging from moderate to high. ICS were administered by MDI with spacer (Brenner 2000), Diskhaler (Camargo 2000) or Turbuhaler (Rowe 1999). Both groups received a fixed-dose five- to seven-day course of oral prednisone.

Co-interventions included various inhaled $beta_2$-agonists in all studies. The studies permitted concurrent medications to be continued, including theophylline, ipratropium bromide and long-acting $beta_2$-agonists, although they did not permit them to be started during the study, and overall these agents were infrequently used. All three studies excluded patients who were currently using ICS or who had recently used oral corticosteroid.

Two of the three studies reported asthma relapse rates as their primary outcome (Rowe 1999; Camargo 2000), and was reported in the third study (Brenner 2000). Asthma relapse was defined similarly in all three studies (an unscheduled visit for worsening asthma symptoms). Secondary outcomes in two of these studies included the Asthma-specific Quality of Life Questionnaire (AQLQ) and seven-point Likert scales for asthma symptoms (Rowe 1999; Camargo 2000). However, the AQLQs used in each study were different; one used the original, full-length, previously validated AQLQ (Rowe 1999), the other study employed the "mini-AQLQ" (Camargo 2000). The third study recorded incidence of a variety of symptoms on a categorical scale (Brenner 2000). PEF (absolute and % predicted) were also reported in two studies (Rowe 1999; Brenner 2000). All three studies recorded incidence of adverse effects, $beta_2$-agonist use and relapse to hospital admission. Length of follow-up in the three studies was from 20 to 24 days.

ICS versus oral corticosteroid

Nine studies compared ICS alone to oral corticosteroid alone (Levy 1996; Francis 1997; Nana 1998; Verona 1998; Volovitz 1998; Fitzgerald 2000; Manjra 2000; Nakanishi 2003; Di Franco 2006). Five involved only children and four involved only adults. In the adult studies, severity was assessed as mild to moderate (mean forced expiratory volume in one second (FEV_1) 60% to 75% predicted on discharge in two of the studies, and PEF 60% to 90% predicted on presentation in the third study, involving people with less severe asthma exacerbations). In the four paediatric studies where the information was available, PEF were generally 70% to 80% predicted on discharge. In all the studies, patients presenting with severe acute asthma were excluded. In seven of the nine studies, high-dose ICS was compared to tapering doses of oral corticosteroid, while two studies compared high-dose ICS to fixed-dose oral corticosteroid (Fitzgerald 2000; Nakanishi 2003). In six studies, a seven-day course of both treatments was administered. In one study, treatment with ICS for 16 days was compared with 16 days of treatment with a tapering dose of oral corticosteroid (Levy 1996), and in another study similar treatment regimens were given for 14 days (Di Franco 2006). In the final study, 24 days of ICS was compared to eight days of oral corticosteroid treatment (tapered) (Volovitz 1998). The route of administration was by Turbuhaler, Diskhaler or MDI with spacer in all but two of the studies (both in children), where a nebuliser was used. Co-interventions included various inhaled $beta_2$-agonists in all studies. The studies allowed concurrent medications, including theophylline, ipratropium bromide and long-acting $beta_2$-agonists to be continued, although they were infrequently used in all but one study where approximately 57% of the patients were on oral $beta_2$-agonists and 55% were on xanthines (Nana 1998). Four of the five paediatric studies comparing ICS to oral corticosteroid either excluded patients on ICS at presentation, or had a very low (< 2%) enrolment of these patients, while about 25% were on ICS at baseline in the fifth study (Nakanishi 2003). All four adult studies comparing ICS versus oral corticosteroid included patients who had previously been on ICS. In two studies, approximately 35% of the patients were taking ICS at presentation, while about 80% of patients in the other two studies were already on ICS. Patients on oral corticosteroid at presentation were excluded from all of the studies. Two of the five paediatric studies used absolute PEF as the primary outcome (Verona 1998; Manjra 2000), and it was also reported in a third study (Volovitz 1998), while one used % predicted FEV_1 as the primary outcome (Nakanishi 2003). Four of these studies did not report relapse rates (Francis 1997;

Verona 1998; Manjra 2000; Nakanishi 2003), and no patients in the fifth study relapsed (Volovitz 1998). Secondary outcomes in these studies included asthma symptoms, incidence of adverse events and beta$_2$-agonist use. One of the three adult studies used change in FEV_1 as the primary outcome (Nana 1998), and one of the adult studies used asthma relapse rates as the primary outcome (Fitzgerald 2000). The third adult study used "treatment failure" as the primary outcome. Patients were categorised as a treatment failure if (a) PEF fell below 60% of the best/predicted value on two consecutive occasions, or (b) a symptom score of 3 (indicating the symptoms were the same or worse than on entry to the study) was recorded on three or more consecutive days, or (c) the patient withdrew because of uncontrolled symptoms or an adverse event related to asthma (Levy 1996). This outcome was pooled with the data for asthma relapse from other studies in the analyses. The fourth study used change in sputum eosinophil percentage as the primary outcome (Di Franco 2006). Other outcomes in the adult studies included the AQLQ in one study, symptom scores (on a variety of scales) in all studies, PEF and incidence of adverse events. Length of treatment and follow-up in the studies of ICS versus oral corticosteroid was seven days in six of the studies, although two of these studies also recorded absolute PEF at 21 days (but no other outcomes at these times) (Manjra 2000; Verona 1998). The other three studies followed patients for 14 (Di Franco 2006), 16 (Levy 1996) and 24 days (Volovitz 1998).

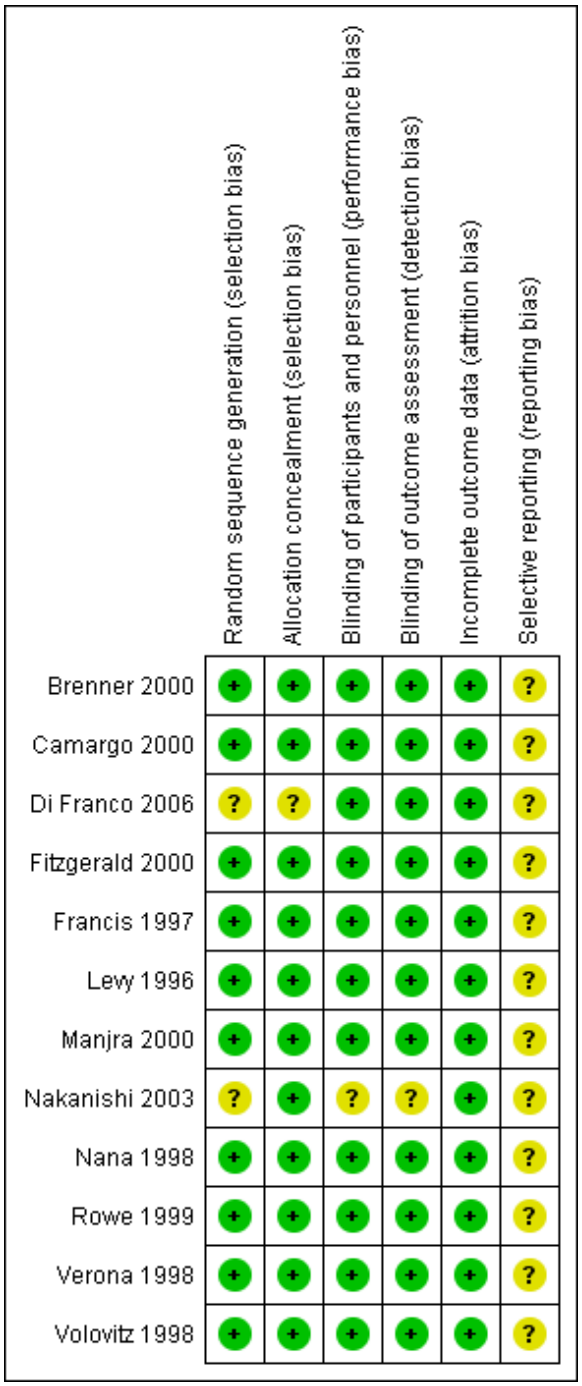
Excluded studies

Prior to 2012, 25 studies failed to meet the eligibility criteria of this review, and in 2012 there were a further 54 bringing the total to 79 (Figure 1). Twenty-two (28%) were excluded on the basis that the treatment focused on treatment in the ED, rather than following discharge; 13 (16%) focused on chronic asthma; in 13 (16%) patients were hospitalised (rather than having been discharged from the ED; six (8%) were not randomised; five (6%) were dose comparisons; four (5%) concerned patient-initiated treatment; two (3%) were reviews; two (3%) compared different ICS; in two (3%) the focus was on the prevention of exacerbations and in another two (3%) systemic corticosteroids were not included in either group. There was a miscellaneous group of additional studies: one (2%) was a comparison between ICS delivery systems; in another the patients were diagnosed with chronic obstructive pulmonary disease rather than asthma; in another the focus was on beta$_2$-agonists (rather than ICS); in another the focus was on intravenous (IV) corticosteroids; in another the exacerbations were induced; another evaluated ED discharge strategy; in another the control group included beta$_2$-agonists or corticosteroids and in another the focus was on home treatment. The reasons for their exclusion are given in Characteristics of excluded studies table.

Risk of bias in included studies

Overall, the methodological quality of the included trials was high. Full details of our judgements can be found in the Characteristics of included studies table and a summary of our judgements can be seen in Figure 2. Most of the trials were double-blind, placebo-controlled, and were reported as using concealment of allocation. Unfortunately, several of the trials in the oral corticosteroid versus ICS comparison did not record relapse rates or admission rates as outcomes, decreasing the power of this review to detect differences between the groups in this outcome. In addition, the definition of relapse varied between trials.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



In all three of the studies of ICS plus oral corticosteroid versus oral corticosteroid, compliance was reported. In two of the studies, compliance was high, with over 90% compliance with oral corticosteroid in both studies, and over 70% compliance with ICS in one of the studies (Camargo 2000), and over 90% compliance with ICS in the second study (Rowe 1999). In the third study, self-reported compliance was much lower (approximately 55%) (Brenner 2000). In the studies of ICS versus oral corticosteroid, compliance was measured in five of the nine studies; however, information on compliance was only available in two, where the compliance with both regimens was reported to be greater than 90% (Volovitz 1998; Fitzgerald 2000).

Allocation

In 10 of the 12 included studies the risk of selection bias was judged to be low (Levy 1996; Francis 1997; Nana 1998; Verona 1998; Volovitz 1998; Rowe 1999; Brenner 2000; Camargo 2000; Fitzgerald 2000; Manjra 2000). In the remaining two, selection bias was judged to be unclear; in Di Franco 2006 the sequence generation and allocation concealment were both assessed as unclear and in Nakanishi 2003 the risk of bias in allocation concealment is unclear.

Blinding

In 11 studies the risk of performance bias and detection bias were regarded as low (Levy 1996; Francis 1997; Nana 1998; Rowe 1999; Verona 1998; Volovitz 1998; Brenner 2000; Camargo 2000; Fitzgerald 2000; Manjra 2000; Di Franco 2006). In Nakanishi 2003 the risk of performance bias and detection bias were assessed as unclear.

Incomplete outcome data

In all 12 included studies attrition bias was judged as low.

Selective reporting

In all 12 trials reporting bias was assessed as unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Any ICS plus oral corticosteroid versus oral corticosteroid for acute asthma following emergency department discharge; **Summary of findings 2** Any ICS versus oral corticosteroid for acute asthma following emergency department discharge

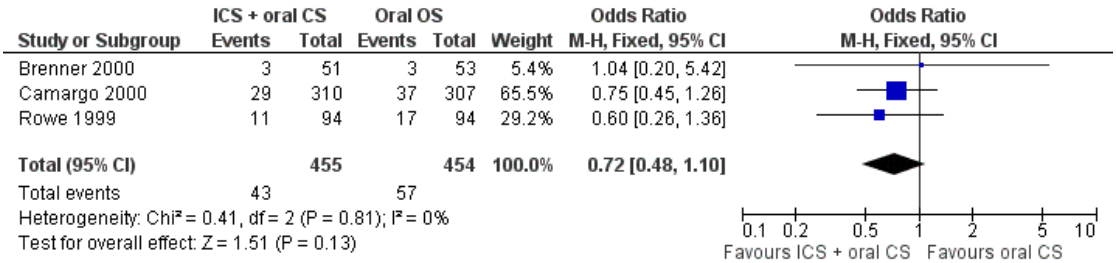
Results of the meta-analyses are reported by outcome. They are reported separately for the two types of studies: comparing ICS plus oral corticosteroids versus oral corticosteroids alone, and comparing ICS alone versus oral corticosteroids alone.

ICS plus oral corticosteroids versus oral corticosteroids alone

Asthma relapse

There were no statistically significant differences in the number of people experiencing an asthma relapse between patients treated with ICS and those on placebo. However, there was a trend towards benefit of ICS at both 7- to 10-day (OR 0.72; 95% CI 0.48 to 1.10; 3 studies; N = 909; Analysis 1.1; Figure 3) and 20- to 24-day follow-up (OR 0.68; 95% CI 0.46 to 1.02; 3 studies; N = 909; Analysis 1.2). The pooled results did not demonstrate significant heterogeneity at seven to 10 (I^2 = 0%) or 20 to 24 (I^2 = 0%) days.

Figure 3. Forest plot of comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid, outcome: 1.1 Asthma relapse at 7-10 days.



Subgroup analyses did not show significant differences in the ORs for relapse between males and females. The OR for relapse for males at seven to 10 days was 0.96 (95% CI 0.21 to 4.43; 3 studies; N = 296; Analysis 1.22), while the OR for relapse for females was 0.79 (95% CI 0.34 to 1.82; 3 studies; N = 424; Analysis 1.22). There was moderate heterogeneity (I^2 = 59% males; 40% females and 45% combined), and the random-effects model was used. At 20 to 24 days, the OR for relapse for males was 0.60 (95% CI 0.22 to 1.62; 3 studies; N = 315; Analysis 1.23), while for females it was 0.78 (95% CI 0.30 to 1.99; 3 studies; N = 446; Analysis 1.23). Again there was moderate heterogeneity in the subgroups (I^2 = 31% males; 58% females and 46% combined). The random-effects model was used for this outcome due to the extent of heterogeneity.

Using the random-effects model, there was minimal change in the overall results for admission rates: the OR for admission at seven to 10 days was 0.72 (95% CI 0.48 to 1.10), and at 20 to 24 days was 0.69 (95% CI 0.46 to 1.03).

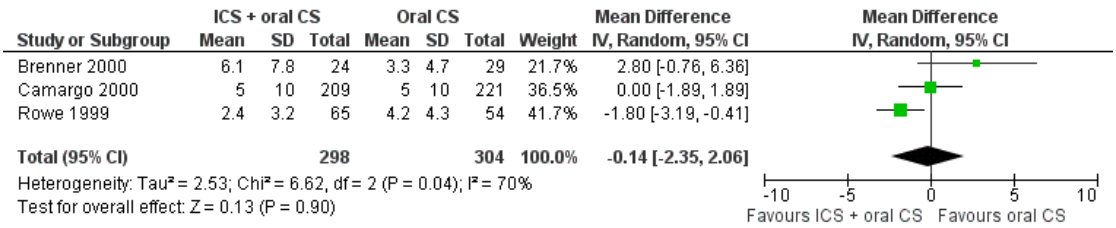
Hospital admission

Hospital admissions were only reported in two studies and were rare events with only 2% of patients being admitted. There was no difference demonstrated in hospital admissions between the groups (OR 0.99; 95% CI 0.39 to 2.52; 2 studies; N = 805; Analysis 1.3), and there was no heterogeneity (I^2 = 0%) between the two studies.

Beta$_2$-agonist use

There was no significant difference in beta$_2$-agonist use between the groups at seven to 10 days (MD 0.51; 95% CI -0.44 to 1.47; 3 studies; N = 672; Analysis 1.4) with no significant statistical heterogeneity (I^2 = 20%). At 20 to 24 days, a high level of heterogeneity (I^2 = 70%) was identified. The overall difference was small (MD -0.14; 95% CI -2.35 to 2.06; 3 studies; N = 602; Analysis 1.5; Figure 4) using the random-effects model.

Figure 4. Forest plot of comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid, outcome: 1.5 Beta$_2$-agonist use at 20-24 days.



Pulmonary function

Two trials recorded PEF (absolute and % predicted). There were no significant differences between the groups in absolute PEF at seven to 10 days (MD -0.88; 95% CI -28.49 to 26.72; 2 studies; N = 205 Analysis 1.6), absolute PEF at 20 to 24 days (MD -4.55; 95% CI -35.91 to 26.81; 2 studies; N = 176; Analysis 1.7), % predicted PEF at seven to 10 days (MD -1.79; 95% CI -11.04 to 7.46; 2 studies; N = 206; Analysis 1.8) or % predicted PEF at 20 to 24 days (MD -2.34; 95% CI -9.44 to 4.77; 2 studies; N = 172; Analysis 1.9).

Quality of life

Two trials reported quality of life. Pooled results did not show a significant effect of ICS at either seven to 10 days (MD 0.19; 95% CI -0.01 to 0.39; Analysis 1.10) or 20 to 24 days (MD 0.33; 95% CI -0.36 to 1.01; Analysis 1.11); however,there was considerable heterogeneity at 20 to 24 days (I^2 = 88%), with one trial showing a significant benefit of ICS and the other showing no effect.

Asthma symptoms

Two studies recorded data on cough, dyspnoea and wheeze on a seven-point Likert scale. At seven to 10 days, there was no statistical difference between the groups in any of the symptoms, although there was a high level of heterogeneity (I^2 = 79%) between the trials for dyspnoea. At 20 to 24 days, there was considerable heterogeneity in all three outcomes (cough: I^2 = 80%; dyspnoea: I^2 = 88%; wheeze: I^2 = 87%), with one trial Rowe 1999 showing a strong, statistically significant benefit of ICS therapy for all three outcomes, and the other (Camargo 2000) demonstrating no effect of ICS therapy. Pooling the results using a random-effects model did not produce statistically significant differences between the

groups. Furthermore, the point estimates for the difference were all < 0.5, which would not be considered clinically important.

Side effects

Two studies recorded data on hoarseness and sore throat (Rowe 1999; Camargo 2000). There were no statistically significant differences between the treatment groups at any time for either side effect. At seven to 10 days, the OR for hoarseness in the group receiving ICS treatment was 0.88 (95% CI 0.53 to 1.46; 2 studies; N = 612; Analysis 1.18) and at 20 to 24 days it was 0.60 (95% CI 0.36 to 1.01; 2 studies; N = 596; Analysis 1.19). There was no noticeable statistical heterogeneity at either time interval (seven to 10 days: I^2 = 25%; 20 to 24 days: I^2 = 55%). For sore throat, the OR was 0.73 (95% CI 0.43 to 1.24; 2 studies; N = 612; Analysis 1.20) at seven to 10 days and 0.64 (95% CI 0.35 to 1.16; 2 studies; N = 596; Analysis 1.21) at 20 to 24 days, with no heterogeneity at seven to 10 days (I^2 = 0%) but moderate heterogeneity at 20 to 24 days (I^2 = 64%).

Subgroup/sensitivity analyses

Pre-specified subgroup analyses comparing asthma relapse in men and women did not identify any significant difference in results according to sex (Analysis 1.22; Analysis 1.23).

We calculated pooled treatment effects for asthma relapse using intention-to-treat analyses. Because of marked differences in the rate of follow-up between the trials, we repeated the analyses excluding all patients who were lost to follow-up. The relapse rates were very similar to those in the primary analysis, with no statistically significant differences between the groups (seven to 10 days: OR 0.72; 95% CI 0.47 to 1.10; 3 studies; N = 725; Analysis 1.24; 20 to 24 days: OR 0.70; 95% CI 0.46 to 1.05; 3 studies; N = 768; Analysis 1.25).

ICS alone versus oral corticosteroid alone

Asthma relapse

Only four of seven studies reported asthma relapse rates, and one of these studies had no patients who relapsed. At seven to 10 days, there was no demonstrated difference in asthma relapse between the groups (OR 1.0; 95% CI 0.66 to 1.52; 4 studies; N = 684; Analysis 2.1; Figure 5). There was no statistical heterogeneity among the studies (I^2 = 0%). Only two studies followed patients beyond 10 days, one of which had no relapses, and at a 16-day follow-up, there was no significant difference in relapse rates between the groups (OR 1.26; 95% CI 0.80 to 1.99; 2 studies; N = 425; Analysis 2.2; Figure 6).

Figure 5. Forest plot of comparison: 2 Any ICS versus oral corticosteroid, outcome: 2.1 Asthma relapse at 7-10 days.

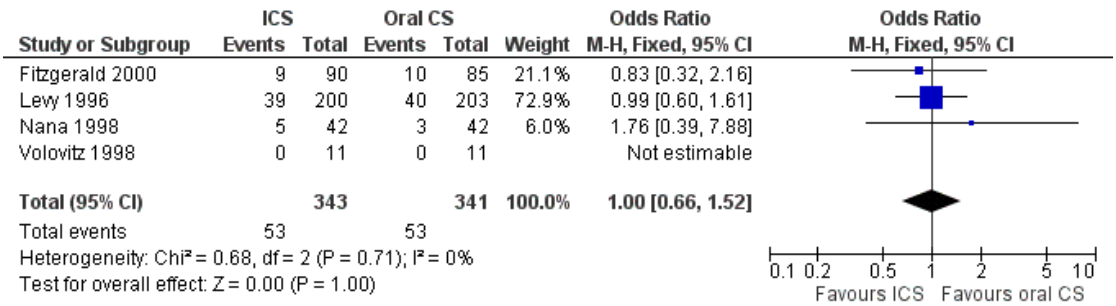
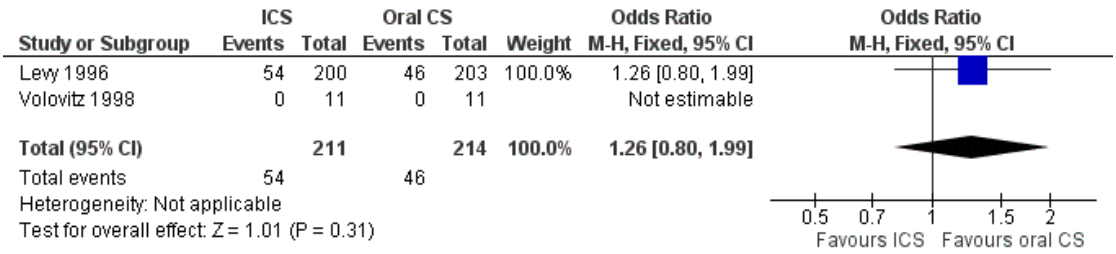


Figure 6. Forest plot of comparison: 2 Any ICS versus oral corticosteroid, outcome: 2.2 Asthma relapse at 16-21 days.



Hospital admission

Three studies reported hospital admission (OR 0.31; 95% CI 0.01 to 7.95; 3 studies; N = 254; Analysis 2.3) and there was no significant difference between the two groups; however, the overall proportions requiring hospital admission were very low.

Pulmonary function

Six studies reported absolute PEF at 7 to 10 days, and four studies at 16 to 21 days, while only two studies reported % predicted PEF at both time points. At 7 to 10 days, the difference in absolute PEF between the two groups was not statistically significant, with the PEF in the ICS treated group higher than in the control group (OR 0.72; 95% CI 0.47 to 1.10; 6 studies; N = 1047; Analysis 2.4). At 16 to 21 days, there was a statistically significant but clinically insignificant improvement in PEF in the ICS-treated group (MD 15.21; 95% CI 1.53 to 28.89; 4 studies; N = 792; Analysis 2.5). There was relatively low heterogeneity (7 to 10 days: I^2 = 33%; 16 to 21: I^2 = 0%). There was no significant difference between the groups for % predicted PEF at 7 to 10 days (MD -0.74; 95% CI -3.12 to 1.64; 2 studies; N = 376; Analysis 2.6), with the point estimate for the difference being very small (< 1% predicted); the heterogeneity was I^2 = 0%.

In 2012, we added two additional outcomes for FEV_1 and FEV_1 % predicted. The analysis for 6 to 10 days following discharge (MD -17.80; 95% CI -26.98 to -8.62; 1 study Nakanishi 2003; N = 55; Analysis 2.8) favours oral corticosteroid treatment. However no difference was found between the two groups at 16 to 21 days (MD -7.20; 95% CI -20.84 to 6.44; 1 study Di Franco 2006; N = 37; Analysis 2.9). As these analyses are each based on a single small trial we would stress the need for caution in interpreting these data. The Nakanishi 2003 study reported % predicted FEV_1 and forced vital capacity (FVC) at 3 and 7 days, while Di Franco 2006 reported % predicted FEV_1 at 14 days only.

beta$_2$-agonist use

Information on beta$_2$-agonist use was only available in three studies at seven to 10 days (Nana 1998; Volovitz 1998; Di Franco 2006); and in one study at 14 to 21 days (Di Franco 2006). As in the previous version of the review there was no significant difference between the treatment groups in beta$_2$-agonist use at seven to 10 days (MD 0.08; 95% CI -0.47 to 0.64; 3 studies; N = 128; Analysis 2.10). Prior to the 2012 update there had been no data available for this outcome at 16 to 21 days; however, there is now one study with relevant data at two weeks (Di Franco 2006, which reported the amount of inhaled rescue medication (assumed to be beta$_2$-agonists), indicating no significant difference between the two conditions (MD -0.10; 95% CI -1.32 to 1.12; 1 study; N = 37; Analysis 2.11).

Quality of life

Only two studies reported quality of life information. There was no significant difference between the groups in quality of life (SMD 0.14; 95% CI -0.12 to 0.40; 2 studies; N = 231; Analysis 2.12).

Asthma symptoms and side effects

Due to insufficient and varied reporting, there was insufficient information to determine the effect of treatment on asthma symptoms and adverse effects of treatment. However, the rate of side effects appeared low and balanced in each study.

The primary outcome for Di Franco 2006 was change in sputum eosinophil percentage between the initial visit and two-week follow-up visit, but they showed no difference between the groups in this relatively small study (20 patients per group). They also provided information on a symptom score at 14 days (when there was no significant difference between the groups); however, this was felt to be different enough from the quality-of-life scores that it was not included in the meta-analysis. Information on specific symptoms (cough, wheeze, dyspnoea), which were pre-specified in the review, were not reported.

Subgroup analyses

There were insufficient data to perform subgroup analyses.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Any ICS versus oral corticosteroid for acute asthma following emergency department discharge

Patient or population: patients with acute asthma following emergency department discharge
Settings:
Intervention: any ICS versus oral corticosteroid

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Any ICS versus oral corticosteroid				
Asthma relapse[1] at 16 to 21 days	**215 per 1000**	**257 per 1000** (180 to 353)	**OR 1.26** (0.8 to 1.99)	425 (2 studies)	⊕⊕⊕◯ **moderate**[2]	Adults in 1 study Levy 1996 and children in the other Volovitz 1998
Hospital admission mean follow-up period: 9 to 10 days	**8 per 1000**	**3 per 1000** (0 to 61)	**OR 0.31** (0.01 to 7.95)	254 (3 studies)	⊕⊕⊕◯ **moderate**[2]	Adults in 1 study Fitzgerald 2000 and children in the other two Nakanishi 2003 and Volovitz 1998
Hoarseness at 16 to 21 days	**24 per 1000**	**39 per 1000** (13 to 112)	**OR 1.62** (0.52 to 5.05)	412 (1 study)	⊕⊕◯◯ **low**[2,3]	Adults in 1 study Levy 1996

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Relapse was defined in the largest study, Levy, as ' ' treatment failure". Patients were categorised as a treatment failure if (a) PEF fell below 60% of the best/predicted value on two consecutive occasions, or (b) a symptom score of 3 (indicating the symptoms were the same or worse than on entry to the study) was recorded on three or more consecutive days, or (c) the patient withdrew because of uncontrolled symptoms or an adverse event related to asthma. In the other two studies relapse was defined as need for additional oral corticosteroid therapy or an unscheduled visit for asthma symptoms.

[2] Point deducted for imprecision due to wide confidence intervals.

[3] Point deducted for hoarseness at 16 to 21 days as data contributed by only one study.

DISCUSSION

Summary of main results

This systematic review examined the best available evidence for the use of ICS in the management of patients with asthma exacerbations after discharge from the ED or other acute care settings. There are several important findings that arise from this meta-analysis. First, despite an exhaustive search and the existence of recommendations supporting the use of ICS in outpatient treatment of acute asthma (Boulet 1998; Emond 1997) only 12 trials were identified, many of which were small, and there were marked variations in the study designs. Clearly this is an area where further research is needed.

Second, there were two distinct potential roles for ICS therapy in this setting: either in addition to standard therapy with systemic corticosteroids, or as a substitute for systemic corticosteroids. For both types of studies in this review (ICS plus oral corticosteroid versus oral corticosteroid alone; ICS versus oral corticosteroid), most pooled results did not demonstrate significant differences between the treatment approaches. This lack of statistical significance has very different implications for the two comparisons, and the two approaches will therefore be discussed separately.

ICS plus oral corticosteroid versus oral corticosteroid

There was a total of 909 patients included in the studies: 455 treated with ICS plus oral corticosteroid, and 454 treated with oral corticosteroid alone. The pooled results of studies on the effect of the addition of ICS to standard oral corticosteroid therapy failed to demonstrate a statistically significant benefit on the primary outcome, asthma relapse, despite a trend in favour of ICS at both seven to 10 and 20 to 24 days. In addition, there appeared to be no benefit on the secondary outcomes of hospital admission or pulmonary function tests. Interpretations of the other pooled outcomes (e.g. quality of life, beta$_2$-agonist use and asthma symptoms) was limited by statistically significant heterogeneity and variable reporting.

Despite the presence of a statistically and clinically important sex difference in one study (Camargo 2000), the sex-treatment interaction did not reach statistical significance in this meta-analysis and heterogeneity was demonstrated. While it is unclear at this time if this subgroup finding is valid, the hypothesis warrants detailed exploration in future research. In addition, none of these studies included children under the age of 12 years, so further study in younger children may be indicated.

The primary role of ICS in chronic stable asthma is clear; however, the role of adding ICS for emergency physicians and other healthcare providers treating acute asthma remains unclear. Since many patients with severe acute asthma already meet criteria for ongoing treatment with ICS by current guidelines, adding the agent may be a wise 'preventive' measure upon ED discharge. In mild or moderate acute asthma where there is a low risk of relapse, treatment may not be immediately beneficial. Since the treatment appears safe and side effects are uncommon, the main issue in these cases may be the cost of the drug. Moreover, the interpretation of the pooled results for the primary outcome suggests the potential benefit may be large (OR = 0.46) and the risk of a detrimental effect is small (OR = 1.02)

Of note, there was no significant effect of ICS therapy demonstrated on pulmonary function tests. The point estimates for the differences between the groups for absolute PEF were less than 5 L/min or less than 3% predicted at all time intervals. This is consistent with the systematic reviews of ICS therapy in the ED treatment of asthma, and of oral corticosteroid therapy in the ED treatment of asthma, where there was minimal effect of oral corticosteroid therapy on pulmonary function tests, despite beneficial effects on other outcomes (Rodrigo 1999; Edmonds 2003; Rowe 2003).

ICS alone versus oral corticosteroid alone

In Edmonds 2000 there were seven studies contributing to this comparison; five were published (Levy 1996; Nana 1998; Volovitz 1998; Fitzgerald 2000; Manjra 2000) and two were unpublished (Francis 1997; Verona 1998; both in abstract form only). A total of 1204 patients were incorporated. Unfortunately, despite the relatively large number of patients included in these trials, the studies varied markedly in their reported outcomes, and smaller numbers of patients contribute to each of the individual outcomes. In 2012 two additional studies were added (Nakanishi 2003; Di Franco 2006) contributing data from a further 92 patients to increase the total to 1296.

There was no statistically significant difference between the treatments for asthma relapse, at either seven to 10 or 16 to 21 days. The important question to be answered is whether or not there is sufficient information to conclude these two treatments are equivalent (similar). At seven to 10 days, the OR for relapse was 1.0, with the 95% CI from 0.66 to 1.52, which suggests potential difference beyond what would be the minimally clinically important difference (MCID). Only one study contributed data to the 16-day outcome, with an OR for relapse of 1.26 (95% CI 0.80 to 1.99), again providing imprecise estimates of the true effectiveness. None of the studies were powered for equivalence, and the pooled results are **not** compatible with equivalent efficacy between the two treatments. Although three studies reported admission rates, the admission rates were very low overall (one patient only), so the point estimate for difference in admission needs to be viewed with caution, as reflected by the wide CI values (OR 0.31; 95% CI 0.01 to 7.95).

These studies included only patients with relatively mild asthma, as evidenced by the inclusion criteria and relapse rates. One of the studies defined relapse as the failure of symptoms or peak flow to improve, a definition different from all other studies included in this review. This definition would likely include less 'severe' relapses, and it is not clear if this is an appropriate surrogate outcome for relapses resulting in an additional acute care visit (Levy 1996).

This was the largest study contributing to this outcome (403 of 684 total patients), and were its data not included, the range of uncertainty for the treatment effect would be much broader.

Several studies used absolute PEF as the primary outcome. There was a small, statistically significant improvement in PEF in the group treated with ICS at 20 to 24 days, with an improvement of 15 L/min compared with the oral corticosteroid-treated group. The minimum difference in pulmonary function tests that is considered clinically significant has been infrequently studied in this setting. In the adult population, a minimum improvement of approximately 30 L/min in PEF (Tiffany 1993), or a 10% to 12% predicted rise in PFT is likely to be necessary to demonstrate a clinically important difference. The small improvement in peak flow demonstrated here would be unlikely to be important to patients, particularly in the absence of other demonstrated benefits of ICS therapy. Only a small number of studies reported rescue medication use: there was no clear benefit to either therapy in this outcome.

Other outcomes, including quality of life, asthma symptom scores and side effects, were recorded and reported in diverse ways, with little information that was amenable to pooling. Many of the trials used new scales with questionable validity for measuring these outcomes. In addition, the information for several of the trials was reported incompletely, precluding the incorporation of these results in the meta-analyses.

In the conclusions for seven of the nine trials, it was stated that ICS therapy may be substituted for oral corticosteroid therapy after an acute asthma attack, as there were no significant differences demonstrated between the treatments. None of these trials (two of which were published in abstract form only) discussed the possibility of type II error in drawing these conclusions, and only one presented a power calculation but did not have the required number of patients in the trial. Four of the trials based their conclusions on a lack of statistically significant differences in results from lung function tests between the treatment groups. However, this may not be an appropriate outcome to use in assessing clinical equivalence. Lung function has not been shown to be responsive to treatment with corticosteroid agents in other systematic reviews in acute asthma (Rodrigo 1999; Edmonds 2003; Rowe 2003), despite improvements in other clinical markers. One trial (Di Franco 2006) was unable to find a significant difference between the treatment groups for changes in percentage of sputum eosinophils, which has been shown to be helpful in monitoring chronic asthma, but is not well studied in acute asthma (Green 2002). The seventh trial did present a priori sample size calculations, but was unable to accrue the required number of patients in the trial and had a calculated power of only 57% to demonstrate a clinically significant difference in relapse rates (Levy 1996).

Overall completeness and applicability of evidence

There was heterogeneity among the studies for several of the secondary outcomes including symptoms and quality-of-life, particularly in the ICS plus oral corticosteroid versus oral corticosteroid comparison. This heterogeneity may affect the pooled result for the primary outcome as well, potentially obscuring a subgroup of patients in whom ICS therapy may provide a more marked benefit. To investigate the heterogeneity further, differences between studies in design, populations, outcomes and interventions used need to be considered. One potential explanation for the heterogeneity between the studies might be the dose of ICS used. The study that showed clear benefit of ICS on several outcomes (Rowe 1999) used high-dose ICS, while the two studies that did not show a beneficial effect of ICS used moderate-dose ICS (Brenner 2000; Camargo 2000). However, this is a between-study comparison made after the completion of the review, and should only be considered as a hypothesis for future research. The small number of studies did not permit other meaningful comparisons to be made in this systematic review. A meta-analysis using individual patient data from the studies may be more informative. In the ICS versus oral corticosteroid comparison, all of the studies included patients with relatively mild asthma exacerbations: these results should not be generalised to those with more severe exacerbations.

Quality of the evidence

It is not surprising that these studies, and a meta-analysis of them, failed to generate conclusive results, as the trials were relatively small. For asthma relapse, if baseline asthma relapse rates were 10%, to show a 50% reduction in the risk of relapse (5% absolute risk reduction), 621 patients would be required in each arm of a trial to demonstrate this difference with a power of 80% and alpha level of 5%. If the goal was to demonstrate a 25% relative risk reduction (2.5% absolute risk reduction), 2764 patients would be needed in each group (for a total sample size of 5528 patients).

While the studies in the ICS versus oral corticosteroid comparison provide some evidence that ICS therapy alone may be effective in people with mild asthma exacerbations upon ED discharge, there is insufficient evidence at this point to support the use of ICS, rather than oral corticosteroid, as the standard of care. People with more severe asthma exacerbations were not included in these studies, so these results cannot be extrapolated to this population. Moreover, the cost differences between the two are also an important consideration (with an approximate cost of USD0.10 per day for prednisone, versus USD0.80 per day for ICS). If further trials in this area support a conclusion of equivalence between these therapies, there would need to be evidence of other compelling reasons to use ICS in place of oral corticosteroid therapy, such as side effect profile, symptom control or compliance, which were not evident in this systematic review. Perhaps the most compelling reason for using ICS on discharge from the ED following an exacerbation is that it can form the start of an appropriate chronic asthma management programme for that patient.

With regard to random sequence generation 10 trials were judged to be low in risk of bias (selection bias). The risk of bias for two of the remaining trials was unclear. In terms of the blinding of participants and personnel 11 trials were judged to be at low risk of performance bias. In just one trial the risk was judged to be unclear. All 12 were regarded as low risk of bias in terms of attrition bias.

Potential biases in the review process

There is a possibility of publication bias in this meta-analysis. By missing unpublished negative trials, we may be over-estimating the effect of ICS therapy when used in addition to oral corticosteroid therapy, or we may be missing trials that would add more support the conclusion that ICS are as efficacious as oral corticosteroid in people with mild asthma. However, a comprehensive search of the published literature was conducted, and attempts to uncover unpublished trials were made by corresponding with authors and the pharmaceutical companies that manufacture ICS. We recognise that unpublished trials may exist.

There is also a possibility of selection bias; however, two independent review authors selected studies for inclusion, and criteria for study inclusion and exclusion were explicitly specified. Finally, this is an evolving area, and it will be important to re-evaluate this topic area in the future.

Agreements and disagreements with other studies or reviews

This review updated the previous systematic review (Edmonds 2000). Despite an extensive search we only found two new studies to include, both in the ICS versus oral corticosteroid comparison, and they had few data amenable to inclusion in the review. Data were added to the previous analyses for hospital admission and beta$_2$-agonist use at 14 to 21 days, and two new outcomes were added: FEV_1 % predicted at six to 10 days and 16 to 21 days to include data from these two studies. However, all of these outcomes had only one study contributing to each time point, and the overall conclusions of the review were unchanged.

AUTHORS' CONCLUSIONS

Implications for practice

1. There is insufficient evidence from primary studies to support the hypothesis that the addition of ICS therapy to standard oral corticosteroid therapy is beneficial in the treatment of acute asthma upon ED discharge.

2. ICS alone do not appear to be less effective than standard oral corticosteroid therapy for acute asthma, but there is insufficient evidence to state that they are of equivalent efficacy. There is some support for the use of ICS alone in people with mild asthma exacerbations; there is no evidence to support this practice in moderate or severe acute asthma exacerbations.

3. Until further research results are available, the mainstay of therapy in outpatients with acute asthma remains oral corticosteroid for five to 10 days (Rowe 2003), or in some cases IM agents.

4. The results of ICS plus oral corticosteroid versus ICS alone do not apply to young children since none of the studies involved patients younger than 12 years of age.

5. The addition of ICS should be made on an individual basis using patient preferences, past asthma control and physician experience.

Implications for research

There are many unanswered questions about the use of ICS in acute asthma treatment upon ED discharge.

1. Additional research is required to determine if there is a beneficial effect of ICS therapy in addition to standard oral corticosteroid therapy in severe acute asthma exacerbations. Despite the lack of overall benefit, this may be because of heterogeneity between the trials. Further research involving predefined subgroups (particularly asthma severity and gender) appears warranted.

2. An individual patient data meta-analysis of these trials may help clarify where further research should be directed.

3. Trials designed to compare the possibility of substituting ICS therapy for standard oral corticosteroid therapy should be designed as equivalence trials, with a clear, a priori definition of what will be accepted as proof of equivalence, and adequate sample sizes to address this question.

4. Future research in this area should focus on clearly defined, clinically important outcomes, with clear definitions for asthma relapse, admission, timing and type of pulmonary function testing, and length of follow-up.

5. Pulmonary function tests should not be used as the primary outcome for these trials. Overall, the primary studies investigating oral corticosteroid and ICS in acute asthma treatment, as well as the meta-analyses, do not show a significant acute effect of corticosteroid therapy on pulmonary function, despite beneficial effects on other, clinically important outcomes such as admission or relapse rates.

6. Further RCTs involving children (especially below 12 years of age) are required to examine the benefit of ICS following discharge from the ED when used in addition to oral corticosteroids.

ACKNOWLEDGEMENTS

The original version of this review in 2000 included the following acknowledgment: the authors wish to acknowledge the assistance of Stephen Milan, Anna Bara and Jane Dennis of the Cochrane Airways Review Group. Several drug companies and authors provided additional information about published and unpublished studies as well. Jennifer Haddon (Astra Pharma, Canada) provided additional data and other references for studies. Dr Elisabeth Stahl (Astra Draco AB) and Toni Maslen (Glaxo Wellcome UK) both provided additional information about an included study. Dr B. Volovitz provided additional information as well as additional data analysis. Glaxo Wellcome UK provided information about their sponsored studies. Dr Mark Levy suggested an additional study for inclusion.

In 2012 the authors responsible for the update of this review would particularly like to acknowledge the excellent support and assistance from Emma Welsh, Liz Stovold and Emma Jackson of the Cochrane Airways Review Group, together with the greatly appreciated guidance from Chris Cates (Cochrane Airways Review Group Co-ordinating Editor). We would also like to thank Alexey Seniukovich and Taixiang Wu for the translation of potentially relevant trials. We are also most grateful to Jos Verbeek for his assistance with the translation of a clinical trial. The support provided by librarians Judith Scammel, Jane Appleton and Hilary Garrett at St Georges University London is also greatly appreciated.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brenner 2000

Methods	Design: parallel group, double-blind, randomised trial
Participants	Eligible: 551 Enrolled: 104 (51 flunisolide: 53 placebo) Completed: 73 (33 flunisolide: 40 placebo) Sex (male/female): flunisolide 43%/57%; placebo 26%/74% Asthma diagnosis: previous physician diagnosis of asthma Inclusion criteria: age 18 to 50 years, previous diagnosis of asthma, with PEF < 70% predicted after 1 $beta_2$-agonist treatment Major exclusions: co-morbid pulmonary diseases such as COPD, sarcoid or pneumocystis pneumonia that could interfere with the diagnosis of asthma, repeat visits during the study period, use of ICS within 1 week, use of OC within 1 month of the study, leaving against medical advice or prior to discharge or unlikely to be compliant with study protocol. Discharge PEF % predicted: flunisolide 76, placebo 76
Interventions	Setting: 1 large, inner city teaching hospital with an annual census of 65,000 Intervention: study group received flunisolide 1 mg twice daily by MDI and aerochamber for 24 days; control group received placebo twice daily by MDI and aerochamber Standard of care: both groups received prednisone 40 mg PO daily for 5 days, and used albuterol MDI as needed. Other asthma medications were not allowed, except for antibiotics
Outcomes	The primary outcome was % predicted PEF at clinic visits on days 3, 7, 12, 21 and 24. Secondary outcomes included symptom assessments, including general well-being, dyspnoea at rest, dyspnoea with exercise, general wheeze and cough. These symptoms were graded on a 4-point scale, with a 1 for any symptoms, 2 if the symptoms were better than at the previous visit, 3 if the symptoms were the same and 4 if they were worse. Presence or absence of wheeze at night was also assessed
Notes	Dr. Brenner contributed to the review and provided an additional reference for possible inclusion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generation of random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation

Brenner 2000 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients in the flunisolide group withdrew because of coughing. In the flunisolide group, 16 patients were lost to follow-up; in the placebo group, 13 patients were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Camargo 2000

Methods	Design: parallel group, double-blind, randomised trial
Participants	Eligible: unknown Randomised: 617 (310/307) Completed: 517 (257/260) Sex (male/female): 46%/54% Asthma diagnosis: doctor's diagnosis Inclusion criteria: acute asthma with initial PEF < 80% predicted, age 12 to 54 years, decision by ED attending to discharge the patient home on prednisone, able to give informed consent Major exclusions: use of ICS in the 4 weeks before ED visit, use of systemic corticosteroids during the 4 weeks before ED visit, prior enrolment in MARC-4 Baseline PEF % predicted (SD): fluticasone 47.3 (16.2), placebo 45.9 (16.7)
Interventions	Setting: 41 EDs, in 16 US states Interventions: treatment group received inhaled fluticasone 250 μg by Diskhaler twice daily for 20 days, while the control group received placebo by Diskhaler twice daily for 20 days Standard of care: both groups received prednisone 50 mg PO daily for 5 days and inhaled albuterol as needed
Outcomes	The primary outcome was asthma relapse (worsening asthma that led the patient to seek urgent medical treatment) Secondary outcomes included quality of life, measured by the mini-AQLQ, $beta_2$ -agonist use, symptoms and side effects. All outcomes were ascertained by telephone follow-up at days 10 and 20
Notes	Dr. Camargo and Sunday Clark provided information about this study on behalf of the MARC investigators

Camargo 2000 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Correspondence with author has confirmed that the trial was double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low. Confirmed with author
Incomplete outcome data (attrition bias) All outcomes	Low risk	53 from the fluticasone group, 47 from the placebo group
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Di Franco 2006

Methods	Design: parallel group, double-blind, double-dummy, randomised trial
Participants	40 non-smoking adult patients at an asthma clinic with an exacerbation of known asthma not requiring hospitalisation were consecutively recruited in this study over the 24-month study period (20 in each group). 18 completed the study in the inhaled fluticasone 1000 mg twice daily group and 19 completed in the oral prednisone group Inclusion criteria: outpatients of the asthma clinic who had attended within the previous 12 months, with an established asthma diagnosis. Exacerbation was defined by the occurrence of daily symptoms for $\geq$ 5 days, not completely controlled by short-acting beta$_2$-agonists, associated with a > 20% decrease in FEV_1 in comparison with the personal best value (measured in the previous year) and with a FEV_1 after bronchodilator of < 70% of predicted Exclusion criteria: patients may have received their usual antiasthma treatment, but were excluded if they had been treated with systemic corticosteroids for this exacerbation Baseline lung function: FEV_1 mean ± SD: 1.55 ± 0.56 L (inhaled fluticasone group) versus 1.45 ± 0.48 L (oral prednisone group) Mean age (SD) (years): 43.1 (11.8) (inhaled fluticasone group) versus 46.0 (15.3) (oral prednisone group) Sex (male/female): fluticasone 4/16, prednisone 4/16 Baseline lung function (pre-bronchodilator); mean ± SD % predicted FEV_1: 53.9 ± 16.8 (inhaled fluticasone group), 51.5 ± 14.4 (oral prednisone group) Baseline ICS use: 14/18 inhaled fluticasone group, 16/19 oral prednisone group

Di Franco 2006 (*Continued*)

Interventions	Group A received inhaled fluticasone propionate 2000 mg/daily (4 puffs of 250 mg in the morning and in the evening with a large spacer) and oral prednisone placebo for 2 weeks. Group B received prednisone 40 mg/day PO tapered to 10 mg/day by reducing the dose by 5 mg every other day and inhaled placebo for 2 weeks. Patients withheld their usual regular ICS treatment but continued to use their previous regular bronchodilator treatment (including oral theophylline), during the study period
Outcomes	Primary outcome: change in sputum eosinophil percentage between visit 1 and 2 weeks after treatment Other outcomes: oxygen saturation, morning and evening PEF, symptom score, use of rescue medications, side effects Blood samples Side effects possibly related to corticosteroids were reported by 3 patients in fluticasone group (oropharyngeal, candidiasis, hoarseness), and by 2 patients in prednisone group
Notes	ICS versus oral corticosteroid comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation unclear
Allocation concealment (selection bias)	Unclear risk	Allocation concealment unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 subjects (1 male and 2 female) were not able to collect spontaneous or induced sputum, and they were excluded from the study
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Fitzgerald 2000

Methods	Design: parallel group, double-blind, double-dummy, randomised trial
Participants	Eligible: volunteer patients Randomised: 185 (92 budesonide; 93 prednisone) Completed: 151 (73 budesonide; 78 prednisone)

Fitzgerald 2000 (*Continued*)

	Sex (male/female): budesonide 38/52, prednisone 37/48 Asthma diagnosis: history of asthma as per ATS criteria Inclusion criteria: age 15 to 50 years (revised from 15 to 70 years part way through study) , acute asthma with a progressive increase in dyspnoea, FEV_1 > 50% predicted prior to discharge, willing to return for follow-up and give informed consent, and able to use a Turbuhaler Major exclusions: intolerance or adverse reactions to oral corticosteroids or ICS, current or previous peptic ulcer disease, insulin-dependent diabetes, tuberculosis or fungal infection, pregnant or lactating, use of oral corticosteroids within 4 weeks, or current use of > 1600 μg/day ICS
Interventions	Setting: multicentre trial in Canadian EDs Intervention: the study group received budesonide 600 μg 4 times daily by Turbuhaler for 7 to 10 days (mean 7.5 days), while the control group received prednisone 40 mg/day PO for 7 to 10 days (mean 7.5 days) Standard of care: participants used inhaled terbutaline as needed and pre-existing asthma medications were continued
Outcomes	Primary outcome was relapse rate Secondary outcomes included pulmonary function tests (PEF and FEV_1), quality of life using AQLQ, symptoms and adverse events
Notes	Jennifer Haddon from AstraZeneca (Canada) provided information about this unpublished study. ICS versus oral corticosteroid comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generation of random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 patients withdrew because of adverse events (5 budesonide, 7 prednisone) and 14 patients withdrew for other unspecified reasons (9 budesonide, 5 prednisone)
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Francis 1997

Methods	Design: parallel group, double-blind, randomised trial
Participants	Eligible: unclear Randomised: 56 (37 fluticasone, 19 prednisolone) Completed: 48 (32 fluticasone, 16 prednisolone) Sex (male/female): fluticasone 73%/27%, prednisolone 74%/26% Asthma diagnosis: acute symptoms of asthma as defined by BTS criteria, established history of recurrent wheeze or asthma symptoms Inclusion criteria: presentation to an acute care setting with as acute exacerbation of asthma, age < 48 months, clinical scoring index ≥ 2 on presentation, parent/guardian ability to use nebulised and complete daily record card, informed consent Major exclusions: use of oral corticosteroids for more than 7 days within 4 weeks, use of systemic corticosteroids or parenteral methylxanthines within 72 hours, severe respiratory dysfunction, a history of mechanical ventilation for respiratory failure, admission for respiratory distress within 4 weeks, concomitant serious illness
Interventions	Setting: multicentre, EDs, clinics or other acute care settings Interventions: the experimental group received inhaled fluticasone propionate, 1 mg twice daily by nebuliser, and placebo oral suspension for 7 days. The control group received inhaled placebo twice daily, and prednisolone 2 mg/kg/day PO for 4 days, then 1 mg/kg/day for 3 days Standard of care: both groups received salbutamol as needed, by nebuliser or MDI with babyhaler. Concurrent medications were continued (4 patients only)
Outcomes	The primary outcome was daily record card symptom scores for cough, wheeze and shortness of breath Secondary outcomes included frequency of nocturnal parental awakening due to child's asthma, daytime and night-time use of Ventolin, clinical scoring index, and parent/guardian and investigator global evaluation of treatment outcomes. Adverse events were also monitored
Notes	Julia Earnshaw of Glaxo Wellcome, UK, provided information about this study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generation of random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low

Francis 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	5 patients (14%) withdrew from the fluticasone group and 3 patients (16%) withdrew from the prednisolone group
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Levy 1996

Methods	Design: parallel group, double-blind, double-dummy, randomised trial
Participants	Eligible: unclear Randomised: 206 fluticasone/207 prednisolone Completed: 200 fluticasone/203 prednisolone Sex (male/female): fluticasone 99/107, prednisolone 84/123 Asthma diagnosis: doctors' diagnosis Inclusion criteria: mild exacerbation, defined as not severe enough to warrant admission but requiring a short course of oral corticosteroids by the clinician's opinion, with a pre-treatment peak flow of 60% to 90% Major exclusions: not stated
Interventions	Setting: 47 general practice centres throughout the UK Intervention: experimental group received fluticasone 1 mg twice daily via a Volumatic, while control group received a reducing course of oral prednisolone, starting at 40 mg and reducing by 5 mg every 2 days, both for a period of 16 days. All concurrent asthma medications, including existing ICS, were continued
Outcomes	Primary outcome was treatment failure, defined as (a) PEF fell below 60% of the best/predicted value on 2 consecutive occasions (morning and evening peak flows recorded) , or (b) a symptom score of 3 was recorded on 3 or more consecutive days (a score of 3 indicated that the symptoms were the same as or worse than on entry to the study), or (c) patient withdrew from the study because of uncontrolled symptoms or an adverse event related to asthma Secondary outcomes included morning and evening peak flow, asthma symptoms score, use of rescue medications (prednisolone 40 mg) and adverse events
Notes	The author provided an additional reference for possible inclusion (Mitchell 1995). Toni Maslen, of Glaxo Wellcome UK provided additional information about this trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generation of random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation

Levy 1996 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 patients were withdrawn due to investigator error, and 3 because they did not complete at least 12 days of the study
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Manjra 2000

Methods	Design: parallel group, double-blind, double-dummy, randomised trial
Participants	Eligible: unclear Randomised: 321 (165 fluticasone/156 prednisolone) Completed: 288 (148 fluticasone/140 prednisolone) Sex (male/female): fluticasone 56%/44%, prednisolone 57%/43% Asthma diagnosis: acute exacerbation of previously diagnosed asthma condition (as defined by BTS guidelines) Inclusion criteria: presentation to an acute care setting with acute, non-life-threatening exacerbation of previously diagnosed asthma; age 4-16 years; PEF 40% to 75% predicted on presentation; able to use mini-Wright peak flow meter, MDI with spacer and complete daily record card; and informed consent Major exclusions: use of oral or parenteral corticosteroids for more than 7 days within the previous 4 weeks, use of systemic corticosteroids or parenteral methylxanthines within the previous 72 hours, severe respiratory dysfunction, history of mechanical ventilation due to respiratory failure, admission within the previous 2 weeks for respiratory disease, any serious systemic disease
Interventions	Setting: multicentre, in EDs, clinics or other acute care settings Interventions: experimental group received inhaled fluticasone propionate 1 mg twice daily by nebuliser for 7 days and oral placebo. The control group received inhaled placebo, and prednisolone 2 mg/kg/day PO for 4 days, then 1 mg/kg/day for 3 days Standard of care: both groups received inhaled salbutamol as needed, and concurrent medications were continued
Outcomes	The primary outcome was morning and evening PEF recorded on daily record cards Secondary outcomes included symptom scores, frequency of nocturnal wakenings due to asthma, beta$_2$-agonist use, clinic assessment of PEF, clinical scoring index, and patient/parent and investigator global evaluation
Notes	Dr. Julia Earnshaw at Glaxo Wellcome UK provided information about this study ICS versus oral corticosteroid comparison

Manjra 2000 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generation of random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 patients (4%) withdrew from the fluticasone group and 5 patients (3%) withdrew from the prednisolone group
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Nakanishi 2003

Methods	Parallel randomised, masked, placebo-controlled study
Participants	58 children enrolled, 55 completed: flunisolide MDI (N = 27) versus oral prednisone (N = 28) Mean age (SD) (months): 132 (30) flunisolide, 125 (38) oral prednisone Sex (male/female): flunisolide: 17/10, oral prednisone: 18/10 Baseline lung function (pre-treatment); mean (SD) % predicted FEV_1: 40.6 (13.8) flunisolide, 45.5 (15.5) oral prednisone Inclusion criteria: children aged 6 to 16 years with an acute exacerbation of asthma Exclusion criteria: initial FEV_1 < 25% or > 80% of predicted, patients requiring hospital admission, and those with underlying lung disease (e.g. cystic fibrosis, bronchopulmonary dysplasia) Baseline ICS use: 7/27 flunisolide, 5/28 oral prednisone
Interventions	All patients received albuterol 0.15 mg/kg (up to 5 mg) and ipratropium bromide 0.25 mg at the discretion of the treating physician by jet nebulisation Bronchodilator therapy was repeated until the PEF was 70% of predicted, at which time informed consent was obtained, and patients were randomised into 1 of 2 treatment groups. Group A received flunisolide, 4 inhalations 1 mg twice daily for 7 days, and daily placebo tablets, while Group B received prednisone 2 mg/kg (maximum of 60 mg/day) PO for 7 days and inhaled placebo twice daily. Outpatient inhalations were given with a pressurised MDI with valved holding chamber

Outcomes	FEV_1 (at baseline, day 3 and day 7), symptoms and twice-daily PEF, vital signs, side effects
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details included in trial report to indicate that Forest Laboratories (New York, NY) prepared placebo inhalers, tablets and the patient randomisation sequence. However, details on how the random sequence was generated are not provided
Allocation concealment (selection bias)	Low risk	Researchers blinded to the randomisation codes throughout the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear whether the masking would have made the trial double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether the masking would have made the trial double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported by authors in trial report as (quote): "Reported side effects were minimal. One patient stopped the oral placebo pills due to taste, and two patients stopped the inhaler for similar reasons, one from each study group. The asthma diary information was not completed for eight patients in the ICS group and six patients in the OCS group. Two patients did not undergo follow-up in the ICS group. One patient in the ICS group required additional corticosteroids after the 7-day study period, and one patient in the OCS group required hospital admission for asthma within 24 hours following ED therapy and enrolment"
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Nana 1998

Methods	Design: parallel group, double-blind, double-dummy, randomised trial
Participants	Eligible: unclear. The patients were initially enrolled in a study comparing terbutaline by Turbuhaler versus MDI in the ED treatment of asthma, and were then randomised into this study at discharge Enrolled: 84 (42 budesonide/42 prednisolone) Completed: 81 (40 budesonide/41 prednisolone) Sex (male/female): budesonide 33%/66%, prednisolone 40%/60% Inclusion criteria: age 16-50 years, initial ED FEV_1 between 20% and 50% of predicted normal value and a pulse of more than 100 beats/min Major exclusions: not stated
Interventions	Setting: patients with acute asthma attending an ED in Thailand Intervention: the experimental group received inhaled budesonide by Turbuhaler, 1600 mg twice daily for 7 days and oral placebo. The control group received oral prednisolone initially 40 mg/day and decreasing by 5 mg/day for 7 days and inhaled placebo Standard of care: both groups received 1 dose of prednisolone 60 mg PO while in the ED, and inhaled terbutaline by Turbuhaler as needed. Other asthma medications were continued during the study (48 patients were on oral xanthines and 49 patients were on oral $beta_2$-agonists)
Outcomes	The primary outcome was change in FEV_1 over the study period Secondary outcomes included clinical symptoms on a visual analogue scale, pulse, blood pressure, morning and evening peak flow, number of doses of terbutaline used and possible adverse events
Notes	Additional information about this study was provided by Elisabeth Stahl of Astra Draco AB, Sweden

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generation of random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients (2 in the budesonide group and 1 in the prednisolone group) stopped treat-

Nana 1998 (*Continued*)

		ment early, 2 because of asthma deterioration and 1 because of a respiratory infection
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Rowe 1999

Methods	Design: parallel group, double-blind, randomised trial
Participants	Eligible: 263 Randomised: 191 Completed: 94 budesonide, 94 placebo Age: mean 26 budesonide, 29 placebo, range: 18 to 60 years Sex (male/female): budesonide 43/51, placebo 30/64 Asthma diagnosis: doctor's diagnosis Recruitment: referred by ED physician Inclusion criteria: PEF < 80% predicted Major exclusions: regular ICS in week prior to presentation, receiving oral corticosteroid at time of presentation Discharge PEF mean (SD) % predicted: budesonide 67 (14), placebo 75 (15)
Interventions	Setting: ED and outpatient treatment for 3 weeks Type: inhaled budesonide Turbuhaler 800 μg twice daily for 3 weeks versus inhaled placebo Turbuhaler twice daily for 3 weeks. Both treatment and control groups received prednisone 50 mg PO x 7 days and prn salbutamol by MDI after discharge
Outcomes	Primary outcome was asthma relapse, defined as an unscheduled visit for worsening asthma Secondary outcomes included admission rates, pulmonary function tests, beta$_2$-agonist use, quality-of-life scores, symptoms and side effects. Compliance was measured by self-report and number of actuations remaining in the inhaler at the end of the study
Notes	ICS plus oral corticosteroid versus oral corticosteroid

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generation of random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind

Rowe 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 patients in the budesonide group and 3 in the placebo group either dropped out or were lost to follow-up. However, they were included in primary analyses
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Verona 1998

Methods	Design: parallel group, double-blind, double-dummy, randomised trial
Participants	Eligible: unclear Randomised: 67 fluticasone, 76 prednisolone Completed: 62 fluticasone, 74 prednisolone Age: mean (SD) (years): fluticasone 10 (3), prednisolone 9 (3) Sex (male/ female): fluticasone 60%/40%, prednisolone 70%/30% Asthma diagnosis: previous diagnosis of asthma as per BTS criteria, with an acute exacerbation Inclusion criteria: patients aged 4-16 years, with an acute exacerbation of previously diagnosed asthma, presenting to the ED, clinic or other acute care setting, with PEF < 80% predicted following 3 hours of treatment. Participants had to be able to use a peak flow meter and MDI with spacer and willing to participate and complete a daily record Major exclusions: use of oral corticosteroids for more the 7 days within the past 4 weeks, or use of systemic corticosteroids in the previous 72 hours, severe exacerbations of asthma (defined as O_2 saturation < 90%, pH 7.25 or increased pCO_2), a history of mechanical ventilations or the presence of other serious systemic diseases
Interventions	Setting: multicentre trial involving EDs, clinics or other acute care settings Interventions: experimental group received fluticasone propionate 500 μg twice daily by MDI with spacer for 7 days and placebo tablets. The control group received prednisolone tablets 2 mg/kg/day for 4 days, then 1 mg/kg/day for 3 days, and placebo MDI inhaler Standard of care: all patients received Ventolin as needed, and continued all regular asthma medications
Outcomes	The primary outcome was morning and evening PEF Secondary outcomes included symptom scores, nocturnal wakenings, $beta_2$-agonist use, PEF and FEV_1 measurements at the clinic, and a clinical scoring index
Notes	Information on this unpublished study was provided by Dr. Julia Earnshaw of Glaxo Wellcome, UK ICS versus oral corticosteroid
Risk of bias	

Verona 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generation of random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 patients withdrew in the fluticasone group, 3 in the prednisone group. Withdrawals were because of: withdrawal of consent (2), adverse events (2), lost to follow-up (2) and inaccurate prednisone dose (2)
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Volovitz 1998

Methods	Design: parallel group, double-blind, double-dummy, randomised trial
Participants	Eligible: unclear Randomised: 24 Completed: 11 budesonide, 11 prednisolone Sex (male/female): budesonide 73%/37%, prednisolone 64%/46% Asthma diagnosis: moderately severe attack with PEF1 35-75% predicted and PIS 8-13 Inclusion criteria: PEF1% 35-75% and PIS 8-13, age 6-16 years Major exclusions: presence of acute febrile illness, regular use of ICS, cromolyn, nedocromil sodium or theophylline in past 2 weeks Baseline FEV_1%: not given, but no significant difference in mean PEF and PIS at beginning of treatment stated
Interventions	Interventions: ED at a paediatric hospital in Israel Intervention 1: single-dose budesonide 1600 μg by Turbohaler Intervention 2: prednisolone 2 mg/kg PO Both groups received terbutaline 5 mg by nebuliser or 0.5 mg by Turbohaler at the start of trial. Intervention 1 group was discharged on budesonide 200 μg 4 times daily by Turbohaler, reduced by 25% every second day, and placebo tablets. From the eighth day, they continued on 200 μg twice daily for 2 weeks. Intervention 2 group was discharged on prednisolone 2 mg/kg/day, reduced by 25% every second day, and placebo Tubohaler
Outcomes	Outcomes evaluated in the ED included PEF, PIS and vital signs

Volovitz 1998 (*Continued*)

Notes	The author was contacted and provided additional information about the study, and data analyses, and an additional reference ICS versus oral corticosteroid

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random sequence
Allocation concealment (selection bias)	Low risk	Third party randomisation with sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient excluded because of pneumonia, and another for non-compliance
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

AQLQ: Asthma Quality of Life Questionnaire; ATS: American Thoracic Society; BTS: British Thoracic Society; COPD: chronic obstructive pulmonary disease; ED: emergency department; FEV_1: forced expiratory volume in one second; ICS; inhaled corticosteroids; MARC-4: Fourth Multicenter Airways Research Collaboration; MDI: metered-dose inhaler; OC: oral contraceptive; PEF: peak expiratory flow; PIS: Pulmonary Index Score; PO: oral; prn: as required; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agarwal 2002	Scope of study limited to patients in the ED or hospital
Agarwal 2003	Scope of study limited to patients in the ED or hospital
Agarwal 2004	Scope of study limited to patients in the ED or hospital
Agarwal 2004a	Scope of study limited to patients in the ED or hospital

(*Continued*)

Agarwal 2005	This study investigated the use of fluticasone for patients with acute asthma while in the ED or hospital
Agarwal 2008	This study investigated the use of fluticasone in the treatment of acute asthma while in the ED or hospital
Agarwal 2009	This study investigated the use of fluticasone for patients with acute asthma while in the ED or hospital
Agarwal 2010	Scope of study limited to patients in the ED
Agarwal 2010a	Scope of study limited to patients in the ED
Allen 2003	This study investigated 2 drug delivery methods for beclomethasone in chronic asthma
Ancheta 2008	Scope of study limited to patients in the ED
Anonymous 1995	This letter reviewed a study comparing tapering versus abrupt withdrawal of oral corticosteroids after an acute asthma attack
Balanag 2003	Scope of study limited to patients in the ED
Bateman 2006	This study investigated the use of ICS in the ED treatment of acute asthma
Bautista 1994	This study investigated the use of ICS in the ED treatment of acute asthma
Becker 2000	Patients were randomised to self-treatment with double-dose ICS versus regular dose ICS for asthma exacerbations
Belda 2007	Some patients in this study were likely to have been hospitalised and were not randomised at discharge
Bilancia 1998	This study included only hospitalised patients
Blandon 2004	Scope of study limited to patients while in the ED
Britton 1997	This study compared high- versus low-dose fluticasone in the prevention of relapse of asthma after an episode of acute asthma
Chhabra 1994	This study compared sequential treatment with beta$_2$-agonists alone with beta$_2$-agonists plus ICS in chronic asthma
Cox 1996	This study compared fluticasone and triamcinolone in chronic asthma
Crain 1998	This study reviewed a study by Pauwels 1997 that investigated the use of long-acting beta$_2$-agonists and ICS in chronic asthma
Cueva 1975	This study investigated beclomethasone use in chronic asthma and its effect on adrenal function
Decimo 2009	This study compared fluticasone versus budesonide in the outpatient treatment of asthma exacerbations in children, with no placebo group

(*Continued*)

Drblik 1999	This study investigated 2 methods of delivering terbutaline in acute asthma in children
Ediger 2006	All the patients in this study were hospitalised
Estrada 2005	Scope of study limited to patients in the ED
Frye 1988	This letter addressed the choice of intravenous corticosteroids in acute asthma
Gross 1996	This study involved patients with chronic asthma
Higenbottam 2000	All patients in this study were hospitalised
Jerez 2002	This study looked at the treatment of acute asthma with ICS versus oral corticosteroid in the ED with 24-hour observation
Joubert 1985	The study included patients with chronic asthma with simulated acute attacks
Khoo 2009	This study randomised people with severe asthma 1 week after hospital discharge, comparing continued oral corticosteroid plus ICS therapy versus ICS therapy alone
La Rosa 1997	The study compared inhaled flunisolide versus placebo. Systemic corticosteroids were not used in either treatment group
Latysheva 1996	This was a non-randomised study that compared betamethasone to dexamethasone in asthma and other allergic conditions
Lee-Wong 2002	This study involved only admitted patients, and randomised patients to either inhaled flunisolide or oral prednisone after 48 hours of treatment with intravenous methylprednisolone
Leuppi 2002	This study involved patients with asthma exacerbations following withdrawal of ICS, and compared a single, high dose of budesonide (3200 μg) followed by their usual dose of ICS versus doubling their standard dose of ICS
Lim 1996	This study involved only hospitalised patients
Macias 2003	This study randomised ED patients with acute asthma to ICS or intravenous corticosteroids: some patients were admitted and other patients were followed as outpatients. The patients were not randomised on ED discharge to treatment groups
Mahakalkar 2002	This is a review article
Mannan 2008	This study investigated patient initiated increase in the baseline dose of ICS at home to prevent ED visits and oral corticosteroid use
McEvoy 1977	This study compared ICS versus placebo in the outpatient treatment of acute asthma
Mendes 2008	This study included patients with mild stable asthma

(*Continued*)

Milani 2004	This study randomised clinic patients to 1 of 3 groups: oral and inhaled placebo, single-dose oral prednisone 1 mg/kg and inhaled placebo, or oral placebo and budesonide 2 mg inhaled (single dose). Although the patients were followed for 72 hours as outpatients, there were no study treatments given after discharge from the clinic
Mitchell 1995	This study included only patients hospitalised with an exacerbation of asthma
Morice 1996	The study involved only patients with chronic obstructive pulmonary disease
Nana 1998a	This study investigated the use of beta$_2$-agonists by dry powder inhaler versus nebuliser in acute asthma. The patients were then re-randomised into the included study Nana 1998
Nuhoglu 2001	This study compared high-dose budesonide versus medium-dose budesonide plus oral methylprednisolone
O'Byrne 2007	This study investigated the use of budesonide to prevent decline in lung function in chronic asthma
O'Byrne 2007a	This was an evaluation of budesonide to prevent exacerbations and decline in lung function in chronic asthma
Oborne 2009	This study looked at patient-initiated quadrupling the dose of maintenance ICS to prevent worsening of an exacerbation
Olaivar 1999	This study investigated the use of budesonide versus placebo in the acute management of asthma over a 4-hour follow-up
Pauwels 2003	This study investigated early initiation of budesonide in mild chronic asthma
Pierson 1974	This study investigated the use of intravenous corticosteroids in acute asthma
Postma 2006	This study included outpatients with asthma exacerbations induced by withdrawal of ICS
Rabe 2006	This study investigated the use of various reliever therapies in maintenance therapy of asthma to prevent exacerbations
Rahman 2007	This study investigated the use of ICS versus oral corticosteroid in the treatment of acute asthma while in the ED
Rahman 2008	This study investigated the use of ICS versus oral corticosteroid in treatment of acute asthma while in the ED
Razi 2008	This study investigated the use of ICS in the treatment of acute asthma while in the ED
Rice 2002	This study looked at the outpatient management of asthma exacerbations by doubling the usual dose of ICS versus placebo or oral corticosteroid in a cross-over design
Salmeron 1989	This study investigated the use of beclomethasone in poorly controlled chronic asthma
Sampayo 2010	This study looked at providing a prescription for ICS versus no prescription at ED discharge, to see if it increased the rate of filling a prescription for ICS

(*Continued*)

Schuh 2006	This study randomised children in the ED to treatment with oral corticosteroids versus fluticasone while in the ED and for 4 days after discharge. The patients were not randomised to treatment at discharge and some patients were admitted
Sekerel 2005	This study compared ICS versus placebo, and systemic corticosteroids were withheld from both groups
Sharma 2003	This study investigated the use of ICS in the treatment of acute asthma while in the ED
Sheikh 1998	This study compared different ICS in chronic asthma
Skoner 2009	This study compared inhaled budesonide versus control which could be $beta_2$-agonists alone or $beta_2$-agonists plus oral corticosteroids
Skorpinski 2006	This study looked at home treatment of asthma exacerbations by increasing the baseline dose of ICS
Starobin 2008	This study investigated the use of ICS versus oral corticosteroid in the ED treatment of acute asthma. The patients were followed after the ED treatment, but some were admitted, while others were treated as outpatients, and they were not randomised to treatment on ED discharge
Svedmyr 1996	This study investigated the prevention of acute asthma attacks with budesonide
Volovitz 2001	This study investigated parent-initiated increased doses of ICS at home to control asthma exacerbations
Wendel 1996	The patients randomised in this study were all admitted to hospital
Wilson 1990	This study investigated the treatment of exacerbations of asthma at home with intermittent beclomethasone dipropionate
Winter 1997	This study included only hospitalised patients
Yang 2000	All patients in this study were admitted to hospital
Yashina 2001	This study investigated the outpatient treatment of asthma exacerbations. There were 3 treatment arms, with varying types and dose of ICS given in all 3 treatment arms
Yi 2003	This study looked at ICS use for in-ED treatment and hospitalised patients with acute asthma
Zhou 2000	This study investigated the use of a spacer in the delivery of beclomethasone in chronic asthma therapy

ED: emergency department; ICS: inhaled corticosteroid.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Acun 2003

Methods	Randomised trial
Participants	42 children with acute moderate asthma exacerbations
Interventions	Inhaled budesonide versus oral prednisolone
Outcomes	Pulmonary Index Scores, heart rate, length of stay and oxygen saturation. FEV_1, FVC in children aged 6 years and above
Notes	Unclear whether patients were hospitalised. Awaiting clarification from author

Ambrosio 1997

Methods	Randomised double-blind prospective trial
Participants	Adults with acute asthma exacerbations
Interventions	Nebulised terbutaline plus budesonide versus terbutaline (in 3 doses with 15-minute intervals)
Outcomes	Hospital admission rates, PEF, adverse effects and vital signs Outcome data collected after each nebulisation
Notes	Trial report unobtainable

FEV: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow.

DATA AND ANALYSES

Comparison 1. Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma relapse at 7-10 days	3	909	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.10]
2 Asthma relapse at 20-24 days	3	909	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.46, 1.02]
3 Hospital admission	2	805	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.39, 2.52]
4 Beta$_2$-agonist use at 7-10 days	3	672	Mean Difference (IV, Fixed, 95% CI)	0.51 [-0.44, 1.47]
5 Beta$_2$-agonist use at 20-24 days	3	602	Mean Difference (IV, Random, 95% CI)	-0.14 [-2.35, 2.06]
6 PEF at 7-10 days	2	205	Mean Difference (IV, Fixed, 95% CI)	-0.88 [-28.49, 26.72]
7 PEF at 20-24 days	2	172	Mean Difference (IV, Fixed, 95% CI)	-4.55 [-35.91, 26.81]
8 PEF% at 7-10 days	2	206	Mean Difference (IV, Random, 95% CI)	-1.79 [-11.04, 7.46]
9 PEF% at 20-24 days	2	172	Mean Difference (IV, Random, 95% CI)	-2.34 [-9.44, 4.77]
10 Quality of life at 7-10 days	2	613	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.01, 0.39]
11 Quality of life at 20-24 days	2	559	Mean Difference (IV, Random, 95% CI)	0.33 [-0.36, 1.01]
12 Cough at 7-10 days	2	620	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.57, 0.07]
13 Cough at 20-24 days	2	571	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.25, 0.31]
14 Wheeze at 7-10 days	2	622	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.48, 0.12]
15 Wheeze at 20-24 days	2	571	Mean Difference (IV, Random, 95% CI)	-0.43 [-1.31, 0.45]
16 Dyspnoea at 7-10 days	2	620	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.92, 0.33]
17 Dyspnoea at 20-24 days	2	571	Mean Difference (IV, Random, 95% CI)	-0.43 [-1.31, 0.45]
18 Hoarseness at 7-10 days	2	612	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.53, 1.46]
19 Hoarseness at 20-24 days	2	596	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.36, 1.01]
20 Sore throat at 7-10 days	2	612	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.43, 1.24]
21 Sore throat at 20-24 days	2	596	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.35, 1.16]
22 Asthma relapse at 7-10 days - gender subgroups	3	720	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.38, 1.52]
22.1 Male	3	296	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.21, 4.43]
22.2 Female	3	424	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.34, 1.82]
23 Asthma relapse at 20-24 days - gender subgroups	3	761	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.37, 1.35]
23.1 Male	3	315	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.22, 1.62]
23.2 Female	3	446	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.30, 1.99]
24 Asthma relapse at 7-10 days; patients lost to follow-up excluded	3	725	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.47, 1.10]
25 Asthma relapse at 20-24 days; patients lost to follow-up excluded	3	768	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.46, 1.05]

Comparison 2. Any ICS versus oral corticosteroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthma relapse at 7-10 days	4	684	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.66, 1.52]
2 Asthma relapse at 16-21 days	2	425	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.80, 1.99]
3 Hospital admission	3	254	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.95]
4 PEF at 7-10 days	6	1047	Mean Difference (IV, Fixed, 95% CI)	10.95 [-0.84, 22.73]
5 PEF at 16-21 days	4	792	Mean Difference (IV, Fixed, 95% CI)	15.21 [1.53, 28.89]
6 PEF% at 7-10 days	2	376	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-3.12, 1.64]
7 PEF% at 16-21 days	2	347	Mean Difference (IV, Fixed, 95% CI)	0.58 [-2.07, 3.23]
8 FEV_1% pred at 6-10 days (outcome not pre-specified in original review)	1	55	Mean Difference (IV, Fixed, 95% CI)	-17.80 [-26.98, -8.62]
9 FEV_1% pred at 16-21 days (outcome not pre-specified in original review)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 $Beta_2$-agonist use at 7-10 days	3	128	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.47, 0.64]
11 $Beta_2$-agonist use at 14-21 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Quality of life at 7-10 days	2	231	Std. Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.12, 0.40]
13 Cough at 7-10 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14 Wheeze at 7-10 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15 Wheeze at 16-21 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16 Hoarseness at 7-10 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
17 Hoarseness at 16-21 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
18 Sore throat at 7-10 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
19 Sore throat at 16-21 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 1 Asthma relapse at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 1 Asthma relapse at 7-10 days

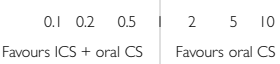
Study or subgroup	ICS + oral CS n/N	Oral OS n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Brenner 2000	3/51	3/53		5.4 %	1.04 [0.20, 5.42]
Camargo 2000	29/310	37/307		65.5 %	0.75 [0.45, 1.26]
Rowe 1999	11/94	17/94		29.2 %	0.60 [0.26, 1.36]
Total (95% CI)	**455**	**454**		**100.0 %**	**0.72 [0.48, 1.10]**

Total events: 43 (ICS + oral CS), 57 (Oral OS)

Heterogeneity: $Chi^2 = 0.41$, df = 2 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 1.51 (P = 0.13)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 2 Asthma relapse at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 2 Asthma relapse at 20-24 days

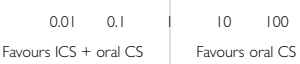
Study or subgroup	ICS + oral CS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Brenner 2000	4/51	4/53		6.3 %	1.04 [0.25, 4.41]
Camargo 2000	30/310	37/307		58.6 %	0.78 [0.47, 1.30]
Rowe 1999	12/94	23/94		35.0 %	0.45 [0.21, 0.97]
Total (95% CI)	**455**	**454**		**100.0 %**	**0.68 [0.46, 1.02]**

Total events: 46 (ICS + oral CS), 64 (Oral CS)

Heterogeneity: Chi^2 = 1.72, df = 2 (P = 0.42); I^2 =0.0%

Test for overall effect: Z = 1.85 (P = 0.064)

Test for subgroup differences: Not applicable

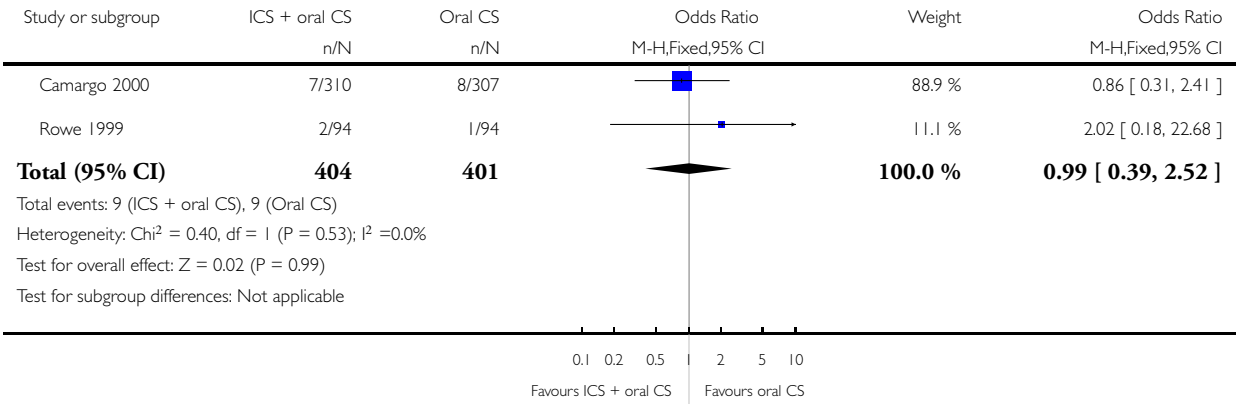


Analysis 1.3. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 3 Hospital admission.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 3 Hospital admission

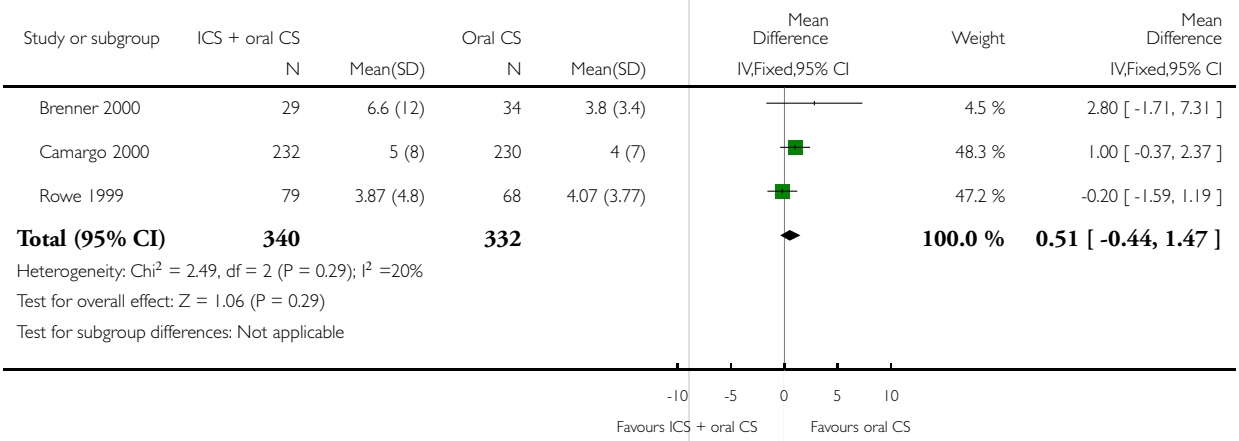


Analysis 1.4. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 4 Beta$_2$-agonist use at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 4 Beta$_2$-agonist use at 7-10 days



Analysis 1.5. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 5 Beta$_2$-agonist use at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

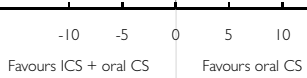
Outcome: 5 Beta$_2$-agonist use at 20-24 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Brenner 2000	24	6.1 (7.8)	29	3.3 (4.7)		21.7 %	2.80 [-0.76, 6.36]
Camargo 2000	209	5 (10)	221	5 (10)		36.5 %	0.0 [-1.89, 1.89]
Rowe 1999	65	2.4 (3.2)	54	4.2 (4.3)		41.7 %	-1.80 [-3.19, -0.41]
Total (95% CI)	**298**		**304**			**100.0 %**	**-0.14 [-2.35, 2.06]**

Heterogeneity: Tau^2 = 2.53; Chi^2 = 6.62, df = 2 (P = 0.04); I^2 =70%

Test for overall effect: Z = 0.13 (P = 0.90)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 6 PEF at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

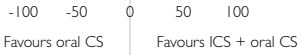
Outcome: 6 PEF at 7-10 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Brenner 2000	29	423 (103.4)	34	390.3 (126.3)		23.7 %	32.70 [-24.03, 89.43]
Rowe 1999	75	433 (98.3)	67	444.3 (93.7)		76.3 %	-11.30 [-42.90, 20.30]
Total (95% CI)	**104**		**101**			**100.0 %**	**-0.88 [-28.49, 26.72]**

Heterogeneity: Chi^2 = 1.76, df = 1 (P = 0.18); I^2 =43%

Test for overall effect: Z = 0.06 (P = 0.95)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 7 PEF at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

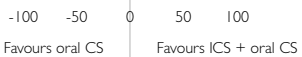
Outcome: 7 PEF at 20-24 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Brenner 2000	25	445.4 (138)	31	413.4 (102.8)		23.2 %	32.00 [-33.08, 97.08]
Rowe 1999	63	437.1 (93.6)	53	452.7 (101.5)		76.8 %	-15.60 [-51.39, 20.19]
Total (95% CI)	**88**		**84**			**100.0 %**	**-4.55 [-35.91, 26.81]**

Heterogeneity: Chi^2 = 1.58, df = 1 (P = 0.21); I^2 =37%

Test for overall effect: Z = 0.28 (P = 0.78)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 8 PEF% at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 8 PEF% at 7-10 days

Study or subgroup	ICS + oral CS		Oral CS		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Brenner 2000	29	82.9 (13.4)	34	79.4 (18)		44.3 %	3.50 [-4.27, 11.27]
Rowe 1999	76	76 (14.3)	67	82 (13.5)		55.7 %	-6.00 [-10.56, -1.44]
Total (95% CI)	**105**		**101**			**100.0 %**	**-1.79 [-11.04, 7.46]**

Heterogeneity: $Tau^2 = 34.56$; $Chi^2 = 4.27$, df = 1 (P = 0.04); $I^2 = 77\%$

Test for overall effect: Z = 0.38 (P = 0.70)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 9 PEF% at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 9 PEF% at 20-24 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Brenner 2000	25	88.1 (19.9)	31	85.5 (16.4)		35.0 %	2.60 [-7.10, 12.30]
Rowe 1999	63	78 (13.6)	53	83 (15.1)		65.0 %	-5.00 [-10.27, 0.27]
Total (95% CI)	**88**		**84**			**100.0 %**	**-2.34 [-9.44, 4.77]**

Heterogeneity: $Tau^2 = 13.00$; $Chi^2 = 1.82$, df = 1 (P = 0.18); $I^2 = 45\%$

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 10 Quality of life at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

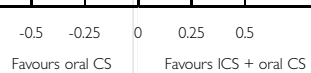
Outcome: 10 Quality of life at 7-10 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Camargo 2000	235	5.4 (1.3)	235	5.3 (1.3)		72.5 %	0.10 [-0.14, 0.34]
Rowe 1999	75	5.45 (1.07)	68	5.03 (1.24)		27.5 %	0.42 [0.04, 0.80]
Total (95% CI)	**310**		**303**			**100.0 %**	**0.19 [-0.01, 0.39]**

Heterogeneity: $Chi^2 = 1.96$, df = 1 (P = 0.16); $I^2 = 49\%$

Test for overall effect: Z = 1.84 (P = 0.065)

Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 11 Quality of life at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 11 Quality of life at 20-24 days

Study or subgroup	ICS + oral CS		Oral CS		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Camargo 2000	214	5.5 (1.3)	226	5.5 (1.2)		53.1 %	0.0 [-0.23, 0.23]
Rowe 1999	65	5.9 (1.09)	54	5.2 (1.2)		46.9 %	0.70 [0.28, 1.12]
Total (95% CI)	**279**		**280**			**100.0 %**	**0.33 [-0.36, 1.01]**

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 8.28$, df = 1 (P = 0.004); $I^2 = 88\%$

Test for overall effect: Z = 0.94 (P = 0.35)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 12 Cough at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

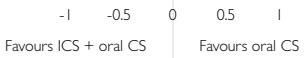
Outcome: 12 Cough at 7-10 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Camargo 2000	238	-4.9 (2.2)	238	-4.7 (2.2)		65.8 %	-0.20 [-0.60, 0.20]
Rowe 1999	78	-4.56 (1.56)	66	-4.21 (1.76)		34.2 %	-0.35 [-0.90, 0.20]
Total (95% CI)	**316**		**304**			**100.0 %**	**-0.25 [-0.57, 0.07]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 1.54 (P = 0.12)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 13 Cough at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

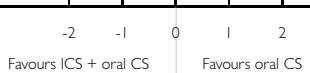
Outcome: 13 Cough at 20-24 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Camargo 2000	220	-5.1 (2.1)	232	-5 (2.1)		53.8 %	-0.10 [-0.49, 0.29]
Rowe 1999	65	-5.6 (1.5)	54	-4.7 (1.7)		46.2 %	-0.90 [-1.48, -0.32]
Total (95% CI)	**285**		**286**			**100.0 %**	**-0.47 [-1.25, 0.31]**

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 5.03$, df = 1 (P = 0.02); $I^2 = 80\%$

Test for overall effect: Z = 1.18 (P = 0.24)

Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 14 Wheeze at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

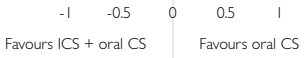
Outcome: 14 Wheeze at 7-10 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Camargo 2000	239	-5.4 (2.1)	239	-5.3 (2.1)		64.5 %	-0.10 [-0.48, 0.28]
Rowe 1999	78	-5.42 (1.42)	66	-5.09 (1.65)		35.5 %	-0.33 [-0.84, 0.18]
Total (95% CI)	**317**		**305**			**100.0 %**	**-0.18 [-0.48, 0.12]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.51$, df = 1 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 1.18 (P = 0.24)

Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 15 Wheeze at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 15 Wheeze at 20-24 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Camargo 2000	221	-5.4 (2)	231	-5.4 (2)		51.9 %	0.0 [-0.37, 0.37]
Rowe 1999	65	-5.9 (1.1)	54	-5 (1.6)		48.1 %	-0.90 [-1.40, -0.40]
Total (95% CI)	**286**		**285**			**100.0 %**	**-0.43 [-1.31, 0.45]**

Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 7.99$, df = 1 (P = 0.005); $I^2 = 87\%$

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable

Analysis 1.16. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 16 Dyspnoea at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

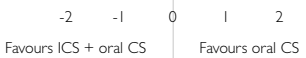
Outcome: 16 Dyspnoea at 7-10 days

Study or subgroup	ICS + oral CS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Camargo 2000	238	-5.2 (1.8)	238	-5.2 (1.8)		54.0 %	0.0 [-0.32, 0.32]
Rowe 1999	78	-5.32 (1.38)	66	-4.68 (1.53)		46.0 %	-0.64 [-1.12, -0.16]
Total (95% CI)	**316**		**304**			**100.0 %**	**-0.29 [-0.92, 0.33]**

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 4.70$, df = 1 (P = 0.03); $I^2 = 79\%$

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 17 Dyspnoea at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 17 Dyspnoea at 20-24 days

Study or subgroup	ICS + oral CS		Oral CS		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Camargo 2000	220	-5.2 (1.9)	232	-5.2 (1.9)		52.2 %	0.0 [-0.35, 0.35]
Rowe 1999	65	-5.8 (1.3)	54	-4.9 (1.5)		47.8 %	-0.90 [-1.41, -0.39]
Total (95% CI)	**285**		**286**			**100.0 %**	**-0.43 [-1.31, 0.45]**

Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 8.13$, df = 1 (P = 0.004); $I^2 = 88\%$

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable

Analysis 1.18. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 18 Hoarseness at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 18 Hoarseness at 7-10 days

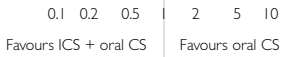
Study or subgroup	ICS + oral CS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Camargo 2000	17/235	14/230		40.4 %	1.20 [0.58, 2.50]
Rowe 1999	22/79	25/68		59.6 %	0.66 [0.33, 1.33]
Total (95% CI)	**314**	**298**		**100.0 %**	**0.88 [0.53, 1.46]**

Total events: 39 (ICS + oral CS), 39 (Oral CS)

Heterogeneity: Chi^2 = 1.33, df = 1 (P = 0.25); I^2 =25%

Test for overall effect: Z = 0.49 (P = 0.62)

Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 19 Hoarseness at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 19 Hoarseness at 20-24 days

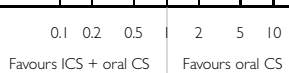
Study or subgroup	ICS + oral CS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Camargo 2000	16/236	19/242		46.2 %	0.85 [0.43, 1.70]
Rowe 1999	16/64	25/54		53.8 %	0.39 [0.18, 0.84]
Total (95% CI)	**300**	**296**		**100.0 %**	**0.60 [0.36, 1.01]**

Total events: 32 (ICS + oral CS), 44 (Oral CS)

Heterogeneity: Chi^2 = 2.22, df = 1 (P = 0.14); I^2 =55%

Test for overall effect: Z = 1.94 (P = 0.053)

Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 20 Sore throat at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 20 Sore throat at 7-10 days

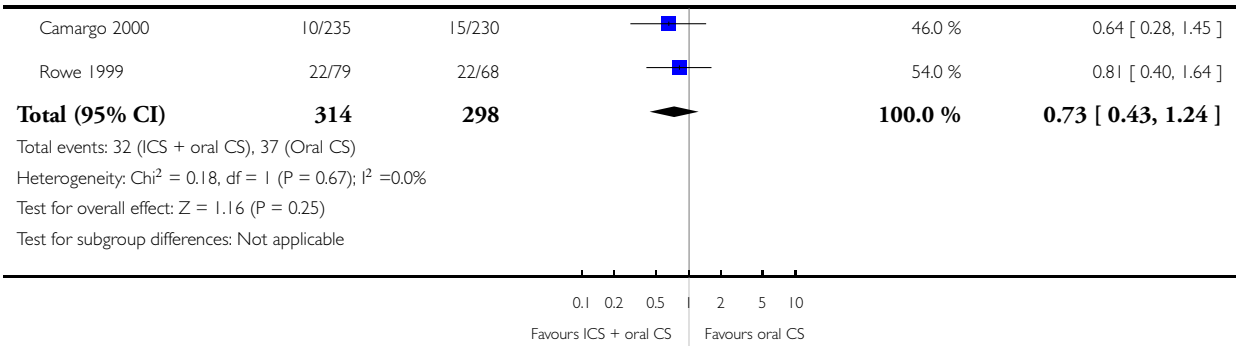
Study or subgroup	ICS + oral CS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Camargo 2000	10/235	15/230		46.0 %	0.64 [0.28, 1.45]
Rowe 1999	22/79	22/68		54.0 %	0.81 [0.40, 1.64]
Total (95% CI)	**314**	**298**		**100.0 %**	**0.73 [0.43, 1.24]**

Total events: 32 (ICS + oral CS), 37 (Oral CS)

Heterogeneity: Chi^2 = 0.18, df = 1 (P = 0.67); I^2 =0.0%

Test for overall effect: Z = 1.16 (P = 0.25)

Test for subgroup differences: Not applicable



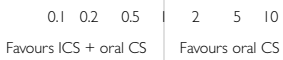
Analysis 1.21. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 21 Sore throat at 20-24 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 21 Sore throat at 20-24 days

Study or subgroup	ICS + oral CS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Camargo 2000	10/236	9/242		31.3 %	1.15 [0.46, 2.87]
Rowe 1999	14/64	22/54		68.7 %	0.41 [0.18, 0.91]
Total (95% CI)	**300**	**296**		**100.0 %**	**0.64 [0.35, 1.16]**
Total events: 24 (ICS + oral CS), 31 (Oral CS)					
Heterogeneity: Chi^2 = 2.76, df = 1 (P = 0.10); I^2 =64%					
Test for overall effect: Z = 1.48 (P = 0.14)					
Test for subgroup differences: Not applicable					



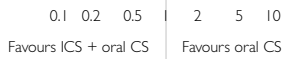
Analysis 1.22. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 22 Asthma relapse at 7-10 days - gender subgroups.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 22 Asthma relapse at 7-10 days - gender subgroups

Study or subgroup	ICS + oral CS n/N	Oral CS n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Male					
Brenner 2000	2/11	0/9		4.3 %	5.00 [0.21, 118.65]
Camargo 2000	9/106	20/97		25.8 %	0.36 [0.15, 0.83]
Rowe 1999	5/43	2/30		11.8 %	1.84 [0.33, 10.19]
Subtotal (95% CI)	**160**	**136**		**41.8 %**	**0.96 [0.21, 4.43]**
Total events: 16 (ICS + oral CS), 22 (Oral CS)					
Heterogeneity: Tau^2 = 1.04; Chi^2 = 4.82, df = 2 (P = 0.09); I^2 =59%					
Test for overall effect: Z = 0.05 (P = 0.96)					
2 Female					
Brenner 2000	1/17	3/26		7.2 %	0.48 [0.05, 5.03]
Camargo 2000	20/128	17/138		29.3 %	1.32 [0.66, 2.65]
Rowe 1999	6/51	15/64		21.7 %	0.44 [0.16, 1.22]
Subtotal (95% CI)	**196**	**228**		**58.2 %**	**0.79 [0.34, 1.82]**
Total events: 27 (ICS + oral CS), 35 (Oral CS)					
Heterogeneity: Tau^2 = 0.22; Chi^2 = 3.34, df = 2 (P = 0.19); I^2 =40%					
Test for overall effect: Z = 0.56 (P = 0.57)					
Total (95% CI)	**356**	**364**		**100.0 %**	**0.76 [0.38, 1.52]**
Total events: 43 (ICS + oral CS), 57 (Oral CS)					
Heterogeneity: Tau^2 = 0.30; Chi^2 = 9.15, df = 5 (P = 0.10); I^2 =45%					
Test for overall effect: Z = 0.78 (P = 0.43)					
Test for subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.82), I^2 =0.0%					

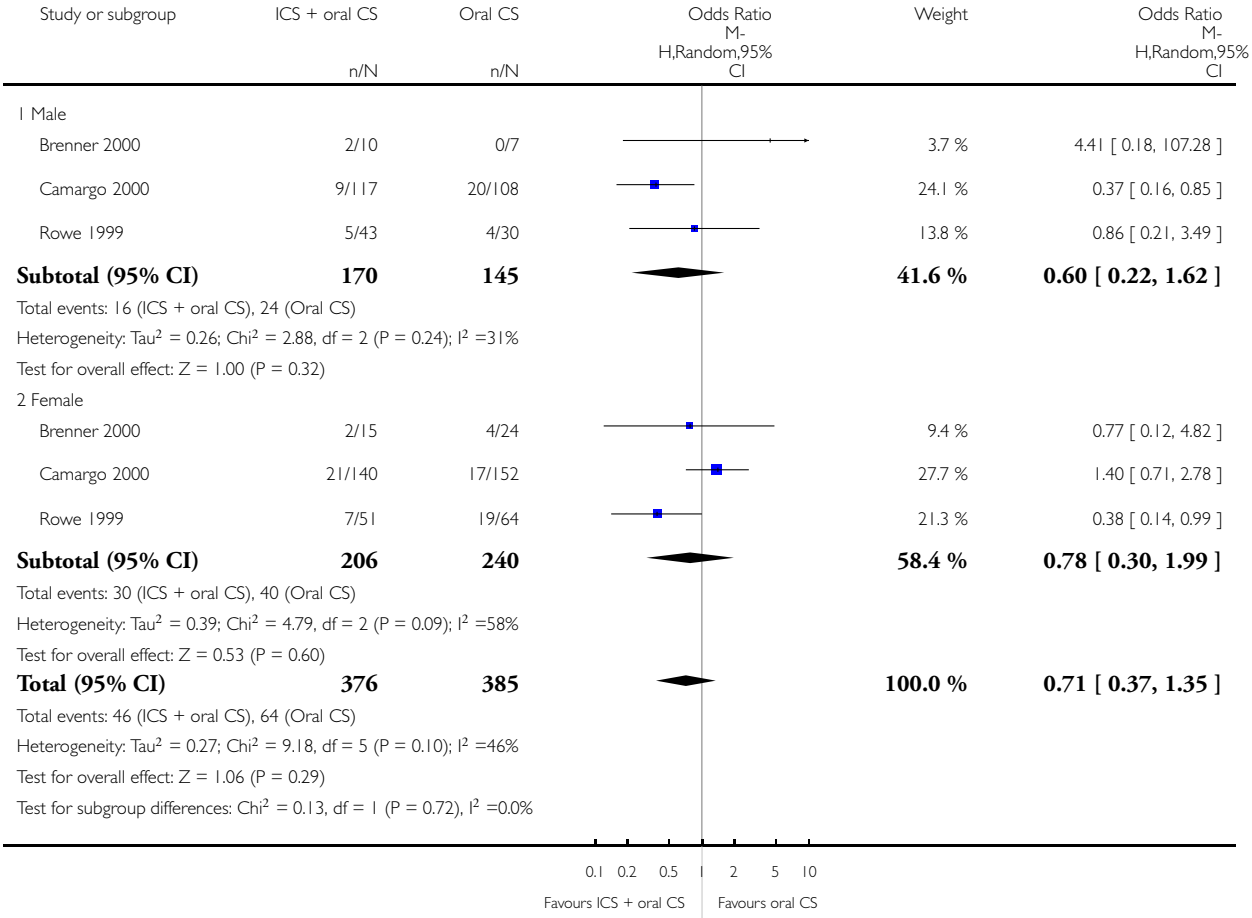


Analysis 1.23. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 23 Asthma relapse at 20-24 days - gender subgroups.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 23 Asthma relapse at 20-24 days - gender subgroups



Analysis 1.24. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 24 Asthma relapse at 7-10 days; patients lost to follow-up excluded.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 24 Asthma relapse at 7-10 days; patients lost to follow-up excluded

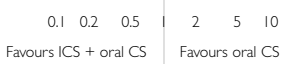
Study or subgroup	ICS + oral CS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Brenner 2000	3/31	4/37		6.5 %	0.88 [0.18, 4.29]
Camargo 2000	29/234	37/235		63.9 %	0.76 [0.45, 1.28]
Rowe 1999	11/94	17/94		29.6 %	0.60 [0.26, 1.36]
Total (95% CI)	**359**	**366**		**100.0 %**	**0.72 [0.47, 1.10]**

Total events: 43 (ICS + oral CS), 58 (Oral CS)

Heterogeneity: $Chi^2 = 0.29$, df = 2 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable



Analysis 1.25. Comparison 1 Any ICS plus oral corticosteroid versus oral corticosteroid, Outcome 25 Asthma relapse at 20-24 days; patients lost to follow-up excluded.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 1 Any ICS plus oral corticosteroid versus oral corticosteroid

Outcome: 25 Asthma relapse at 20-24 days; patients lost to follow-up excluded

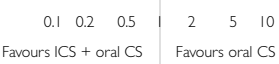
Study or subgroup	ICS + oral CS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Brenner 2000	4/28	4/35		5.5 %	1.29 [0.29, 5.70]
Camargo 2000	30/257	37/260		58.4 %	0.80 [0.48, 1.33]
Rowe 1999	12/94	23/94		36.1 %	0.45 [0.21, 0.97]
Total (95% CI)	**379**	**389**		**100.0 %**	**0.70 [0.46, 1.05]**

Total events: 46 (ICS + oral CS), 64 (Oral CS)

Heterogeneity: $Chi^2 = 2.15$, df = 2 (P = 0.34); $I^2 = 7\%$

Test for overall effect: Z = 1.72 (P = 0.086)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Any ICS versus oral corticosteroid, Outcome 1 Asthma relapse at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 1 Asthma relapse at 7-10 days

Study or subgroup	ICS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Fitzgerald 2000	9/90	10/85		0.83 [0.32, 2.16]
Levy 1996	39/200	40/203		0.99 [0.60, 1.61]
Nana 1998	5/42	3/42		1.76 [0.39, 7.88]
Volovitz 1998	0/11	0/11		0.0 [0.0, 0.0]
Total (95% CI)	**343**	**341**		**1.00 [0.66, 1.52]**

Total events: 53 (ICS), 53 (Oral CS)

Heterogeneity: Chi^2 = 0.68, df = 2 (P = 0.71); I^2 =0.0%

Test for overall effect: Z = 0.00 (P = 1.0)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Any ICS versus oral corticosteroid, Outcome 2 Asthma relapse at 16-21 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 2 Asthma relapse at 16-21 days

Study or subgroup	ICS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Levy 1996	54/200	46/203		1.26 [0.80, 1.99]
Volovitz 1998	0/11	0/11		0.0 [0.0, 0.0]
Total (95% CI)	**211**	**214**		**1.26 [0.80, 1.99]**

Total events: 54 (ICS), 46 (Oral CS)

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Any ICS versus oral corticosteroid, Outcome 3 Hospital admission.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 3 Hospital admission

Study or subgroup	ICS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Fitzgerald 2000	0/90	0/85		0.0 [0.0, 0.0]
Nakanishi 2003	0/29	1/28		0.31 [0.01, 7.95]
Volovitz 1998	0/11	0/11		0.0 [0.0, 0.0]
Total (95% CI)	**130**	**124**		**0.31 [0.01, 7.95]**

Total events: 0 (ICS), 1 (Oral CS)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.71 (P = 0.48)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Any ICS versus oral corticosteroid, Outcome 4 PEF at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

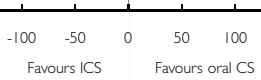
Outcome: 4 PEF at 7-10 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fitzgerald 2000	75	485.7 (115.4)	70	487.1 (100.2)		11.3 %	-1.40 [-36.52, 33.72]
Levy 1996	182	397.6 (107.6)	172	395.3 (102.2)		29.1 %	2.30 [-19.56, 24.16]
Manjra 2000	159	264 (83)	150	248 (85)		39.5 %	16.00 [-2.75, 34.75]
Nana 1998	39	253 (114)	40	278 (132)		4.7 %	-25.00 [-79.35, 29.35]
Verona 1998	64	299 (99)	74	255 (97)		12.9 %	44.00 [11.19, 76.81]
Volovitz 1998	11	283.2 (92.4)	11	298.5 (84.5)		2.5 %	-15.30 [-89.29, 58.69]
Total (95% CI)	**530**		**517**			**100.0 %**	**10.95 [-0.84, 22.73]**

Heterogeneity: Chi^2 = 7.42, df = 5 (P = 0.19); I^2 =33%

Test for overall effect: Z = 1.82 (P = 0.069)

Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2 Any ICS versus oral corticosteroid, Outcome 5 PEF at 16-21 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

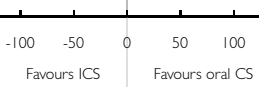
Outcome: 5 PEF at 16-21 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Levy 1996	165	415.2 (109.9)	162	408.8 (107.5)		33.7 %	6.40 [-17.16, 29.96]
Manjra 2000	158	276 (88)	151	262 (91)		46.9 %	14.00 [-5.97, 33.97]
Verona 1998	62	306 (98)	74	266 (101)		16.6 %	40.00 [6.46, 73.54]
Volovitz 1998	10	302.3 (96.6)	10	308.5 (91.6)		2.7 %	-6.20 [-88.71, 76.31]
Total (95% CI)	**395**		**397**			**100.0 %**	**15.21 [1.53, 28.89]**

Heterogeneity: $Chi^2 = 2.91$, df = 3 (P = 0.41); $I^2 = 0.0\%$

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2 Any ICS versus oral corticosteroid, Outcome 6 PEF% at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

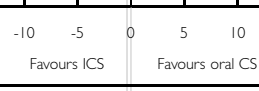
Outcome: 6 PEF% at 7-10 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Levy 1996	182	81.4 (12.2)	172	82.2 (11.1)		96.1 %	-0.80 [-3.23, 1.63]
Volovitz 1998	11	100.3 (16.6)	11	99.5 (11.8)		3.9 %	0.80 [-11.24, 12.84]
Total (95% CI)	**193**		**183**			**100.0 %**	**-0.74 [-3.12, 1.64]**

Heterogeneity: $Chi^2 = 0.07$, df = 1 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2 Any ICS versus oral corticosteroid, Outcome 7 PEF% at 16-21 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 7 PEF% at 16-21 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Levy 1996	165	85 (13)	162	84.8 (12.3)		93.1 %	0.20 [-2.54, 2.94]
Volovitz 1998	10	103.3 (11.1)	10	97.6 (11.9)		6.9 %	5.70 [-4.39, 15.79]
Total (95% CI)	**175**		**172**			**100.0 %**	**0.58 [-2.07, 3.23]**

Heterogeneity: Chi^2 = 1.06, df = 1 (P = 0.30); I^2 =6%

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable

Analysis 2.8. Comparison 2 Any ICS versus oral corticosteroid, Outcome 8 FEV_1% pred at 6-10 days (outcome not pre-specified in original review).

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 8 FEV_1% pred at 6-10 days (outcome not pre-specified in original review)

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Nakanishi 2003	27	77.3 (10.6)	28	95.1 (22.3)		100.0 %	-17.80 [-26.98, -8.62]
Total (95% CI)	**27**		**28**			**100.0 %**	**-17.80 [-26.98, -8.62]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.80 (P = 0.00014)

Test for subgroup differences: Not applicable

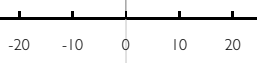
Analysis 2.9. Comparison 2 Any ICS versus oral corticosteroid, Outcome 9 FEV_1% pred at 16-21 days (outcome not pre-specified in original review).

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 9 FEV_1% pred at 16-21 days (outcome not pre-specified in original review)

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Di Franco 2006	18	76.4 (21.2)	19	83.6 (21.1)		-7.20 [-20.84, 6.44]



Analysis 2.10. Comparison 2 Any ICS versus oral corticosteroid, Outcome 10 Beta$_2$-agonist use at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 10 Beta$_2$-agonist use at 7-10 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Di Franco 2006	13	3.8 (3.3)	14	4.1 (4.7)		3.3 %	-0.30 [-3.35, 2.75]
Nana 1998	39	1.4 (1.7)	40	1.6 (1.9)		48.9 %	-0.20 [-0.99, 0.59]
Volovitz 1998	11	1.6 (0.8)	11	1.2 (1.1)		47.8 %	0.40 [-0.40, 1.20]
Total (95% CI)	**63**		**65**			**100.0 %**	**0.08 [-0.47, 0.64]**

Heterogeneity: Chi^2 = 1.15, df = 2 (P = 0.56); I^2 =0.0%

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable

Analysis 2.11. Comparison 2 Any ICS versus oral corticosteroid, Outcome 11 Beta$_2$-agonist use at 14-21 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 11 Beta$_2$-agonist use at 14-21 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Di Franco 2006	13	0.5 (1.8)	14	0.6 (1.4)		-0.10 [-1.32, 1.12]

Analysis 2.12. Comparison 2 Any ICS versus oral corticosteroid, Outcome 12 Quality of life at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

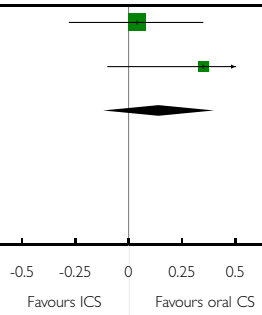
Outcome: 12 Quality of life at 7-10 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Fitzgerald 2000	73	-5.11 (1)	79	-5.15 (1.19)		66.1 %	0.04 [-0.28, 0.35]
Nana 1998	39	12.1 (23)	40	5.7 (11.8)		33.9 %	0.35 [-0.10, 0.79]
Total (95% CI)	**112**		**119**			**100.0 %**	**0.14 [-0.12, 0.40]**

Heterogeneity: Chi^2 = 1.25, df = 1 (P = 0.26); I^2 =20%

Test for overall effect: Z = 1.07 (P = 0.28)

Test for subgroup differences: Not applicable



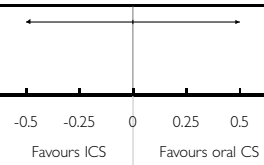
Analysis 2.13. Comparison 2 Any ICS versus oral corticosteroid, Outcome 13 Cough at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 13 Cough at 7-10 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Volovitz 1998	11	0.5 (0.71)	11	0.5 (0.71)		0.0 [-0.59, 0.59]



Analysis 2.14. Comparison 2 Any ICS versus oral corticosteroid, Outcome 14 Wheeze at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 14 Wheeze at 7-10 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Volovitz 1998	11	0.27 (0.47)	11	0.09 (0.3)		0.18 [-0.15, 0.51]

Analysis 2.15. Comparison 2 Any ICS versus oral corticosteroid, Outcome 15 Wheeze at 16-21 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 15 Wheeze at 16-21 days

Study or subgroup	ICS N	Mean(SD)	Oral CS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Volovitz 1998	10	0.18 (0.6)	11	0.22 (0.67)		-0.04 [-0.58, 0.50]

Analysis 2.16. Comparison 2 Any ICS versus oral corticosteroid, Outcome 16 Hoarseness at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 16 Hoarseness at 7-10 days

Study or subgroup	ICS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Fitzgerald 2000	0/91	1/87		0.32 [0.01, 7.84]

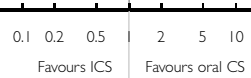
Analysis 2.17. Comparison 2 Any ICS versus oral corticosteroid, Outcome 17 Hoarseness at 16-21 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 17 Hoarseness at 16-21 days

Study or subgroup	ICS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Levy 1996	8/206	5/206		1.62 [0.52, 5.05]



Analysis 2.18. Comparison 2 Any ICS versus oral corticosteroid, Outcome 18 Sore throat at 7-10 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 18 Sore throat at 7-10 days

Study or subgroup	ICS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Francis 1997	0/37	2/19		0.09 [0.00, 2.05]

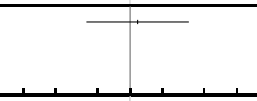
Analysis 2.19. Comparison 2 Any ICS versus oral corticosteroid, Outcome 19 Sore throat at 16-21 days.

Review: Inhaled steroids for acute asthma following emergency department discharge

Comparison: 2 Any ICS versus oral corticosteroid

Outcome: 19 Sore throat at 16-21 days

Study or subgroup	ICS n/N	Oral CS n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Levy 1996	7/206	6/207		1.18 [0.39, 3.57]



ADDITIONAL TABLES

Table 1. Summary of included studies comparing ICS plus oral corticosteroids to oral corticosteroids alone

Study	ICS + oral corticosteroids N	Corticosteroids N	Age	Location	Duration and delivery for ICS + corticosteroids	Duration and delivery for placebo + corticosteroids	Standard of care
Brenner 2000	28	35	Adults	US	Flunisolide 1 mg twice daily by MDI and aerochamber for 24 days	Placebo twice daily by MDI and aerochamber	Oral prednisone 40 mg daily for 5 days, and used albuterol MDI as needed
Camargo 2000	257	260	Predominantly adults	US	250 μg inhaled fluticasone by Diskhaler twice daily for 20 days	Placebo by Diskhaler twice daily for 20 days	Oral prednisone 50 mg daily for 5 days, and inhaled albuterol as needed
Rowe 1999	94	94	Adults	Canada	Inhaled budesonide Turbuhaler 800 μg twice daily for 3 weeks	Inhaled placebo Turbuhaler twice daily for 3 weeks	Both treatment and control groups received prednisone 50 mg PO x 7 days and prn salbutamol by MDI after discharge

ICS: inhaled corticosteroids; MDI: metered-dose inhaler; PO: oral.

Table 2. Summary of included studies comparing ICS alone to oral corticosteroid alone

Study	ICS N	Corticosteroids N	Age	Location	Duration and delivery for ICS	Duration and delivery for corticosteroids	Standard of care
Di Franco 2006	18	19	Adults	Italy	Inhaled fluticasone propionate (FP) 2000 mg/daily (4 puffs of 250 mg in the morning and in the evening with	Oral prednisone 40 mg/day tapered to 10 mg/day by reducing the dose by 5 mg every other day and in-	

Table 2. Summary of included studies comparing ICS alone to oral corticosteroid alone (*Continued*)

					a large spacer) and oral prednisone placebo for 2 weeks	haled placebo for 2 weeks. Patients held their usual regular ICS treatment but continued to use their previous regular bronchodilator treatment (including oral theophylline), during the study period	
Fitzgerald 2000	90	85	Adults	Canada	Budesonide 600 μg 4 times daily by Turbuhaler for 7 to 10 days (mean 7.5 days)	Oral prednisone, 40 mg daily, for 7 to 10 days (mean 7.5 days)	Participants used inhaled terbutaline as needed and pre-existing asthma medications were continued
Francis 1997	37	19	Children	Multicentre study based in the UK	Inhaled fluticasone propionate, 1 mg twice daily by nebuliser, and placebo oral suspension for 7 days	Inhaled placebo twice daily, and oral prednisolone 2 mg/kg/day for 4 days, then 1 mg/kg/day for 3 days	Both groups received salbutamol as needed, by nebuliser or MDI with babyhaler. Concurrent medications were continued (4 patients only)
Levy 1996	200	203	Adults	UK	Fluticasone 1 mg twice daily via a Volumatic for a period of 16 days	Reducing course of oral prednisolone, starting at 40 mg and reducing by 5 mg every 2 days, for a period of 16 days	All concurrent asthma medications, including existing ICS, were continued
Manjra 2000	158	151	Children	multicentre study based in the UK	Fluticasone propionate, 1 mg twice daily by nebuliser for 7 days and oral placebo	Inhaled placebo, and oral prednisolone, 2 mg/kg/day for 4 days, then 1 mg/kg/day for 3 days	Both groups received inhaled salbutamol as needed, and concurrent medications were continued

Table 2. Summary of included studies comparing ICS alone to oral corticosteroid alone (*Continued*)

Nakanishi 2003	29	28	Children	US	Flunisolide, 4 inhalations (1 mg) twice daily for 7 days, and daily placebo tablets	Oral prednisone, 2 mg/kg (maximum of 60 mg/day) for 7 days and inhaled placebo twice daily. Outpatient inhalations were given with a pressurised MDI with valved holding chamber	
Nana 1998	42	42	Adults	Thailand	Inhaled budesonide by Turbuhaler, 1600 mg twice daily for 7 days, and oral placebo	Oral prednisolone initially 40 mg per day and decreasing by 5 mg/day for 7 days, and inhaled placebo	Both groups received 1 dose of oral prednisolone 60 mg PO while in the emergency department, and inhaled terbutaline by Turbuhaler as needed. Other asthma medications were continued during the study (48 patients were on oral xanthines and 49 patients were on oral beta$_2$-agonists)
Verona 1998	62	74	Children	Multicentre study based in the UK	Fluticasone propionate (FP) 500 μg twice daily by MDI with spacer for 7 days, and placebo tablets	Prednisolone tablets, 2 mg/kg/day for 4 days, 1 mg/kg/day for 3 days, and placebo MDI inhaler	All patients received Ventolin as needed, and continued all regular asthma medications
Volovitz 1998	11	11	Children	Israel	Single-dose budesonide 1600 μg by turbohaler	Prednisolone 2 mg/kg PO	Both groups received terbutaline 5 mg by nebuliser or 0.

Table 2. Summary of included studies comparing ICS alone to oral corticosteroid alone (*Continued*)

							5 mg by turbohaler at the start of trial. Intervention 1 group was discharged on budesonide 200 μg 4 times daily by turbohaler, reduced by 25% every second day, and placebo tablets. From the eighth day, they continued on 200 μg twice daily for 2 weeks. Intervention 2 group was discharged on prednisolone 2 mg/kg/day, reduced by 25% every second day, and placebo Tubohaler

ICS: inhaled corticosteroid; MDI: metered-dose inhaler; PO: oral.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*T he Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.

4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Database search strategies 2003 to 2012

Cochrane Airways Group Register of trials (CAGR)

(emergenc* or acute* or status or sever* or exacerbat* or hospital* or intensiv* or admit* or admission or discharg*) and ((steroid* or corticosteroid* or glucocorticoid* or fluticasone or flovent or flixotide or beclomethasone or beclometasone or becloforte or becotide or QVAR or budesonide or pulmicort or flunisolide or aerobid or bronalide or triamcinolone or kenalog or beclovent or azmacort or vanceril or aerobec or ciclesonide or Alvesco) and (inhal* or nebuli* or aerosol*))

Clinicaltrials.gov

steroid | Interventional Studies | acute asthma
budesonide| Interventional Studies | acute asthma
fluticasone| Interventional Studies | acute asthma

Appendix 3. Search strategies pre-2003

The Cochrane Airways Review Group has developed an "Asthma and Wheez* RCT" register was searched with the following terms: Emerg* OR acute OR status AND dexa* OR deca* OR fluticasone OR Flovent OR beclomethasone OR Becloforte OR budesonide OR Pulmicort OR flunisolide OR Aerobid OR Bronalide OR triamcinalone OR Beclovent OR Azmacort OR Vanceril OR Becotide OR Flixotide OR Aerobec

Randomised controlled trials are identified in the register using the following search strategy: placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study.

WHAT'S NEW

Last assessed as up-to-date: 28 September 2012.

Date	Event	Description
28 September 2012	New citation required but conclusions have not changed	Two studies added.
28 September 2012	New search has been performed	new literature search run. Two trials (Di Franco 2006 (40 adults); Nakanishi 2003 (58 children)) were added to the review. Both compared high-dose ICS therapy with oral corticosteroid therapy. Inclusion of these studies did not challenge the conclusions in the previous version of the review

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 2000

Date	Event	Description
30 July 2008	Amended	Converted to new review format.
21 March 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For the 2000 version of this review:

Edmonds ML: initiated the review, wrote the protocol, performed searches, performed quality assessments, entered data and performed analysis, and was primary author of review and updated versions.

Camargo CA Jr: protocol development, methodological input, statistical support and assumed major editorial role.

Brenner BE Jr: protocol development and manuscript review.

Rowe BH: co-authored protocol, performed selection for inclusion and quality assessment, data extraction and data entry, manuscript review, conversion to RevMan 4 and assigned editor for Cochrane Airways Review Group.

In the 2012 revision of this review Milan SJ and Edmonds M independently selected trials for inclusion from initial searches, and Edmonds M selected trials for inclusion from full trial reports. Milan SJ updated the 'Risk of bias' tables for trials already included in the review and similarly for any new trials identified in the update and they were checked by Edmonds M. Milan SJ and Edmonds M also worked jointly on the remaining aspects of the 2012 update. Rowe BH provided design input, manuscript review, and was the assigned editor for the Cochrane Airways Review Group.

DECLARATIONS OF INTEREST

The authors who have been involved in this review have done so without any known conflicts of interest. Drs. Rowe, Brenner and Camargo were involved as lead investigators in the primary studies of oral corticosteroid plus ICS versus oral corticosteroid alone. Drs. Camargo, Rowe and Brenner have received unrestricted educational grants for research from Astra, Boehringer-Ingelheim, Forest, Glaxo Wellcome, Merck and Sepracor. However, none of the authors is considered a paid consultant by any pharmaceutical company that produces ICS agents.

SOURCES OF SUPPORT

Internal sources

- Department of Emergency Medicine, University of Alberta, Edmonton, AB, Canada.
- NHS Research and Development, UK.
- National Institute of Health Research (SJM), UK.

External sources

- HL-03533 NIH (CA Camargo Jr), USA.
- Canadian Institutes of Health Research (CIHR), Ottawa, ON (BH Rowe), Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2012 update of this review heterogeneity was assessed mainly in relation to I^2. Risk of bias was assessed in accordance with Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Inhalation; Anti-Asthmatic Agents [*administration & dosage]; Anti-Inflammatory Agents [administration & dosage]; Asthma [*drug therapy]; Emergency Service, Hospital; Glucocorticoids [*administration & dosage]; Patient Discharge; Randomized Controlled Trials as Topic; Steroids

MeSH check words

Humans