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Early use of inhaled corticosteroids in the emergency department treatment of acute asthma (Review)

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Early use of inhaled corticosteroids in the emergency department treatment of acute asthma.
Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD002308.
DOI: 10.1002/14651858.CD002308.pub2.

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[Intervention Review]

Early use of inhaled corticosteroids in the emergency department treatment of acute asthma

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Editorial group: Cochrane Airways Group.
Publication status and date: Edited (no change to conclusions), published in Issue 8, 2018.

Citation: Edmonds ML, Milan SJ, Camargo Jr CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD002308. DOI: 10.1002/14651858.CD002308.pub2.

ABSTRACT

Background

Systemic corticosteroid therapy is central to the management of acute asthma. The use of inhaled corticosteroids (ICS) may also be beneficial in this setting.

Objectives

To determine the benefit of ICS for the treatment of patients with acute asthma managed in the emergency department (ED).

Search methods

We identified controlled clinical trials from the Cochrane Airways Group specialised register of controlled trials. Bibliographies from included studies, known reviews, and texts also were searched. The latest search was September 2012.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs. Studies were included if patients presented to the ED or its equivalent with acute asthma, and were treated with ICS or placebo, in addition to standard therapy. Two review authors independently selected potentially relevant articles, and then independently selected articles for inclusion. Methodological quality was independently assessed by two review authors. There were three different types of studies that were included in this review: 1) studies comparing ICS vs. placebo, with no systemic corticosteroids given to either treatment group, 2) studies comparing ICS vs. placebo, with systemic corticosteroids given to both treatment groups, and 3) studies comparing ICS alone versus systemic corticosteroids. For the analysis, the first two types of studies were included as separate subgroups in the primary analysis (ICS vs. placebo), while the third type of study was included in the secondary analysis (ICS vs. systemic corticosteroid).

Data collection and analysis

Data were extracted independently by two review authors if the authors were unable to verify the validity of extracted information. Missing data were obtained from the authors or calculated from other data presented in the paper. Where appropriate, individual and pooled dichotomous outcomes were reported as odds ratios (OR) 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 a random-effects model was used for sensitivity analysis. Heterogeneity is reported using I-squared (I^2) statistics.

Main results

Twenty trials were selected for inclusion in the primary analysis (13 paediatric, seven adult), with a total number of 1403 patients. Patients treated with ICS were less likely to be admitted to hospital (OR 0.44; 95% CI 0.31 to 0.62; 12 studies; 960 patients) and heterogeneity (I^2 = 27%) was modest. This represents a reduction from 32 to 17 hospital admissions per 100 patients treated with ICS in comparison with placebo. Subgroup analysis of hospital admissions based on concomitant systemic corticosteroid use revealed that both subgroups indicated benefit from ICS in reducing hospital admissions (ICS and systemic corticosteroid versus systemic corticosteroid: OR 0.54; 95% CI 0.36 to 0.81; 5 studies; N = 433; ICS versus placebo: OR 0.27; 95% CI 0.14 to 0.52; 7 studies; N = 527). However, there was moderate heterogeneity in the subgroup using ICS in addition to systemic steroids (I^2 = 52%). Patients receiving ICS demonstrated small, significant improvements in peak expiratory flow (PEF: MD 7%; 95% CI 3% to 11%) and forced expiratory volume in one second (FEV_1: MD 6%; 95% CI 2% to 10%) at three to four hours post treatment). Only a small number of studies reported these outcomes such that they could be included in the meta-analysis and most of the studies in this comparison did not administer systemic corticosteroids to either treatment group. There was no evidence of significant adverse effects from ICS treatment with regard to tremor or nausea and vomiting. In the secondary analysis of studies comparing ICS alone versus systemic corticosteroid alone, heterogeneity among the studies complicated pooling of data or drawing reliable conclusions.

Authors' conclusions

ICS therapy reduces hospital admissions in patients with acute asthma who are not treated with oral or intravenous corticosteroids. They may also reduce admissions when they are used in addition to systemic corticosteroids; however, the most recent evidence is conflicting. There is insufficient evidence that ICS therapy results in clinically important changes in pulmonary function or clinical scores when used in acute asthma in addition to systemic corticosteroids. Also, there is insufficient evidence that ICS therapy can be used in place of systemic corticosteroid therapy when treating acute asthma. Further research is needed to clarify the most appropriate drug dosage and delivery device, and to define which patients are most likely to benefit from ICS therapy. Use of similar measures and reporting methods of lung function, and a common, validated, clinical score would be helpful in future versions of this meta-analysis.

PLAIN LANGUAGE SUMMARY

Early use of inhaled corticosteroids in the emergency department treatment of acute asthma

Asthma is one of the most common chronic diseases in the world. It is estimated that 300 million people of all ages, and all ethnic backgrounds, suffer from asthma, with 1 in every 250 deaths worldwide attributed to asthma. In an asthma attack, the airways (passages to the lungs) narrow from muscle spasm and swelling (inflammation). Corticosteroid drugs can be used to reduce the swelling. Corticosteroids can be inhaled, or taken systemically by mouth (orally) or through a drip into the veins (intravenously).

Standard treatment for asthma attacks is to administer $beta_2$-agonists (to open up the airways) and systemic corticosteroids (to reduce the inflammation). The purpose of this review was to determine if the use of inhaled corticosteroid (ICS) agents is beneficial in emergency department treatment settings. A total of 90 studies were identified for this review; 20 were deemed relevant and selected for inclusion (13 paediatric, 7 adult), with a total number of 1403 patients.

This review found that inhaled corticosteroids used alone or in combination with systemic corticosteroids helped to relieve asthma attacks, were well tolerated and had few side effects. However, the most effective drug and dosage are unclear. The studies in the review included a variety of ICSmedications: beclomethasone (Beclovent/Becloforte/QVAR), budesonide (Pulmicort), dexamethasone sodium phosphate, fluticasone propionate (Flovent or Flixotide), Flunisolide (Aerobid) and triamcinolone (Azmacort). The review also found that ICS administered in this setting resulted in fewer hospital admissions. There was a reduction from 32 to 17 hospital admissions per hundred patients treated with ICS agents compared with placebo. At this time there is insufficient evidence to support using ICS agents alone as a replacement for systemic corticosteroid therapy in acute asthma attacks

However, there are many unanswered questions about the use of ICS in the emergency department treatment setting. Future research should focus on optimal dosage, dosage frequency and delivery device, identification of effective ICS agents, clearly defined outcomes (such as admissions criteria, pulmonary function testing and follow-up after discharge from emergency departments).

Summary of findings for the main comparison. ICS versus placebo

ICS versus placebo

Patient or population: people with acute asthma
Settings: emergency department
Intervention: ICS therapy

Control: placebo

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	ICS therapy				
Hospital admission	**316 per 1000**	**169 per 1000** (125 to 220)	**OR 0.44** (0.31 to 0.61)	959 (12 studies)	⊕⊕⊖⊖ **low[1]**	There was conflicting evidence from the studies of ICS in addition to systemic corticosteroids (I^2 = 52%)
FEV_1 at 1 hour	The mean FEV_1 ranged from **1.41 to 2.17 L**	The mean FEV_1 at 1 hour in the intervention groups was **0.28 L higher** (0.22 lower to 0.77 higher)	MD 0.28 (95% CI -0.22 to 0.77)	248 (4 studies)	⊕⊕⊖⊖ **low[2]**	
FEV_1 at 3 to 4 hours	The mean FEV_1 ranged from **1.7 to 2.1 L**	The mean FEV_1 at 3 to 4 hours in the intervention groups was **0.15 L higher** (0.09 lower to 0.39 higher)	MD 0.15 (95% CI -0.09 to 0.39)	319 (4 studies)	⊕⊕⊕⊖ **moderate[3]**	
Adverse effects - nausea/vomiting	**64 per 1000**	**21 per 1000** (2 to 178)	**OR 0.32** (0.03 to 3.18)	94 (1 study)	⊕⊕⊖⊖ **low[4]**	

*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; FEV_1: forced expiratory volume in one second; 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] Point deducted in hospital admissions due to variability in risk of bias among contributing trials and a point deducted due to heterogeneity.
[2] Point deducted in FEV_1 at 1 hour due to variability in risk of bias among contributing trials, and an additional point deducted for the very high level of heterogeneity (I^2 = 90%).
[3] Point deducted in FEV_1 at 3 to 4 hours due to heterogeneity (I^2 = 55%).
[4] 2 points deducted due to wide CI and only one study contributing to outcome.

Summary of findings 2. ICS versus systemic corticosteroids

ICS versus systemic corticosteroids

Patient or population: people with acute asthma
Settings: emergency department
Intervention: ICS versus systemic 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	ICS versus systemic corticosteroid				
Hospital admission	**181 per 1000**	**110 per 1000** (52 to 215)	**OR 0.56** (0.25 to 1.24)	763 (10 studies)	⊕⊕⊝⊝ **low**[1]	

*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] Variability in risk of bias among included studies and 61% I^2 heterogeneity with regard to hospital admissions in ICS versus systemic corticosteroid comparison.

BACKGROUND

Description of the condition

Acute asthma exacerbation is a common presenting complaint to the emergency department (ED). In the US, acute asthma exacerbations account for almost two million ED visits per year (Mannino 1998). Approximately 10% to 20% of these patients will require admission to the hospital, and, of those discharged from the ED after apparently successful treatment, approximately 10% to 20% will relapse within two weeks (Griswold 2005; Rowe 2008a; Rowe 2010). Several national (Boulet 2000; BTS 1997; BTS/SIGN 2011; NAEPP 1997; EPR3 2007) and international (GINA 2011; Masoli 2004; NHLBI/WHO 1995) guidelines have been produced for the management of acute asthma.

Description of the intervention

There is general agreement that bronchodilators and systemic corticosteroids are first-line agents for acute asthma. Beta$_2$-agonists are used to provide rapid symptom relief, whereas corticosteroids are used to counter airway inflammation and hasten resolution of the asthma exacerbation. There remain numerous controversies regarding the optimal agent, dose, frequency of delivery and route of delivery for both bronchodilators and corticosteroids in the acute setting. Current practice patterns usually include the use of beta$_2$-agonists via a nebuliser or metered-dose inhaled (MDI) and spacer and oral or intravenous (IV) corticosteroids administered early in the ED treatment of acute asthma (Griswold 2005). While inhaled corticosteroids (ICS) are used more commonly after ED discharge, their use is uncommon in the ED setting (Barnes 1995; BTS/SIGN 2011).

How the intervention might work

ICS have the potential to be of benefit in the acute setting. 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). Potential advantages of ICS in acute asthma therapy might include fewer 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 (Gibbs 2000; Rodrigo 1998). Furthermore, ancillary evidence from studies of patients with croup suggests that ICS agents may act on the airways over the short term to improve outcomes (Ausejo 1999).

Why it is important to do this review

Only a limited number of trials have examined the use of ICS in acute asthma and they have yielded inconsistent results. The previous version of this systematic review (Edmonds 2003) concluded that "inhaled steroids reduced hospital admissions in patients with acute asthma, but it is unclear if there is a benefit of ICS when used in addition to systemic corticosteroids. There is insufficient evidence that ICS therapy results in clinically important changes in pulmonary function or clinical scores when used in acute asthma. Similarly, there is insufficient evidence that ICS alone is as effective as systemic corticosteroid. Further research is needed to clarify if there is a benefit of ICS when used in addition to systemic corticosteroid." The 2012 update of the review evaluated these conclusions in relation to randomised controlled trials (RCTs) published since the publication of the previous version of the review.

Separate reviews are available in *The Cochrane Library* for: increased versus stable doses of ICS for exacerbations of chronic asthma in adults and children (Quon 2010), early ED treatment of acute asthma with systemic corticosteroids (Rowe 2008) and ICS for acute asthma following ED discharge (Edmonds 2009).

OBJECTIVES

To determine the effect of ICS therapy on outcomes in the ED treatment for acute asthma. The two comparisons were:

1. ICS versus placebo;
2. ICS versus systemic corticosteroids.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs or quasi-RCTs (e.g. allocation on days of the week or flipping a coin).

Types of participants

We included studies involving patients presenting to an ED or its equivalent. We included trials involving participants from other settings if the people enrolled at the ED were reported separately (e.g., if stratified randomisation was employed). Studies recruiting paediatric or adult participants were reviewed, and this designation formed one of the subgroup analyses. Studies of young children (< two years of age) with bronchiolitis or viral-induced wheeze were excluded.

Types of interventions

Patients must have been randomised to receive either single- or multiple-dose ICS early in their ED treatment. 'Inhaled corticosteroid' administration was defined as any corticosteroid agent administered by MDI, dry powder inhaler, or nebuliser in the ED. We included trials where people may also have received additional asthma medications (such as systemic corticosteroid and beta$_2$-agonists by any route, ipratropium bromide, theophylline compounds, magnesium sulphate or anti-histamines). Data for these co-interventions were recorded or requested from the authors who were available for contact, where it was not reported in the articles.

We included the following comparisons:

1. ICS versus placebo:
   a. with concomitant systemic corticosteroids in both groups;
   b. with no concomitant systemic corticosteroids in either group;
2. ICS versus systemic corticosteroids.

Types of outcome measures

Primary outcomes

1. Admission to hospital (based on the criteria reported in the manuscript).

Secondary outcomes

1. Pulmonary function tests (absolute and percent predicted peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1));
2. Adverse effects;
3. Physiological outcomes (e.g., clinical scores, pulse rate, respiratory rate, arterial oxygen saturation, blood pressure, arterial pH, etc.).

Several studies included a clinical score, such as the pulmonary index or pulmonary index score (PIS), and others that are scoring systems to evaluate patients with acute asthma. These scores were generally a composite score assessing a number of physical examination parameters often including heart rate, respiratory rate, presence and severity of wheezing, accessory muscle use and severity of dyspnoea. (Becker 1984)

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR coded as 'asthma'. For the review version up to 2005 we used the search strategy in Appendix 2, while for the 2012 update, we used the strategy described in Appendix 3. We also conducted a search of ClinicalTrials.gov. All databases were searched from their inception with no restriction on language of publication.

The latest search was conducted in September 2012.

Searching other resources

For the 2005 version, additional efforts to locate potential trials were as follows:

- reference lists of all available primary studies and review articles were reviewed to identify potentially relevant citations;
- 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;
- we contacted scientific advisors of the various pharmaceutical industries that manufacture known ICS agents (AstraZeneca: budesonide; GlaxoSmithKline: fluticasone and beclomethasone; Forest laboratories: flunisolide) to request any unpublished, or interim results on relevant research;
- we handsearched abstracts from the Society for Academic Emergency Medicine (1997 to 2000, published in *Academic Emergency Medicine*), the American College of Chest Physicians (1995 to 2000, published in *Chest*) the British Thoracic Society (published in *Thorax*) and the American Thoracic Society (1997 to 1999 published in *American Journal of Respiratory and Critical Care Medicine*) meetings;
- we made personal contact with colleagues, collaborators and other trialists working in the field of asthma was made to identify potentially relevant studies.

In 2012 we checked the reference sections of included papers to search for additional potentially relevant trials.

Data collection and analysis

Selection of studies

Prior to the 2012 update two review authors (MLE, BHR) independently examined the references returned by searches 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

Prior to the 2012 update data extraction was performed independently by two review authors (BHR, MLE), and the authors of trials were contacted to provide missing data where possible. In some cases, expansion of graphic representations of data from the manuscripts was used to estimate missing data. The data were checked and entered into Review Manager (RevMan 2011) by one review author. In the 2012 update data extraction was performed by SJM and checked by MLE, and entered into RevMan (RevMan 2011) by SJM and checked by MLE.

Assessment of risk of bias in included studies

The risk of bias of included studies was assessed using the Cochrane Collaboration's risk of bias tool (Higgins 2011). Two review authors (MLE and SJM) assessed the risk of bias for all included studies with regards 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 randomised controlled trial.

Measures of treatment effect

For dichotomous variables, data are expressed as odds ratios (OR) with 95% confidence intervals (CI). Data for continuous variables were reported as mean differences (MD) 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, we attempted to contact authors for clarification. We reported intention-to-treat analyses.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of forest plots. The I^2 statistic was also considered and interpreted in relation to the following guidance:

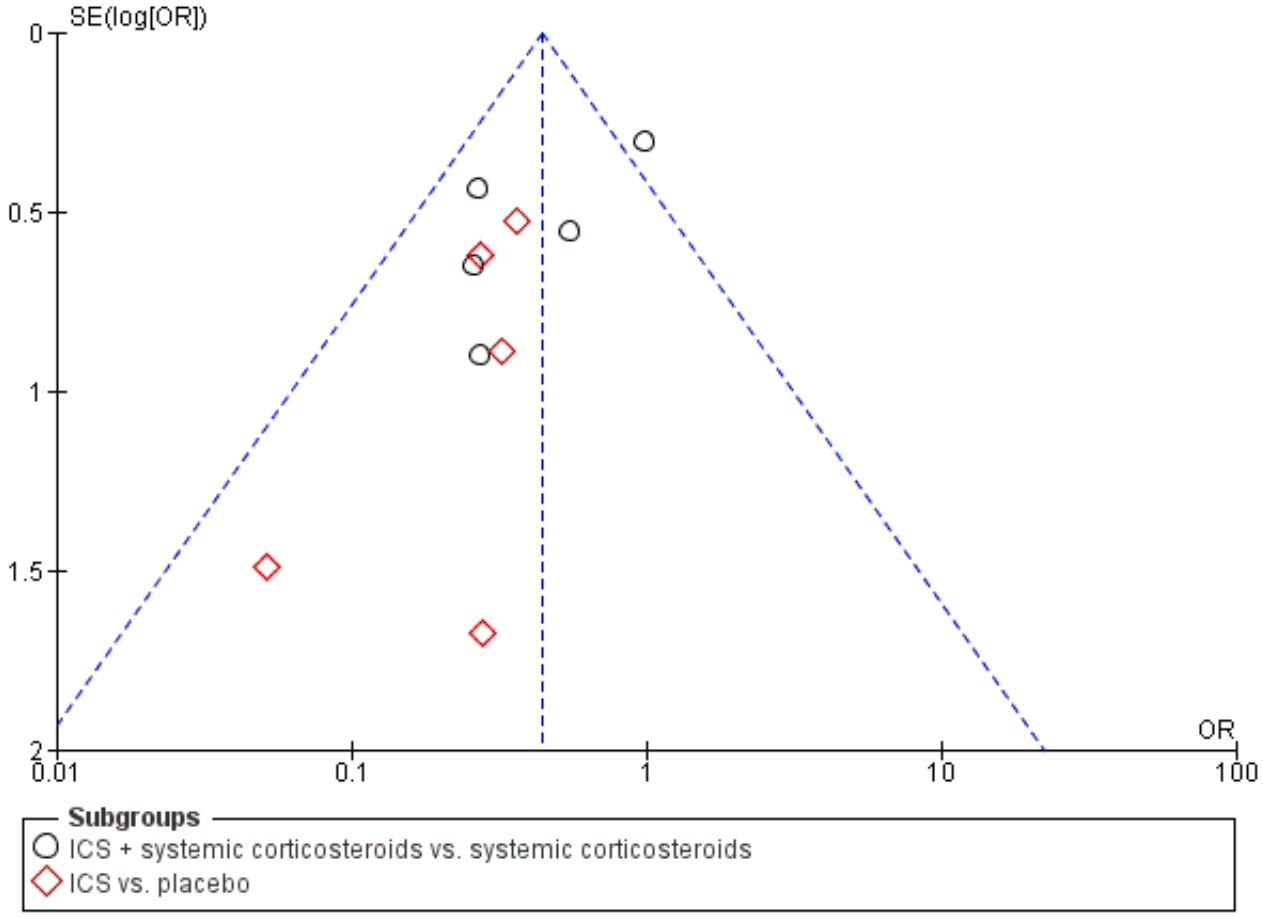
- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity (Higgins 2011).

The Chi^2 test was similarly considered (P -value < 0.10); however, we regarded the I^2 statistic as our primary measure of heterogeneity.

Assessment of reporting biases

We planned to evaluate publication bias using visual inspection of funnel plots if there was an adequate number of trials aggregated in the analyses (more than 10). However, we recognised that an asymmetric funnel plot can reflect heterogeneity, outcome reporting bias and small study effects and is therefore not necessarily a reflection of publication bias. A sufficient number of trials in the analysis provided the opportunity to include funnel plots for the primary analyses, and they are presented in Figure 1 and Figure 2.

Figure 1. Funnel plot of comparison: 1 ICS therapy, outcome: 1.1 Hospital admission.



Data synthesis

We combined trials were combined using RevMan (RevMan 2011). Continuous variables were combined using a MD or standardised mean difference (SMD) and reported together with a 95% CI. We combined dichotomous variables using an OR with 95% CI.

Subgroup analysis and investigation of heterogeneity

We specified the following three specific subgroups a priori:

1. adults compared to children;
2. severe asthma compared to those with less severe asthma (categorised by % predicted PEF), and by the placebo group hospital admissions);
3. high versus low dose (high dose was defined as 2 mg or more beclomethasone dipropionate (BDP) equivalence).

Sensitivity analysis

We conducted sensitivity analyses based on methodological quality and fixed- versus random-effects models.

RESULTS

Description of studies

Results of the search

The initial search in 1998 identified 352 articles. There were a total of 187 original citations; 15 articles were deemed potentially relevant by one or both of the two review authors, with substantial agreement (kappa = 0.78) between the two review authors. These 15 articles were retrieved and the full-text manuscripts were reviewed for inclusion. From the full text, using specific criteria, two review authors independently selected trials for inclusion in the review. Five articles were identified by both review authors for inclusion, with 100% simple agreement and a kappa of 1.0. Six further articles were identified using other methods (one by author

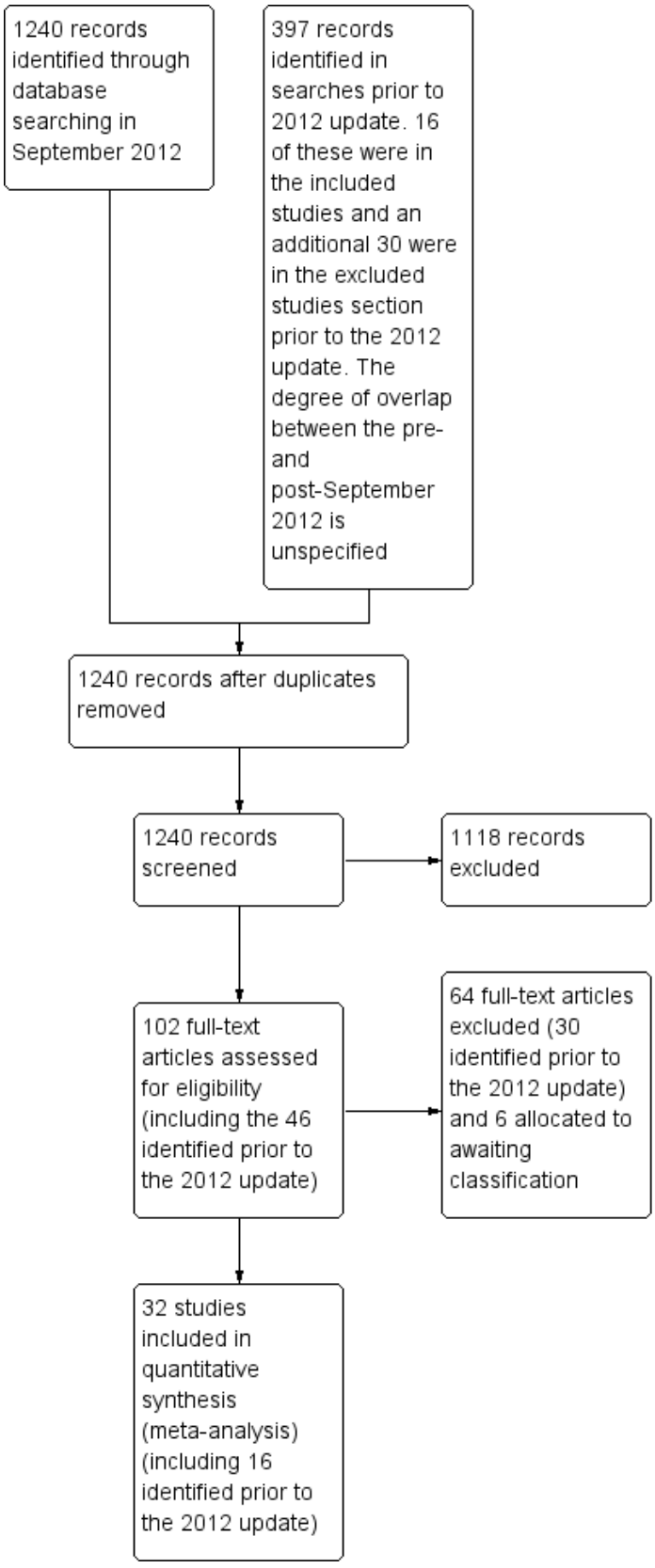
contact, two by searching abstracts from recent meetings and three in the updates from the register or computerised searches), which were selected for inclusion for a total of 11 articles; seven in the primary analysis and four in the secondary analysis.

In the update search in April 1999 we identified 42 articles with 33 original citations. One of these articles was selected for inclusion in the secondary analysis (Volovitz 1998). In an update search in February 2001 using EMBASE and MEDLINE, two further trials were selected for inclusion, one in the primary analysis (Singhi 1999), and one in the secondary analysis (Devidayal 1999). One further article was added from searching abstracts for inclusion in the secondary analysis (Schuh 2000). An update search in April 2002 identified one further trial for inclusion (Tsai 2001). An update search in February 2003 did not find any new studies for inclusion.

The update search in February 2005 identified five full trials for inclusion. Three of these trials were included in the primary analysis (Milani 2004; Rodrigo 2003; Sharma 2003) and three trials were included in the secondary analysis (Macias 2003; Milani 2004; Rodrigo 2005). One trial (Milani 2004) had three treatment arms (ICS, systemic corticosteroid and placebo) and so contributed to both the primary and secondary analyses. Six trials have been published in abstract form only; author contact was unsuccessful. Three were judged as potentially eligible for inclusion in the primary analysis (Agarwal 2003; Blandon 2004; Olaivar 1999) and two for inclusion in the secondary analysis (Acun 2003; Sari 2004). Three of these were included in the 2012 update (Blandon 2004; Olaivar 1999; Sari 2004).

In the 2012 update 1240 trial reports were identified (Figure 2) and this produced a further 16 included studies to bring the total to 32. The new studies were Ancheta 2008 (24 patients), Bateman 2006 (115 patients), Bautista 1994 (30 patients), Belda 2007 (39 patients), Blandon 2004 (86 patients), Estrada 2005 (100 patients), Go 2010 (33 patients), Nuhoglu 2005 (26 patients), Olaivar 1999 (55 patients), Rahman 2008 (100 patients), Razi 2012 (100 patients), Sari 2004 (76 patients), Schuh 2006 (69 patients), Sekerel 2005 (67 patients), Starobin 2008 (33 patients) and Upham 2011 (180 patients). This added a further 1173 (49%) patients to the 1201 already in the review, bringing the total to 2374.

Figure 2. Study flow diagram.



Included studies

All 32 studies were published after 1992. There were studies from all over the world; five were from centres in Canada; four from the Philippines; three each from the US, Uruguay, India and Turkey; two each from South Africa, Israel and Mexico; and one from each of Indonesia, Brazil and Taiwan. Twenty studies were included in the primary analysis that compared ICS versus placebo; seven studies (Bateman 2006; Guttman 1997; Nuhoglu 2005; Razi 2012; Starobin 2008; Sung 1998; Upham 2011) compared ICS versus placebo with both groups receiving systemic corticosteroid and 13 studies compared ICS versus placebo with systemic corticosteroid withheld from both treatment groups (Afilalo 1999; Blandon 2004; Bautista 1994; Estrada 2005; Milani 2004; Olaivar 1999; Pansegrouw 1992; Rodrigo 1998; Rodrigo 2003; Sekerel 2005; Sharma 2003; Singhi 1999; Tsai 2001).

Fourteen studies compared ICS versus systemic corticosteroid (Ancheta 2008; Belda 2007; Devidayal 1999; Go 2010; Macias 2003; Milani 2004; Scarfone 1995; Schuh 2000; Schuh 2006; Volovitz 1998; Rahman 2008; Rodrigo 2005; Sari 2004; Starobin 2008). Two of the studies (Milani 2004; Starobin 2008) had three treatment arms (ICS, systemic corticosteroid and placebo) and so were included in both comparisons. Details of the characteristics of all three comparisons can be found in Table 1; Table 2 and Table 3.

Populations

In the comparison ICS versus placebo, 13 of the studies involved children (Bautista 1994; Blandon 2004; Estrada 2005; Milani 2004; Nuhoglu 2005; Olaivar 1999; Razi 2012; Sekerel 2005; Sharma 2003; Singhi 1999; Sung 1998; Tsai 2001; Upham 2011), and seven involved adults (Afilalo 1999; Bateman 2006; Guttman 1997; Pansegrouw 1992; Rodrigo 1998; Rodrigo 2003; Starobin 2008). In the adult studies, the populations varied from only those with severe asthma (forced expiratory volume in one second (FEV_1) < 40% to 50% predicted or investigator-assigned severity (Bateman 2006; Rodrigo 1998; Rodrigo 2005; Upham 2011), to only those with mild to moderate asthma (FEV_1 = 40% to 70% predicted (Afilalo 1999; Guttman 1997). All of the paediatric studies excluded patients with very severe asthma (pulmonary index > 13 or equivalent), and four excluded those with only mild asthma (pulmonary index < 8 or equivalent).

In the studies comparing ICS versus systemic corticosteroid, eight involved children (Ancheta 2008; Devidayal 1999; Macias 2003; Milani 2004; Scarfone 1995; Schuh 2000; Schuh 2006; Volovitz 1998) and six involved adults (Belda 2007; Go 2010; Rahman 2008; Rodrigo 2005; Sari 2004; Starobin 2008).

Most of the studies in the secondary analysis comparing ICS versus systemic corticosteroid involved patients with mild to moderate exacerbations, although three included children with moderate to severe asthma exacerbations (Ancheta 2008; Macias 2003; Schuh 2000) and one included adults with severe asthma (Rodrigo 2005).

Interventions

ICS were administered early in the course of ED treatment; usually at the time of the first $beta_2$-agonist treatment. Total doses ranged from low (BDP 200 µg; Pansegrouw 1992) to very high (flunisolide 18 mg; Rodrigo 1998). The route of administration was via nebuliser or MDI with spacer in the paediatric studies, and predominantly via MDI with spacer in all the adult studies. In the analysis of ICS versus systemic corticosteroid, the doses of ICS were generally moderate to high. The dose, frequency and agents used in this review varied widely; however, there appears to be evidence of effect despite this heterogeneity. For example, various ICS agents were used (budesonide most often {14 studies}), the median single dose was 900 µg, the median frequency of treatment was 2 activations, and the median cumulative dose was 2 mg over up to 6 hours of observation. Delivery was most commonly by nebuliser or MDI with spacer. The dose, frequency and agents for the trials using each comparison are listed separately in Table 1, Table 2 and Table 3.

Co-interventions

All studies gave $beta_2$-agonists to participants, although the type varied. Systemic corticosteroids were administered to both the experimental and control groups in six studies (Bateman 2006; Guttman 1997; Nuhoglu 2005; Razi 2012; Sung 1998; Upham 2011); however, Razi 2012 gave intramuscular systemic corticosteroids (rather than using the oral or intra-venous routes suggested in guidelines (BTS/SIGN 2011)). Fourteen studies compared ICS versus placebo with systemic corticosteroid withheld from both treatment groups (Afilalo 1999; Bautista 1994; Blandon 2004; Estrada 2005; Milani 2004; Olaivar 1999; Pansegrouw 1992; Rodrigo 1998; Rodrigo 2003; Sekerel 2005; Sharma 2003; Singhi 1999; Starobin 2008; Tsai 2001). In one study, systemic corticosteroids and aminophylline were administered to patients who failed to improve after two hours of treatment, while maintaining the study blinding (Singhi 1999).

Fourteen studies compared ICS with systemic corticosteroid (Ancheta 2008; Belda 2007; Devidayal 1999; Go 2010; Macias 2003; Milani 2004; Rahman 2008; Rodrigo 2005; Sari 2004; Scarfone 1995; Schuh 2000; Schuh 2006; Starobin 2008; Volovitz 1998). Two of the studies (Milani 2004; Starobin 2008) had three treatment arms (ICS, systemic corticosteroid and placebo) and so were included in both the primary and secondary analyses. Ipratropium bromide was given in a number of the studies to all included patients.

Outcomes

Outcomes were measured at different time points. Most trials included pulmonary function tests or a clinical score (in paediatric studies), and hospital admissions. The criteria for admission, and the timing of admission decisions, varied among the trials, with only one trial reporting pre-specified admission criteria (Singhi 1999). Reporting of symptom scores and adverse effects also were variable, and further information about adverse effects had to be provided by authors. Vital signs were reported frequently or were requested from the authors in the initial version of this review, when not reported.

Excluded studies

Sixty-five studies failed to meet the eligibility criteria of this review and the reasons for their exclusion are provided in Characteristics of excluded studies. The primary reasons for exclusion are as follows: patients were hospitalised rather than treated just in the ED (18 (28%)), patients with stable asthma 10 (15%), comparison between systemic corticosteroids versus placebo nine (14%), outpatient treatment of acute asthma eight (12%), treatment of acute asthma after ED four (6%), non-randomised studies five (8%), review three (5%), dose comparison in ICS two (3%), combination therapy (corticosteroids plus $beta_2$-agonists versus $beta_2$-agonists alone) two (3%), combination therapy (corticosteroids + $beta_2$-agonists

versus placebo) one (2%), IV corticosteroids one (2%), prevention of ER visits one (2%) and delivery of ICS one (2%).

Risk of bias in included studies

Full details of the risk of bias can be found in Characteristics of included studies. A graphical display of our judgements can be found in Figure 3 and Figure 4.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

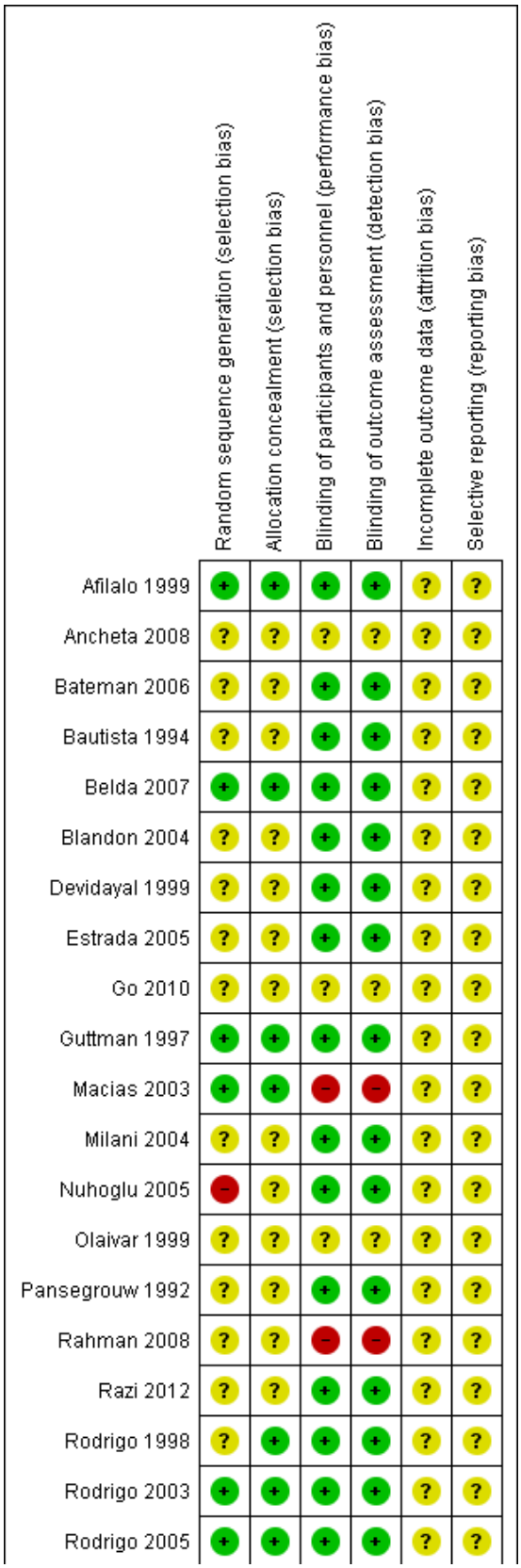


Figure 3. (Continued)

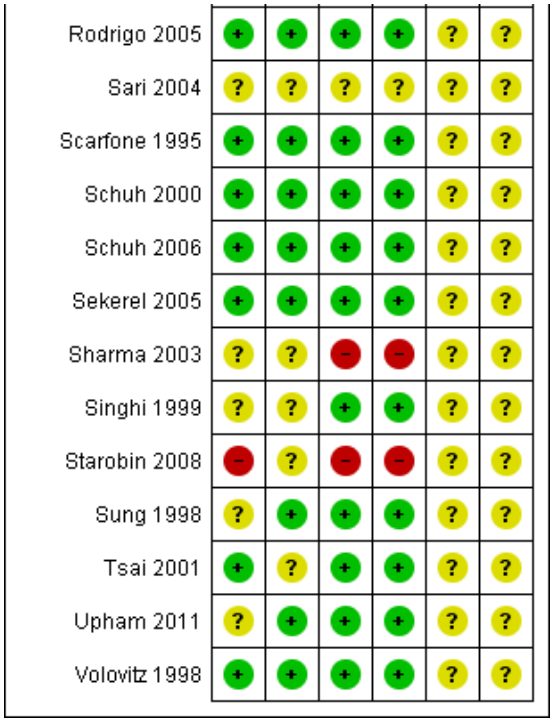
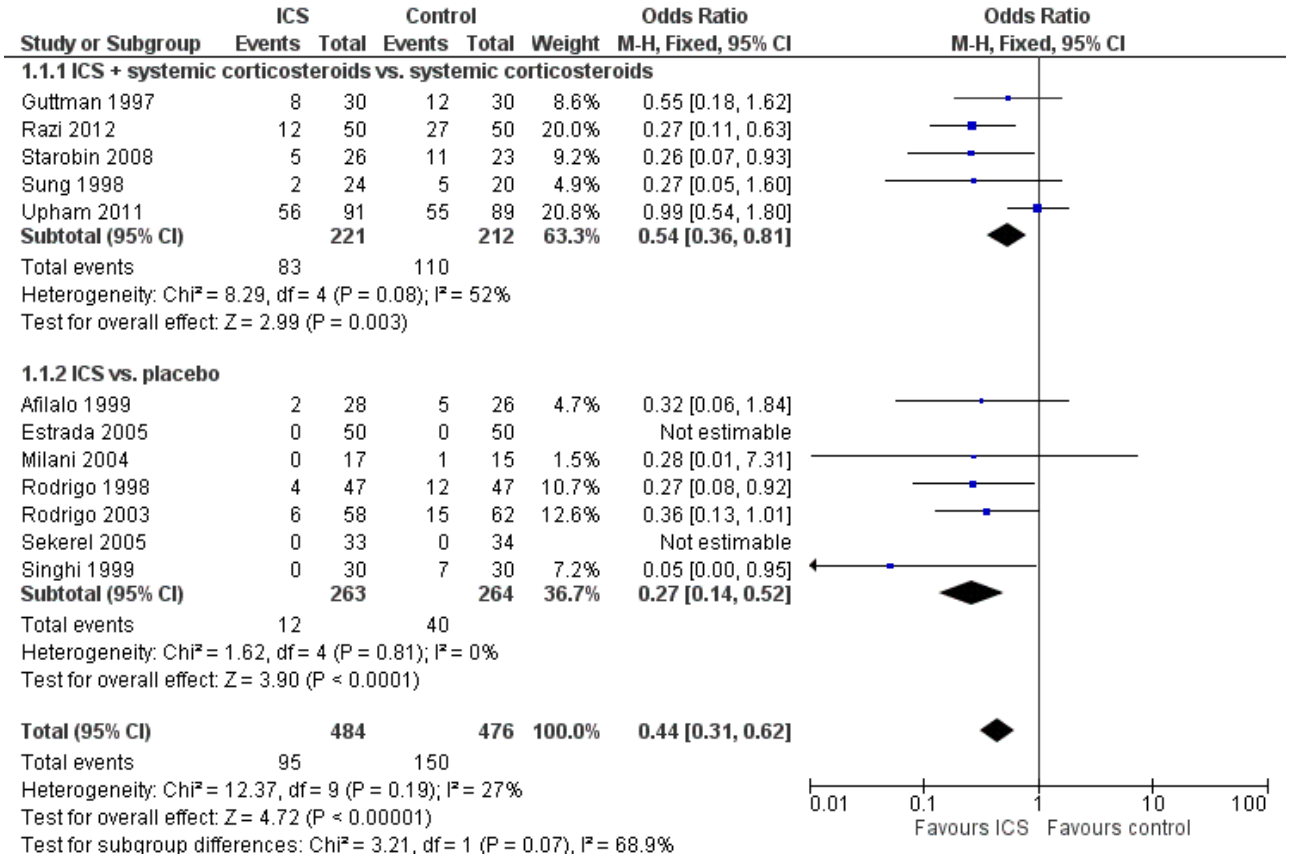


Figure 4. Forest plot of comparison: 1 ICS versus placebo, outcome: 1.1 Admission to hospital.



Allocation

The quality of reported randomisation was variable. Less than half of the 32 studies were judged as low risk of bias. Eleven (34%) studies were assessed as low risk of selection bias (Afilalo 1999; Belda 2007; Guttman 1997; Macias 2003; Rodrigo 2003; Rodrigo 2005; Scarfone 1995; Schuh 2000; Schuh 2006; Sekerel 2005; Volovitz 1998), while two (6%) were judged to be at high risk of selection bias (Nuhoglu 2005; Starobin 2008). The remaining 19 studies were at unclear risk on this respect.

Blinding

Twenty-four trials (75%) were assessed as low risk of performance and detection bias (Afilalo 1999; Bateman 2006; Bautista 1994; Belda 2007; Blandon 2004; Devidayal 1999; Estrada 2005; Guttman 1997; Milani 2004; Nuhoglu 2005; Pansegrouw 1992; Razi 2012; Rodrigo 1998; Rodrigo 2003; Rodrigo 2005; Scarfone 1995; Schuh 2000; Schuh 2006; Sekerel 2005; Singhi 1999; Sung 1998; Tsai 2001; Upham 2011; Volovitz 1998). Four (13%) were regarded as unclear in terms of risk of performance and detection bias (Ancheta 2008; Go 2010; Olaivar 1999; Sari 2004) and four were assessed as high risk of bias (Macias 2003; Rahman 2008; Sharma 2003; Starobin 2008).

Incomplete outcome data

It was unclear if any of the studies encountered attrition. However, as these trials are very short we evaluated trials where no patients were reported as having been withdrawn to be at no higher risk of bias than those where it was reported that several failed to complete the trial. In acute asthma trials it is conceivable that all participants will complete the trial and this may not be reported explicitly.

Selective reporting

In all 32 included studies reporting bias was judged to be unclear. There was no apparent indication of selective reporting in any of the trials; however, hospital admissions were reported in 12 of the 20 trials comparing ICS versus placebo and in 10 of the 14 trials in the secondary analysis where ICS alone was compared to systemic corticosteroid alone.

Effects of interventions

See: **Summary of findings for the main comparison** ICS versus placebo; **Summary of findings 2** ICS versus systemic corticosteroids

Inhaled corticosteroids versus placebo

Twelve studies involving 959 patients compared ICS with placebo (N = 484 ICS treated, N = 475 placebo) in our primary outcome, admission to hospital.

Admission to hospital

Admission to hospital is reported in Analysis 1.1 and indicates a significant reduction in hospital admissions in patients treated with ICS (OR 0.44; 95% CI 0.31 to 0.62; 12 studies; N = 960) and the heterogeneity (I^2 = 27%) was modest. Closer inspection of Analysis 1.1 reveals that both subgroups - ICS plus systemic corticosteroids versus systemic corticosteroids (OR 0.54; 95% CI 0.36 to 0.81; 5 studies; N = 433) and ICS versus placebo (OR 0.27; 95% 0.14 to 0.52; 7 studies; N = 527) - indicate benefit from ICS in reducing hospital admissions (Figure 4). However, there was heterogeneity within the subgroup of trials using ICS plus systemic corticosteroids (I^2 = 52%), and using a random effects model the confidence interval widens to OR 0.46 (95% CI 0.24 to 0.88). The two newest trials showed divergent results, but Razi 2012 is not yet fully reported. The large reduction in hospital admissions found in Razi 2012 contrasts with Upham 2011, the most recent fully reported study, which did not find a reduction in hospital admissions. The distribution of these effects is shown in the funnel plot in Figure 1.

Three additional randomised studies were identified that we could not include in the meta-analysis (as the number of participants in each group with the outcome were not reported). A summary of the results is included below to ensure that they are available to provide context for the above data. In Bautista 1994 (30 children) hospital admissions were reported as 13% in the budesonide plus beta$_2$-agonist group whereas in the group receiving beta$_2$-agonists alone it was 73% and is therefore consistent with the effect observed in Analysis 1.1. In Bateman 2006 "treatment failure" was reported, which was defined as the need for additional asthma treatment or hospitalisation. The data for hospitalisations could not be extracted separately but treatment failure was reported in 10% of those receiving ICS and 16% of those receiving placebo, in keeping with the findings of the included studies. However, in Olaivar 1999, a low dose of budesonide was compared to placebo, with both groups receiving beta$_2$-agonists, and they found no difference in the number of "good responders" between the groups.

Pulmonary function tests

A variety of pulmonary function tests were recorded during the ED stay (absolute and % predicted PEF and FEV_1 over a range of time points) and they are reported separately in Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13; Analysis 1.14; Analysis 1.15; Analysis 1.16 and Analysis 1.17. Results were pooled at one, two, three to four, and five hours after the start of treatment.

Pooled results showed a benefit of ICS therapy on % predicted FEV_1 at two and four hours post treatment (two hours MD 3.81; 95% CI 0.28 to 7.33; 4 studies; N = 319; Analysis 1.7; four hour MD 5.93; 95% CI 2.11 to 9.75; 4 studies; N = 319; Analysis 1.8), without significant visual or statistical heterogeneity (two hours: I^2 = 0%; four hours: I^2 = 23%). There was a trend towards benefit at one hour that was not statistically significant. At six hours post treatment, there was no significant difference between the treatments; the largest study with the most marked benefit of ICS therapy followed patients for only three hours so did not contribute to the six-hour analyses. Analysis of absolute FEV_1 showed no statistically significant difference between treatments but there was marked heterogeneity. This was most marked at one hour (I^2 = 90%). Despite adjusting for the baseline difference in the trial with the largest difference, significant heterogeneity remained. This heterogeneity was also present at two-hour (I^2 = 61%) and 3- to 4-hour analyses (I^2 = 65%).

In the analyses of % predicted PEF, there was a small, statistically significant benefit of ICS therapy at both one and two hours (one hour MD 5.66; 95% CI 2.01 to 9.32; 4 studies; N = 324; Analysis 1.14; two hour MD 7.46; 95% CI 3.77 to 11.15; 5 studies; N = 384; Analysis 1.15). There was no statistically significant heterogeneity in the analyses for % predicted PEF (P > 0.1 at all time intervals).

Heterogeneity was present in the results for absolute PEF in both the two and three- to four-hour analyses, with no significant differences between the groups when the random-effects model was used.

Eight additional relevant randomised studies were identified that we could not include in the meta-analysis and a summary of the results are reported below to provide context for the above data. In Bateman 2006 (115 patients) data were reported for FEV_1 with respect to change from baseline (whereas the analyses in this review focus on absolute levels at fixed time points or in terms of % predicted) and there were no significant differences between the two groups (budesonide/formoterol versus formoterol alone). Estrada 2005 (100 children) similarly reported no significant difference in improvement between fluticasone plus salbutamol versus salbutamol alone; Olaivar 1999 (65 children) also reported no significant difference between budesonide and placebo in change in FEV_1. Sekerel 2005 (67 children) reported levels of improvement in FEV_1 from baseline for the treatment and control groups, and the difference between the two groups was not significant (P = 0.24). The randomised trial by Blandon 2004 (86 children) reported no significant differences between the two groups (nebulised budesonide plus albuterol versus albuterol alone) in terms of improvement in PEF; as these data reflect change in PEF rather than absolute values they were not included in the meta-analysis.

However, three further studies reporting change in PEF scores have reported an advantage for ICS. Bautista 1994 (30 children) reported "budesonide + $beta_2$-agonist improves the PEF (49.1 to 173) and Pulmonary Index Score at 1 hour (P < 0.05) compared with those given $beta_2$-agonists alone (41.6 to 77.5) with no untoward drug reactions among the subjects in the combination group". Nuhoglu 2005 (26 children) reported a significant difference between budesonide versus placebo (with both groups receiving parenteral methylprednisolone) with regard to their baseline/one hour after treatment change in PEF (P = 0.0155); however, it should be noted that there was considerable difference between the two groups in baseline mean PEF L/min (150.00 ± 32.19 SD in the budesonide group and 192.86 ± 58.63 SD in the placebo arm). Starobin 2008 (49 adult patients) also found that with respect to the before and after ED treatment percentage of PEF improvement in a comparison between fluticasone plus methylprednisolone versus methylprednisolone alone there was a significantly superior improvement with the combined intervention (MD 4.4; 95% CI 1.74 to 7.06).

It is therefore difficult to provide a clear overall conclusion with respect to pulmonary function data considering trials that cannot be incorporated into the meta-analysis. Five studies (Bateman 2006; Blandon 2004; Estrada 2005; Olaivar 1999; Sekerel 2005) (433 patients in total) report no significant advantage, whereas three studies (Bautista 1994; Nuhoglu 2005; Starobin 2008) (105 patients in total) report additional benefit with ICS.

Clinical scores

A range of different clinical scores, including the pulmonary index, PIS and other novel scores (including combinations of measures of accessory muscle use, respiratory rate, wheezing, retractions, dyspnoea and oxygen saturation) were combined using an SMD technique and random-effects model. At three to four hours there was a modest, statistically significant difference favouring ICS (SMD 0.33; 95% CI 0.05 to 0.62; 4 studies; N = 198; Analysis 1.19), with no significant heterogeneity (I^2 = 0%).

However at an earlier time point (one to two hours) there appeared to be no benefit from ICS with regard to clinical scores (SMD -0.34; 95% CI -0.60 to -0.07; 4 studies; N = 176; Analysis 1.18)

Three additional studies were identified that were relevant to this outcome but reported change scores that could not be included in the meta-analysis. Razi 2012 (100 children) observed a significant improvement in PIS with regard to change from baseline to 120 minutes between budesonide versus placebo (P = 0.026). Upham 2011 (179 children) reported no difference between budesonide and placebo with respect to change in asthma scores from baseline and two hours (P = 0.64). Starobin 2008 (49 adult patients) reported a dyspnoea score (baseline dyspnoea index), which was scored from 0 (no dyspnoea) to 3 (severe dyspnoea), and did not find a difference between the group receiving fluticasone plus IV methylprednisolone versus the group receiving IV methylprednisolone alone.

Vital signs

Data for heart rate, respiratory rate, oxygen saturation and systolic blood pressure were pooled (Analysis 1.20). There was no significant difference between the two groups with regards to oxygen saturation (MD -0.18; 95% CI -0.66 to 0.31; 5 studies; N = 301). There was also no significant difference between the two groups in respiratory rate (MD 0.57; 95% CI -1.69 to 2.83; 3 studies; N = 198) and systolic blood pressure (MD -0.32; 95% CI -6.00 to 5.36; 3 studies; N = 128). However, there was a small difference with respect to heart rate, with a higher level in the group treated with ICS (MD 3.99; 95% CI 0.59 to 7.39; 5 studies; N = 363)

Four additional randomised studies were identified that we could not include in the meta-analyses; the results are included below to provide context for the above data. In Bateman 2006 (115 patients) data were reported in insufficient detail to be accommodated in the meta-analyses for vital signs, electrocardiograph (ECG) parameters, respiratory rate and oxygen saturation. There were no significant differences between the two groups apart from with respect to heart rate where a lower maximum value was observed in the budesonide group (P = 0.026), but the absolute difference was small (91.6 versus 94.3 beats per minute). With regard to SaO_2 levels, Estrada 2005 (100 children) reported no significant difference between fluticasone plus salbutamol versus salbutamol alone and Razi 2012 (100 children) observed no significant difference in SaO_2 levels between budesonide versus placebo; these data were not reported in sufficient detail to be included in the meta-analyses.

Upham 2011 (180 children) reported no significant difference between budesonide and placebo with respect to change in respiratory rate, heart rate or SaO_2 levels from baseline and two hours; the data were reported as medians and interquartile ranges and therefore could not be included in the meta-analyses.

The narrative inclusion of these additional studies is broadly consistent with the results presented in Analysis 1.20 with regard to oxygen saturation. In terms of heart rates the finding reported in Bateman 2006 is inconsistent with the overall findings reported in Analysis 1.20. However, the differences found in heart rate were small.

Adverse effects

Six studies reported no significant adverse effects of the treatments (Afilalo 1999; Bautista 1994; Estrada 2005 Guttman 1997; Starobin 2008; Sung 1998). Eight studies did not report any adverse effect data (Blandon 2004; Nuhoglu 2005; Olaivar 1999; Pansegrouw 1992; Razi 2012; Sekerel 2005; Singhi 1999; Tsai 2001). Five studies reported a number of minor adverse events, with no significant differences between the groups (Bateman 2006; Milani 2004; Rodrigo 1998; Rodrigo 2003; Upham 2011). One study reported an increase in hypokalaemia in the treatment group (Sharma 2003) over the first hour of treatment, although the difference was small. There were few data in the two pre-specified outcomes of nausea/vomiting and tremor, and no significant differences were found between the groups in these outcomes.

Subgroup analyses

Age group

There was no clear evidence of a difference in hospital admissions between children (OR 0.52; 95% CI 0.33 to 0.80; 7 studies N = 583) and adults (OR 0.35; 95% CI 0.20 to 0.60; 5 studies; N = 377) (Analysis 1.23).

Dosage

This analysis was included to compare high-dose versus low-dose therapy (high-dose therapy defined as 2 mg or greater of BDP equivalent dosing). The small number of trials and different protocols did not permit meaningful comparison of the dose of ICS use and comparisons should be interpreted with a degree of caution. The high- versus low-dose analysis (Analysis 1.23) indicated that a significant effect was obtained in favour of ICS in both subgroups. In the high-dose subgroup there were eight studies (Afilalo 1999; Estrada 2005; Guttman 1997; Razi 2012; Rodrigo 1998; Rodrigo 2003; Sekerel 2005; Upham 2011) (OR 0.51; 95% CI 0.35 to 0.74; 8 studies; 775 patients) and in the low-dose subgroup there were four studies (Milani 2004; Singhi 1999; Starobin 2008; Sung 1998) (OR 0.20; 95% CI 0.08 to 0.49; 4 studies; 185 patients). The basis for our grouping on high and low dose for different ICS is based on Colice 2000.

Delivery devices

We performed a post-hoc comparison of the studies using a nebuliser to deliver ICS and those that reported using an MDI and spacer. The results of this analysis for hospital admissions are shown in Analysis 1.24, and there was no significant difference between the two methods of delivery. There was a significant reduction in the risk of admission with nebuliser (OR 0.53; 95% CI 0.35 to 0.82) and with MDI and spacer (OR 0.32; 95% CI 0.18 to 0.59), and the test for differences between the two subgroups was negative (I^2 = 45.6%).

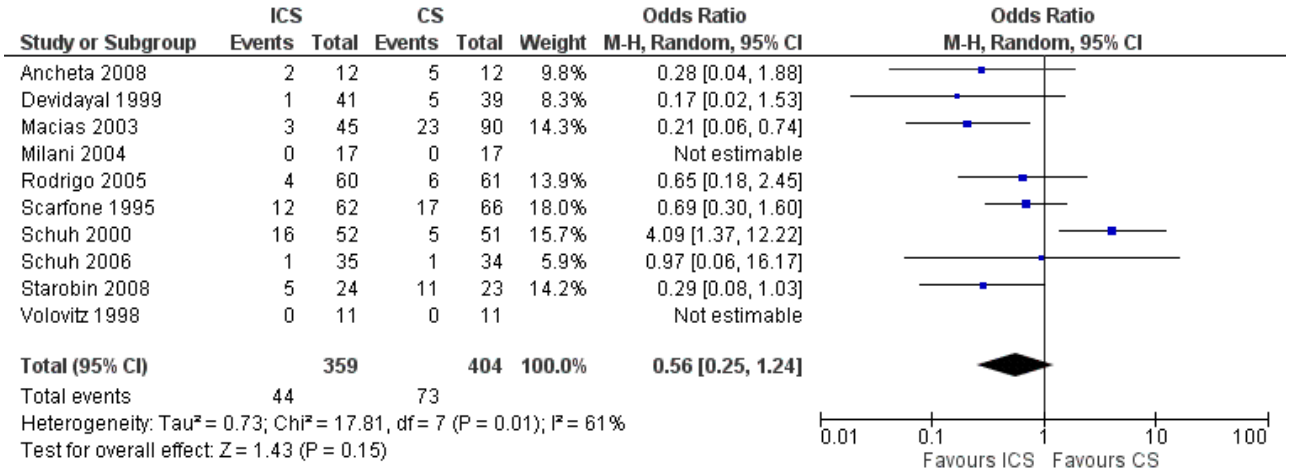
Protocols

Thirteen studies compared ICS versus placebo with no systemic corticosteroids given in either treatment group (Afilalo 1999; Bautista 1994; Blandon 2004; Estrada 2005; Milani 2004; Olaivar 1999; Pansegrouw 1992; Rodrigo 1998; Rodrigo 2003; Sekerel 2005; Sharma 2003; Singhi 1999; Tsai 2001) and seven studies compared ICS plus systemic corticosteroid versus systemic corticosteroid alone (Bateman 2006; Guttman 1997; Nuhoglu 2005; Razi 2012; Starobin 2008; Sung 1998; Upham 2011). With respect to admissions (Analysis 1.1), this comparison confirms an advantage for ICS in this outcome overall (OR 0.44; 95% CI 0.31 to 0.62; 12 studies; 960 patients) and the heterogeneity (I^2 = 27%) was modest. The subgroups in Analysis 1.1 by protocol (whether systemic corticosteroid were given as standard therapy or not) reveals similar benefits in the two subgroups. For ICS plus systemic corticosteroids versus systemic corticosteroids there is a clear benefit for ICS (OR 0.54; 95% CI 0.36 to 0.81) and similarly in the ICS versus placebo subgroup (OR 0.27; 95% CI 0.14 to 0.52) there is a significant benefit from ICS in terms of hospital admissions. However, the large reduction in hospital admissions reported from Razi 2012, contrasts with the results from Upham 2011, the most recent fully reported study, resulting in considerable heterogeneity in this subgroup (I^2 = 52%).

Inhaled corticosteroids versus systemic corticosteroids

Fourteen trials compared ICS versus systemic corticosteroid: 10 contributed to this analysis. Eight were paediatric studies (N = 595): Ancheta 2008 (24 children); Devidayal 1999 (80 children); Macias 2003 (135 children); Milani 2004 (34 children); Scarfone 1995 (128 children); Schuh 2000 (103 children); Schuh 2006 (69 children) and Volovitz 1998 (22 children). A further two were with adults (N = 168): Rodrigo 2005 (121 adults) and Starobin 2008 (47 patients). Analysis 2.1 (OR 0.56; 95% 0.25 to 1.24; 10 studies; N = 763) indicated no clear advantage for either ICS or systemic corticosteroid in terms of hospital admissions (Figure 5). However, there was very high level of heterogeneity (I^2= 61%) and this result should be interpreted with degree of caution.

Figure 5. Forest plot of comparison: 2 ICS versus systemic steroids, outcome: 2.1 Admission to hospital.



No admissions data were reported in Belda 2007, Rahman 2008 or Sari 2004. Go 2010 (33 adults) reported that their ICS group had a significantly higher number of admissions than their IV hydrocortisone group, but numbers were not included in the published abstract so could not be incorporated in the meta-analysis.

DISCUSSION

Summary of main results

This systematic review examined the available clinical evidence for the use of ICS in the ED management of acute asthma. The primary meta-analysis was based on 20 studies that included 1403 patients. The pooled results showed a beneficial effect of ICS therapy compared to placebo in preventing hospital admission, with a significant (OR 0.44; 95% CI 0.31 to 0.62) reduction in admission following the administration of ICS in the ED. Given a hospital admission level of 32% in the placebo group, approximately eight patients would require ICS treatment to prevent one admission (95% CI 6 to 14) The review shows a beneficial effect of ICS versus placebo in preventing hospital admission even in the studies where systemic corticosteroid was administered to all patients as standard therapy; however,disparate results from the new studies added in the 2012 update for this subgroup have contributed to increased heterogeneity.

Only a small number of trials reported data on pulmonary function tests in a manner that could be included in the meta-analysis; however, the effects of ICS on measurement of lung function found in the review were small. The minimum difference in pulmonary function tests that is considered clinically significant has been widely debated. This value remains unclear, not identified through empirical studies, and much of this research is based on stable asthma. However, a minimum improvement of 10% to 12% in FEV_1, or approximately 30 L/minute in PEF (Karras 2000; Tiffany 1993), is likely to be necessary to demonstrate an important clinical difference. Based on these guidelines, the improvement of 6% in FEV_1 at three to four hours, or 7% in the PEF would be of questionable clinical importance. There was heterogeneity in the results of the absolute FEV_1 and PEF. This may have been due to baseline differences in pulmonary function tests between the groups, which were statistically and clinically significant. Other possible causes include differences in the populations, interventions, designs and methods of measuring the pulmonary function tests. However, the small number of studies did not permit meaningful analysis of these differences.

The pulmonary index (a clinical score) has been shown to correlate with pulmonary function test results including FEV_1, FEV_1/FVC and $FEV_{25-75\%}$, and with hospital admission (Becker 1984). Five of the trials used clinical scores that were quite similar to the pulmonary index and reported them in a manner they could be included in the review. A modest, statistically significant improvement in clinical score between the groups was demonstrated at three to four hours (SMD -0.33; 95% CI -0.62 to -0.05). This difference would represent an insignificant clinical change for most patients. For example, from the cited studies, this would represent an improvement from 0.1 points in clinical index (Rodrigo 1998) to 0.8 (Sung 1998) in the PIS. Moreover, in view of the use of an SMD measure to combine different scores, and the small magnitude of the difference, this result and any conclusions based on it should be viewed with caution.

Overall completeness and applicability of evidence

Very few adverse effects of ICS therapy were reported in any of the studies, and this was confirmed with corresponding authors. Most importantly, no increase in cough or bronchospasm, occasionally attributed to ICS therapy (Passalacqua 2000), was observed. The lack of effect on vital signs also supports the safety of ICS therapy.

Twelve of the twenty published trials did not show a beneficial effect of ICS on the primary outcome of the trial. Nonetheless, the possibility of publication bias in favour of ICS remains. However, a comprehensive search strategy was conducted using a systematic strategy. Attempts to find unpublished trials were also made, including extensive correspondence with the authors of the studies included in the 2003 review as well as other experts in the field, searching of abstracts from recent conferences and contact with the pharmaceutical companies that manufacture ICS. Four unpublished trials were identified and included in the review (Bautista 1994; Blandon 2004; Olaivar 1999; Razi 2012); although we were only successful in contacting one of the authors (Razi 2012). While the results of the unpublished studies appear consistent

with those of the published studies, many of the details of these studies are missing. One of these studies comparing ICS versus placebo (Bautista 1994) reported a significantly decreased number of hospital admissions and improved pulmonary function tests in the group treated with ICS, while one abstract stated that the group treated with ICS had a trend towards improvement in % predicted FEV_1 that was not statistically significant (Olaivar 1999). The third study found no significant differences between the treatment groups (Blandon 2004) in PEF. All of these studies were relatively small, and these results appear consistent with those of the published studies.

Six studies remain in the awaiting assessment section of this review: four of these studies related to the primary analysis. Three have published in abstract form only, and it is unclear whether the patients included in the studies were treated in the ED or after hospital admission (Agarwal 2003; Agarwal 2005; Agarwal 2009). The one published study was unobtainable (Ambrosio 1997).

A secondary analysis was performed including 14 studies where ICS alone was compared to systemic corticosteroid alone. Owing to the diverse outcomes reported in the studies, only hospital admissions were compared (with 10 studies reporting hospital admissions). There was significant heterogeneity between the studies for hospital admissions. The small number of studies, and the small number of outcomes amenable to pooling, precluded further investigation of the sources of the heterogeneity. Pooling of hospital admission data using the random-effects model resulted in an OR of 0.56 (95% CI 0.25 to 1.24). This result does not exclude the possibility of either treatment being significantly better (or worse) than the other. In addition, many of these studies included patients with relatively mild asthma. Two unpublished studies are awaiting assessment for inclusion in the secondary analysis (Acun 2003; Jerez 2002); both were relatively small and did not report significant differences between the treatment groups in the published abstracts in clinical outcomes.

Quality of the evidence

The quality of reported randomisation was variable and less than half of the 32 studies were judged as low risk of bias. Fifty-nine per cent of trials were at unclear risk of selection bias while two (6%) were judged to be at high risk of selection bias. The majority (75%) of trials were at low risk of performance and detection bias while four were assessed as high risk of bias. Overall we felt that the evidence was of moderate quality and the effect that risks of bias had on our confidence in the treatment effects can be seen in Summary of findings for the main comparison and Summary of findings 2.

Potential biases in the review process

As with most systematic reviews there is a risk of publication bias with regard to the identification of unpublished negative trials, and therefore the effect of ICS therapy may be overestimated and conversely the possibility of failure to identify unpublished positive trials may underestimate the treatment effect. Having said that, the review was based on a comprehensive search with a systematic strategy to minimise the risk of bias. We believe we have identified the majority of the research considering the questions addressed by the review.

We are also conscious of the risk of study selection bias. However, each phase of the review was conducted by two independent review authors, and we feel confident that the studies excluded were assessed against consistent and relevant criteria.

Agreements and disagreements with other studies or reviews

The 2012 update provides further support for the findings of the earlier systematic review (Edmonds 2003). In Edmonds 2003, there was a beneficial effect of ICS compared to placebo when used early in the ED treatment of acute asthma, but it was not conclusive if there was benefit when ICS is used in addition to systemic corticosteroid therapy, which would be considered the standard of care (BTS/SIGN 2011). The 2012 update shows a statistically significant benefit of ICS therapy when used in addition to systemic corticosteroid therapy, but there is statistical heterogeneity in this subgroup which may reflect the clinical heterogeneity among the trials . Despite the addition of more studies to the secondary analysis, it remains unclear whether ICS could be used in place of systemic corticosteroid in the ED treatment of acute asthma, as there is marked heterogeneity between the studies that could not be explained on the basis of obvious differences in the study characteristics.

The 2012 update reports additional subgroup analyses comparing the results in adults and children, high and low doses of ICS and nebulised versus MDI and spacer delivery. All of these subgroups now demonstrate significant reductions in hospital admissions and there are no significant differences between the subgroups.

AUTHORS' CONCLUSIONS

Implications for practice

- There is insufficient evidence that ICS therapy alone can be used to replace systemic corticosteroid therapy, therefore systemic corticosteroids should not be withheld from patients with acute asthma presenting to the ED.
- ICS therapy decreases hospital admissions in patients compared to treatment with placebo, and may be considered in addition to systemic corticosteroid treatment (although the most recent evidence is conflicting).
- ICS are well tolerated with few short term side effects across a wide variety of doses.
- ICS appear to decrease hospital admissions to a similar degree in both children and adults

Implications for research

There are many unanswered questions about the use of ICS in the ED treatment of acute asthma and we believe the following merit further research:

- additional studies are required to determine the optimal dose and delivery device, type of ICS and frequency of administration of ICS;
- studies investigating the effect of ICS based on prior ICS and $beta_2$-agonist use are needed. One study suggested a marked benefit of ICS therapy in patients who had been unresponsive to $beta_2$-agonists in the hours prior to ED presentation (Pansegrouw 1992). Further research is needed to confirm the validity of this subgroup;

- a large randomised controlled trial would be less susceptible to the effect of marked baseline pulmonary function test differences between the treatment groups, which was observed in some of these small studies;
- future research should focus on clearly defined outcomes, with specific criteria for admission, relapse, timing and type of pulmonary function testing, and length of follow-up in the ED and after discharge.

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 Group (CAG) for their assistance in the original review and Toby Lasserson and librarian Elizabeth Stovold for their assistance in the updates. We would also like to acknowledge the assistance of the corresponding authors: Drs M. Afilalo, A. Guttman and G. Rodrigo for providing additional information about the design of their studies, feedback on the data abstracted and additional data analyses, to Drs. T. Klassen and B. Volovitz for providing original data and feedback about abstracted data, and to Dr. R. Scarfone for providing additional information about the design of his study. Drs A. Guttman and B. Volovitz also provided additional references. In addition, we would like to thank Dr Yevgeny Filanovsky for providing translation of the article by Latysheva et al and Dr Molly Gong for providing translation of the article by Yang et al. Finally, we would like to thank the reviewers for their comprehensive appraisal of this review and Professor Paul Jones (past CAG Co-ordinating Editor) and Dr Christopher Cates (current CAG Co-ordinating Editor) for their helpful suggestions.

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 Coordinating Editor). We are most grateful to Jos Verbeek, Alexey Seniukovich and Chao Liu for assistance with the translation of clinical trial reports. The support provided by librarians Judith Scammel, Jane Appleton and Hilary Garrett at St Georges University London is also greatly appreciated. As well, we would like to thank the corresponding authors Drs J. Belda and D. Starobin for providing further information about their studies, and Dr C. Razi for providing unpublished data from his study.

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CHARACTERISTICS OF STUDIES

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

Afilalo 1999

Methods	Design: randomised controlled trial Method of randomisation: computer-generated block randomisation Means of allocation concealment: randomisation code concealed Blinding: double-blind, placebo controlled Withdrawal/drop-outs: 2 withdrawn from the BDP group (1 because of deterioration, 1 because patient discharged self early), 3 withdrawn from the placebo group (1 because of deterioration, 2 because patient discharged self early)
Participants	Eligible: 193 Randomised: 54 (28/26) Completed: 49 (26/23) Sex (M/F): BDP 8/20, placebo 12/14 Asthma diagnosis: physician diagnosis Inclusion criteria: FEV_1 40-69% predicted, ≥ 18 years of age, able to perform spirometry, informed consent Major exclusions: in extremis, long-term systemic corticosteroid treatment (> 1 month) within 6 months of presentation, use of high-dose ICS (> 1 mg/day), use of systemic corticosteroid within previous 2 months Baseline FEV_1% (SD): BDP52 (9), placebo 51 (10)
Interventions	Setting: ED at an urban teaching hospital in Canada Intervention: BDP by MDI 1 mg at 0, 30 min, 1 h, 2 h, 4 h (total 5 mg) versus placebo MDI at the same time intervals Standard of care: salbutamol 2.5 mg by wet nebuliser prior to each MDI treatment. Oxygen at an FiO_2 of 0.35 was given at the physician's discretion
Outcomes	Primary outcome was improvement in FEV_1% predicted. Secondary outcome was hospitalisations. Other outcomes included other PFTs, vital signs, and Borg dyspnoea scale
Notes	The author was contacted and provided additional information about the study and further data

Afilalo 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation list and medications provided by pharmaceutical company
Allocation concealment (selection bias)	Low risk	Randomisation code concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind and the MDIs were identical in appearance
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	Unclear risk	2 withdrawn from the BDP group (1 because of deterioration, 1 because patient discharged self early), 3 withdrawn from the placebo group (1 because of deterioration, 2 because patient discharged self early)
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Ancheta 2008

Methods	Design: randomised controlled trial
Participants	Children with severe asthma exacerbations. 12 in each group Baseline lung function: mean PEF (SD): fluticasone 40.22 (8.23), hydrocortisone 39.10 (9.17) Mean baseline MPIS (SD): fluticasone 12.75 (1.06), hydrocortisone 13.08 (1.16)
Interventions	Intervention: fluticasone propionate (1500 µg total) 125 µg/actuation 4 actuations via MDI and spacer administered every 20 min for 3 doses Control: single dose of IV hydrocortisone (4 mg/kg; maximum of 200 mg)
Outcomes	Baseline to 6 h change (for PEF and MPIS). No numerical data included for the baseline to 6 h change for MPIS as reported narratively, % admitted and adverse events
Notes	ICS versus systemic corticosteroid subgroup Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear (abstract)

Ancheta 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear (abstract)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Trial reported as double blind, although unclear how this may have been maintained in practice with inhaled versus IV interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial reported as double blind, although unclear how this may have been maintained in practice with inhaled versus IV interventions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No patients were withdrawn from the trial
Selective reporting (reporting bias)	Unclear risk	Details of data recorded at all time points not included in trial report

Bateman 2006

Methods	Design: randomised controlled trial
Participants	Budesonide/formoterol (N = 58) Formoterol (N = 57) Mean age (years): budesonide/formoterol 45.9 (range 13 to 78), formoterol 43.9 (range 12 to 72) Sex (M/F): budesonide/formoterol 22/36, formoterol 20/37 Baseline lung function; FEV_1 (L): budesonide/formoterol 1.12 (range 0.6–1.9), formoterol 1.15 (range 0.7–2.0) Baseline lung function; FEV_1 (% predicted): budesonide/formoterol 40 (range 26–55), formoterol 41 (range 30–55) Inclusion criteria: all patients were required to have asthma, as defined by the American Thoracic Society criteria (including symptoms of wheeze, episodic cough and dyspnoea), with a pre-bronchodilator FEV_1 measured on arrival in the acute setting ≥ 30% and ≤ 55% of predicted normal. In addition, patients had to have a relative lack of reversibility, as demonstrated by their FEV_1 improving by 8% or less of predicted normal, 10 min after receiving salbutamol 400 µg from a pressurised MDI Major exclusions: acute severe asthma (defined as an inability to generate an FEV_1 value, an FEV_1 of less than 30% predicted, or asthma requiring transfer to an intensive care unit on initial assessment); use of ICS within the 8 h preceding the baseline measurements; receipt of oral or other systemic corticosteroids in the 48 h before the baseline measurements; beta-blocker therapy (including eye drops); any significant disease or concomitant disorder; and known sensitivity to the study medication or lactose. Patients ≥ 45 years of age with a history of ≥ 10 pack-years of smoking were also excluded from the study
Interventions	Intervention: budesonide/formoterol; 320/9 µg, 2 inhalations at t = -5 min and a further 2 inhalations at t = 0 min (total dose 1280/36 µg), plus 2 inhalations of formoterol placebo containing lactose at t = -5 min and at t = 0 min Control: formoterol 9 µg, 2 inhalations at t = -5 min and a further 2 inhalations at t = 0 min (total dose 36 µg), plus 2 inhalations of budesonide/formoterol placebo containing lactose at t = -5 min and at t = 0 min)

Bateman 2006 *(Continued)*

	Also: oral prednisolone; 5 mg per tablet, 12 tablets (total dose 60 mg)) was administered to all patients 90 min after they received the second dose of study medication Both groups received salbutamol 400 µg by MDI prior to randomisation During the treatment period, patients were not permitted to receive any asthma medication other than the investigational product, although oxygen therapy was allowed. Other medication considered necessary for the patient's safety and well-being, and early withdrawal from the study, were permitted at the discretion of the investigator
Outcomes	Lung function (FEV_1 mean % change from baseline at 3, 15, 60, 90 and 180 min), RR, treatment success, treatment failure and effectiveness of medication, adverse events, clinical laboratory data and other safety evaluations
Notes	ICS versus placebo, both received systemic corticosteroid and LABA Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear – method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Unclear – method of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy, randomised, parallel-group multicentre study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 patient, who was randomised into the formoterol group, discontinued the study because of worsening asthma. The full analysis set comprised all randomised patients
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Bautista 1994

Methods	Design: randomised controlled trial
Participants	30 children aged 6 to 18 years with no intake of corticosteroids in the 4 weeks prior to the study
Interventions	Intervention: budesonide + $beta_2$-agonist at 20-min intervals (up to 3 doses) Control: $beta_2$-agonist inhalation at 20-min intervals (up to 3 doses)

Bautista 1994 *(Continued)*

Outcomes	PEF and PIS at 0, 30 and 60 min at 48 h on follow-up, hospital admissions
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Conference abstract with limited information
Allocation concealment (selection bias)	Unclear risk	Conference abstract with limited information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported as double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Conference abstract with limited information
Selective reporting (reporting bias)	Unclear risk	Conference abstract with limited information

Belda 2007

Methods	Design: randomised controlled trial
Participants	Moderate-severe asthma. 45 recruited (6 drop-outs). Fluticasone: 19, prednisone: 20 Age (mean (range)) (years): fluticasone: 39 (20 to 69), prednisone: 34 (19 to 68) Sex (M/F): fluticasone: 4/15, prednisone: 7/13 Baseline lung function; Mean (SD) FEV_1 (L): fluticasone: 2.11 (0.74), prednisone: 2.09 (0.98) Baseline lung function; Mean (SD) FEV_1 (% predicted): fluticasone: 69 (19), prednisone: 62 (20) Inclusion criteria: patients aged 16 to 65 years with a moderate to severe asthma exacerbation (but not life threatening). Asthma diagnosis from current or previous history of chest tightness, wheezing, dyspnoea or cough in association with variable airflow limitation (documented from either methacholine airway hyper-responsiveness if FEV_1 was ≥ 70% of predicted value, or 12% increases in FEV_1 after inhaled salbutamol 200 µg if FEV_1 was < 70% Exclusion criteria: smokers or ex-smokers within the last year, treatment with oral or IV corticosteroids, cromoglycate, nedocromil, theophylline, allergen desensitisation injections and leukotriene antagonists at any time in 4 weeks prior to the study Patients with life-threatening exacerbations of asthma or other serious medical conditions were excluded (e.g. heart disease, gastrointestinal, liver or renal disease), and those with chest diseases that could interfere with study outcomes

Belda 2007 *(Continued)*

Interventions	Run in: 15 min with nebulised salbutamol and oxygen to see if suitable for study Intervention: fluticasone (16 puffs: total 4000 µg/day) (by MDI) + placebo of prednisone Control: prednisone (30 mg/day) + placebo of fluticasone (by MDI) Reported as: ongoing therapy with LABAs was permitted but was balanced between 2 groups in block randomisation
Outcomes	Spirometry, induced sputum for differential cell counts, albumin and alpha$_2$-macroglobulin levels and blood eosinophils, interleukin-5 and granulocyte macrophage colony-stimulating factor levels were obtained before treatment and at 2, 6 and 24 h after treatment
Notes	ICS versus systemic corticosteroid subgroup Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Codified by hospital pharmacy department who packed and blinded medications
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	Unclear risk	4 excluded because sputum samples unsuitable for processing (2 in each group). 2 excluded because chest radiograph infiltrates were compatible with pneumonia
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Blandon 2004

Methods	Design: randomised controlled trial
Participants	Children (aged 7 to 17 years) with moderate acute asthma: 40 randomised to budesonide + albuterol, 46 to albuterol alone Age (mean (SD)) (years): budesonide + albuterol: 10.04 (2.31), albuterol 10. 71 (2.06) Sex (M/F): budesonide + albuterol: 21/19, albuterol: 26/20
Interventions	Intervention: budesonide 550 µg + albuterol 0.15 mg/kg dose x 1 dose Control: albuterol 0.15 mg/kg x 1 dose

Blandon 2004 *(Continued)*

Outcomes	Symptoms and PEF (% change) before and after treatment
Notes	ICS versus placebo Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear (abstract – limited information)
Allocation concealment (selection bias)	Unclear risk	Unclear (abstract – limited information)
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	Unclear risk	Unclear (abstract – limited information)
Selective reporting (reporting bias)	Unclear risk	Unclear (abstract – limited information). Peak flow % change reported but no data presented on symptoms

Devidayal 1999

Methods	Design: randomised controlled trial Method of randomisation: not stated Means of allocation concealment: identical drug packages, but concealment not described Blinding: double-blind, double-dummy Withdrawals/drop-outs: none
Participants	Eligible: 110 Randomised: 80 (41/39) Completed: 80 (41/39) Sex (M/F): budesonide group: 76%/24%, placebo group: 74%/26% Asthma diagnosis: doctor's diagnosis Inclusion criteria: ≥ 1 attack of acute asthma requiring bronchodilators within the previous 6 months, evidence of wheezing and hyperinflation, age 2 to 12 years Major exclusions: presence of other significant acute or chronic diseases, use of oral or ICS within the previous 24 h Baseline PEF: budesonide 64%, placebo 62%
Interventions	Setting: paediatric ED in Chandigarh, India Intervention: budesonide group received budesonide 800 µg by nebuliser every 30 min for 3 doses and oral placebo, while the prednisolone group received prednisolone 2 mg/kg once orally, and nebulised placebo

Devidayal 1999 *(Continued)*

	All patients received nebulised salbutamol 0.15 mg/kg every 30 min for 3 doses. If the response after 3 doses of salbutamol was inadequate, subjects received salbutamol 3 mg/kg hourly, IV hydrocortisone and aminophylline If there was no response to this therapy, patients were given IV magnesium sulphate 50 mg/kg and were admitted to intensive care
Outcomes	Outcomes included a respiratory distress score, PIS, PEF, SaO_2, RR, HR, duration in emergency/hospital and need for hospitalisation
Notes	This trial was only included in the secondary analysis comparing ICS versus systemic corticosteroids New reference in 2003 update: the author was not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
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	Unclear risk	No report of patients being withdrawn from trial
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Estrada 2005

Methods	Design: randomised controlled trial
Participants	Children with moderate acute asthma Randomised: salbutamol/fluticasone: 50, salbutamol: 50 Age (mean (SD)) (years): salbutamol/fluticasone: 9.8 (2.4), salbutamol: 9.9 (2.6) Sex (M/F): salbutamol/fluticasone: 25/25, salbutamol: 32/18 Baseline lung function; mean SaO_2 % median (range): salbutamol/fluticasone: 93 (91–95), salbutamol: 93 (90–95) Baseline lung function; mean % predicted PEF_1 (SD): median (range): salbutamol/fluticasone: 71.2 (54.8–83.9), salbutamol: 72.3 (55.6–85.8) Inclusion criteria: patients with acute moderate asthma requiring nebulised treatment, who did

Estrada 2005 *(Continued)*

	had not used inhaled or oral corticosteroids or sodium cromoglycate in the 2 weeks previous to the study, had no clinical evidence or history of any systemic disease or abnormal cardiac, liver or renal or neurological function
Interventions	Intervention: patients were randomised to 1 of 3 treatment groups. In 2 groups, different dosing regimens of salbutamol/fluticasone were compared to the third arm where salbutamol alone was given. For the review, the arm receiving the higher dose of fluticasone was included as the intervention group. In this group, patients received salbutamol 30 µL/kg and fluticasone 500 µg/dose x 3 doses, each combined dose administered every 15 min Control: 3 doses of salbutamol 30 µL/kg per dose x 3 doses, each dose administered every 15 min Evaluation was performed within 10 min immediately after patients arrived to the ED Medications were given via a Plarre nebuliser (salbutamol and fluticasone nebulised together)
Outcomes	Pulse oximetry (SaO_2), PEF and a Wood et al clinical scale were monitored as efficacy outcomes at baseline (pre-dose) and at 15, 30, 45, 60, 90 and 120 min after the first nebulisation The clinical evaluation was performed according to a scale developed and validated by Wood et al. It evaluates SaO_2 (%), cyanosis, respiratory sounds, accessory muscle use, wheezing and alertness. A maximum score of 10 is obtainable for the most severe episodes, whereas a minimum score of 0 reflects normal, physiological, parameters
Notes	ICS versus placebo Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Patient eligibility and randomisation was performed by 1 of the investigators who did not participate in therapy or clinical evaluations
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	Unclear risk	Appears no patients were withdrawn
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Go 2010

Methods	Design: randomised controlled trial

Go 2010 *(Continued)*

Participants	Age: 18 to 60 years Randomised: ICS 16, systemic corticosteroid 17 Groups were reported to be comparable in terms of demographic variables except for oxygen saturation and corticosteroid use at baseline Inclusion criteria: adults with known bronchial asthma Exclusion criteria: status asthmaticus, COPD or corticosteroid intake in past 2 weeks
Interventions	Intervention: inhaled fluticasone (dose not stated) via ultrasonic nebuliser every 15 min with inhaled short-acting beta$_2$-agonists Control: hydrocortisone 250 mg/mL IV single dose with inhaled short-acting beta$_2$-agonists
Outcomes	Baseline demographic and clinical factors including vital signs, wheeze, RR, oxygen saturation, baseline PEF and mean rate of change in PEF post intervention
Notes	ICS versus systemic corticosteroid comparison Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Conference abstract – very limited information. It is stated that the patients were randomised to treatment
Allocation concealment (selection bias)	Unclear risk	Conference abstract – very limited information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Conference abstract – very limited information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Conference abstract – very limited information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Conference abstract – very limited information
Selective reporting (reporting bias)	Unclear risk	Conference abstract – very limited information

Guttman 1997

Methods	Design: randomised controlled trial Method of randomisation: computer-generated randomisation Means of allocation concealment: randomisation sequence concealed Blinding: double-blind, placebo controlled Withdrawal/drop-outs: 3 patients in BDP group and 1 in placebo group released themselves prior to completion, and 1 in the placebo group was withdrawn early because of deterioration in respiratory

Guttman 1997 *(Continued)*

	status. 2 patients initially randomised were later found to meet exclusion criteria and were excluded from the analyses
Participants	Eligible: 60 Randomised: 30/30 (2 others excluded after randomisation) Completed: 27/28 Sex (M/F): BDP 16/14, placebo 16/14 Asthma diagnosis: as per American Thoracic Society criteria, FEV_1 < 70% predicted Inclusion criteria: having at least 1 indication for IV corticosteroids, defined as: FEV_1 < 40% predicted; chronic corticosteroid therapy (> 1 month) within 6 months of presentation; high-dose ICS (> 1 mg/day) on presentation: and a short course of oral corticosteroids (< 1 month) within 2 months of presentation Major exclusions: in extremis, history of coronary artery disease, documented pneumonia, previously enrolled Baseline FEV_1% mean (SD): BDP 32.4 (9.1), placebo 30.6 (9.1)
Interventions	Setting: ED at an urban teaching hospital in Canada Intervention: BDP 1 mg by MDI plus spacer at 0, 0.5, 1, 2, 4, 6, 8 (total 7 mg) versus placebo MDI at same time intervals Standard of care: all patients received methylprednisolone 80 mg IV at 0 h and 40 mg IV at 6 h, salbutamol 2.5 mg by wet nebuliser at 0, 0.5, 1, 2, 4, 6, 8, 10 h. If FEV_1 was < 40% predicated at 0, 0.5 h, salbutamol 5.0 mg was given instead of 2.5 mg Aminophylline and ipratropium were not permitted
Outcomes	Primary outcome was the change in % predicted FEV_1 Other outcomes included other PFTs, Borg Dyspnoea Scale, vital signs, serum potassium and hospital admissions
Notes	The author was contacted and provided an additional reference, as well as additional information about the study and more data

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	Randomisation sequence concealed
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	Unclear risk	3 patients in BDP group and 1 in placebo group released themselves prior to completion, and 1 in the placebo group was withdrawn early because of deterioration in respiratory status. 2 patients initially randomised were later found to meet exclusion criteria and were excluded from the analyses
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Macias 2003

Methods	Design: randomised controlled trial Method of randomisation: randomisation table Means of allocation concealment: sealed packets Blinding: none Description of withdrawals/drop-outs: 3 patients were excluded after randomisation because they did not meet the inclusion criteria
Participants	Eligible: unclear Randomised: unclear Completed: (inhaled/oral/IV corticosteroids): 45/45/45 Sex (M/F): inhaled 32/13, oral 25/20, IV 26/19 Age (mean (SD)) (years): inhaled 9.5 (2.4), oral 10.8(3.0), IV 9.5(2.6) Asthma diagnosis: at least 1 prior episode of wheezing Inclusion criteria: at least 6 years of age, Wood score of 4 or 5, 1 or more prior episodes of wheezing Exclusion criteria: saw a doctor for asthma or was on corticosteroids within the week prior to presentation, unable to use MDI, no phone Baseline severity; mean PEF (SD): inhaled 45.3 (13.7), oral 43.5 (19.5), IV 40.6 (15.8)
Interventions	Setting: 2 paediatric ED in the US (Texas, Colorado) Intervention: this study had 3 treatment arms. Group 1 received triamcinolone 600 µg by MDI with spacer. Group 2 received prednisone 2 mg/kg orally, with a maximum dose of 80 mg. Group 3 received IV methylprednisolone 2 mg/kg, with a maximum dose of 80 mg. All patients received nebulised albuterol 0.15 mg/kg (maximum 5 mg) every 4 h, and ipratropium bromide 0.5 mg nebulised every 4 h. In addition, if deemed necessary by the attending physicians, patients received either oral prednisone or IV methylprednisolone prior to randomisation
Outcomes	The primary outcome was admission to hospital. Other outcomes included number of albuterol treatments given, oxygen saturation and PEF
Notes	This trial was only included in the secondary analysis comparing ICS versus systemic corticosteroid. The results for hospital admissions were combined for the groups using IV and oral corticosteroids and compared to the group using ICS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated by random number table
Allocation concealment (selection bias)	Low risk	Sealed packets
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 patients were excluded after randomisation because they did not meet the inclusion criteria

Macias 2003 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Milani 2004

Methods	Design: randomised controlled trial Method of randomisation: not stated Means of allocation concealment: not stated Withdrawals/drop-outs: 1 patient in the placebo/placebo group was excluded from the study at 60 min because of worsening clinical status and was admitted Blinding: double-blind, placebo controlled
Participants	Eligible: unclear Randomised: (placebo/inhaled/oral corticosteroids): 15/17/17 Completed: placebo 14, inhaled 17, oral 17 Sex (M/F): placebo 9/6, inhaled 8/9, oral 8/9 Age (mean (SD)) (months): placebo 49.6 (15.6), inhaled 51.1 (18.7), oral 47.3 (16.3) Asthma diagnosis: ≥ 3 previous episodes, current episode lasting ≥ 6 h Inclusion criteria: moderate acute asthma defined as audible wheeze, use of accessory muscles, increased RR and an inability either to walk or to speak more than 3 to 5 words per breath Exclusion criteria: chronic or acute cardiopulmonary disease, use of systemic corticosteroids within the past 14 days, use of ICS within the past 72 h, severe exacerbations, other previous medical conditions
Interventions	Setting: patients with acute asthma who sought treatment at the paediatric walk-in clinic at 1 hospital in Brazil Intervention: this trial had 3 treatment groups. Group 1 received inhaled placebo and oral placebo. Group 2 received inhaled placebo and oral prednisone 1 mg/kg. Group 3 received nebulised budesonide 2 mg and oral placebo All patients received nebulised salbutamol 0.15 mg/kg. This was repeated if the patients' severity scores or oxygen saturations worsened. After 4 h' observation, patients were discharged with a prescription for inhaled bronchodilators
Outcomes	Primary outcome were clinical severity scores and oxygen saturations. The clinical severity score was calculated based on: RR, wheezing, retraction, dyspnoea and oxygen saturation
Notes	This trial was included in July 2005 in both the primary and secondary analyses. The author was not contacted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double-blind
Blinding of outcome assessment (detection bias)	Low risk	Blinding of study personnel responsible for outcome assessment indicates the risk of detection bias would be low

Milani 2004 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 patient in the placebo/placebo group was excluded from the study at 60 min because of worsening clinical status and was admitted
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Nuhoglu 2005

Methods	Design: randomised controlled trial
Participants	26 children with moderate asthma Randomised: nebulised budesonide 12, placebo 14 Age (mean ± SD) (years): nebulised budesonide 7.90 ± 2.34, placebo 9.36 ± 2.55 Sex (M/F): nebulised budesonide 7/5, placebo 8/6 Baseline PEF L/Min (mean ± SD): nebulised budesonide 150.00 ± 32.19, placebo 192.86 ± 63 Baseline PIS (mean ± SD): nebulised budesonide 6.08 ± 1.00, placebo 6.07 ± 1.44 Inclusion criteria: patients aged 5 to 15 years, with a diagnosis of asthma, with a PIS ≥ 3 and ≤ 6, and who were able to use a peak flow meter
Interventions	Intervention: nebulised budesonide 1 mg Control: placebo (nebulised saline) Both groups received 3 consecutive doses of nebulised salbutamol 0.15 mg/kg/dose and 1 dose of IM methylprednisolone 1 mg/kg/dose
Outcomes	PIS and peak flow (before and after at 0 and 1 h)
Notes	ICS versus placebo, both groups received systemic corticosteroid Trial added in 2012 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Reported as "the randomisation was performed according to the patients' social security number. Odd numbers got into Group I, even numbers got into Group II."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind

Nuhoglu 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind, and it was reported that PIS and PEFs were measured by a paediatrician blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were no drop-outs
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Olaivar 1999

Methods	Design: randomised controlled trial
Participants	65 children aged 5 to 18 years. All had baseline FEV_1 < 70% of predicted Randomised: nebulised budesonide + terbutaline 33, nebulised terbutaline 32 "Decision to admit, discharge and prescribe steroids was based on the Philippine consensus"
Interventions	Intervention: nebulised budesonide (0.5 µg) + terbutaline (2.5 mg) x 3 doses, given 20 min apart Control: nebulised placebo + terbutaline (2.5 mg) x 3 doses, given 20 min apart
Outcomes	FEV_1 20 min after nebulisation completed and on second, third and fourth hour from start of treatment Patients were classified as good responders if FEV_1 returned to > 80% of predicted and this response was sustained for 4 h (or poor if response was not prompt and sustained and FEV_1 remained < 80% of predicted)
Notes	ICS versus placebo comparison Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Conference abstract – limited details reported
Allocation concealment (selection bias)	Unclear risk	Conference abstract – limited details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Conference abstract – limited details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Conference abstract – limited details reported
Incomplete outcome data (attrition bias)	Unclear risk	Conference abstract – limited details reported

Olaivar 1999 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Conference abstract – limited details reported

Pansegrouw 1992

Methods	Design: randomised, double-blind, placebo-controlled, parallel group study Method of randomisation: randomisation stated, method not described Means of allocation concealment: unclear Blinding: placebo inhaler Withdrawal/drop-outs: 3 patients in the placebo group were withdrawn after developing life-threatening asthma and were replaced
Participants	Eligible: 40 (consecutive) Randomised: 20/20 Completed: 20/20 Sex: not stated Asthma diagnosis: "atopic asthmatics" defined as: I) a previous history of episodic increase in airway hyperirritability presenting as cough and/or increased sputum production and/or bronchospasm, which was reversible either with medications or spontaneously; and ii) an increased blood or sputum eosinophil count and/or increased serum immunoglobulin E levels and positive reactions to allergens on either skin tests or radio-allergosorbent tests Inclusion criteria: "acute resistant asthma" defined as no response to an inhaled fenoterol, with no improvement clinically or in flow/volume curve measurements Other inclusion criteria were: FEV_1 and FVC < 70% predicted, age 18 to 70 years, and misuse of $beta_2$-agonist bronchodilator inhalers during the present asthma attack Exclusion criteria: left ventricular failure, infective lung disease, degenerative lung disease and pulmonary embolism Baseline FEV_1: BDP group approximately 1.2 L/min, placebo group approximately 0.9 L/min
Interventions	Setting: 2 EDs in Bloemfontein, South Africa Intervention: both groups received an initial dose of fenoterol 400 µg by MDI. 5 min later the intervention group received BDP 200 µg by MDI, while the placebo group received placebo MDI. 5 min later both groups received 400 µg formoterol by MDI
Outcomes	Primary outcome was FEV_1, measured on presentation; prior to BDP/placebo inhalation; prior to repeat fenoterol inhalation; and at 5, 15, 30, 45 and 60 min after the second fenoterol inhalation Other outcomes included clinical evaluation of symptoms
Notes	ICS versus placebo. The author did not respond to requests for further information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported as double blind

Pansegrouw 1992 *(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	Unclear risk	3 patients in the placebo group were withdrawn after developing life-threatening asthma and were replaced in the trial
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Rahman 2008

Methods	Design: randomised controlled trial
Participants	100 consecutive participants selected for the study but no details on how many per group
Interventions	Intervention: BDP 2 puffs at 10-min intervals (3000 µg/hour) delivered by MDI into spacer for 120 min along with oxygen supplement and salbutamol nebulisation Control: IV corticosteroid 500 mg (type not specified) along with oxygen supplement and salbutamol nebulisation
Outcomes	RR, HR, PEF measured immediately before starting treatment and at 30 min intervals for 2 h
Notes	Trial added in 2012 update. ICS versus systemic corticosteroid comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as single blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as single blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Razi 2012

Methods	Design: randomised controlled trial
Participants	100 children aged 6 months to 6 years Inclusion criteria: children admitted to the ED with acute wheezing with a history of recurrent wheezing, PIS 7 and 13 Major exclusions: systemic corticosteroid use in the previous 30 days; chronic lung, cardiac, hepatic or renal disease; immune deficiency; suspected croup or foreign body From communication with the author, there were no significant differences between the groups in their baseline characteristics
Interventions	Intervention: 3 doses of budesonide 1 mg/2 mL with salbutamol 0.15 mg/kg/dose (maximum 5 mg) driven by 100% oxygen at a flow of 6 L/min at 0, 20 and 40 min Control: normal saline (2 mL) in addition to salbutamol 0.15 mg/kg/dose (maximum 5 mg) for 3 doses at the same time intervals (information provided by author) Both groups received 1 dose of IM methylprednisolone 1 mg/kg/dose at the initial of the treatment, ipratropium bromide, and additional doses of salbutamol at 80, 120 and 180 min
Outcomes	Changes in PIS from 0 to 120 min, discharge rates at 120, 180 and 240 min, hospitalisations and SaO_2
Notes	ICS versus placebo, both groups received IM systemic corticosteroid Trial added in 2012 update. No results reported at clinicaltrials.gov/ct2/show/NCT00733317 but results were obtained directly from the trialist

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was described as randomised
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	Unclear risk	Attrition bias unclear
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Rodrigo 1998

Methods	Design: randomised, controlled trial Method of randomisation: central randomisation. Method not described Means of allocation concealment: randomisation list concealed from all study personnel Blinding: double-blind, placebo controlled Withdrawal/drop-outs: none
Participants	Eligible: 94 Randomised: 47/47 Completed: 47/47 Age; (mean (SD)) (years): treatment 31.1 (9.7), control 33.8 (9.7) Sex (M/F): treatment 32%/68%, control 36%/64% Asthma diagnosis: criteria for asthma of the American Thoracic Society Inclusion criteria: ages 18 to 50 years, FEV_1 and PEF < 50% predicted, informed consent Major exclusions: chronic cough; cardiac, hepatic, renal, or other medical diseases; pregnancy Baseline FEV_1% (SD): treatment 27.6 (10.3), control 25.9 (8.3)
Interventions	Setting: ED of a hospital in Montevideo, Uruguay Intervention: treatment group received salbutamol 400 µg by MDI with spacer, followed by flunisolide, 1 mg every 10 min by MDI with spacer for 3 h (total dose of flunisolide 18 mg) Standard of care: control group received salbutamol 400 µg every 10 min by MDI and spacer, followed by placebo MDI with spacer
Outcomes	Primary outcome change in FEV_1. Other outcomes included other PFTs, vital signs; a clinical index (assessing the presence of dyspnoea, accessory-muscle use and wheezing); and symptoms including nausea, palpitations, tremor, anxiety and headache
Notes	The author was contacted and provided additional information about the study and more data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	Low risk	Randomisation list concealed from all study personnel
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	Unclear risk	No indication of patients being withdrawn from the trial
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Rodrigo 2003

Methods	Design: randomised, double-blind, placebo controlled trial Method of randomisation: random number table Means of allocation concealment: opaque envelopes containing identical canisters Blinding: double-blind, placebo controlled Withdrawals/drop-outs: 2 patients were withdrawn early from the ICS group, and 3 from the control group, because they did not meet the inclusion criteria
Participants	Eligible: unclear Randomised: 58/62 Completed: 56/60 Age (mean (SD)) (years): treatment 34.0 (10.4), control 33.7 (11.0) Sex (M/F): treatment 36%/64%, control 37%/63% Asthma diagnosis: criteria of American Thoracic Society Inclusion criteria: age 18 to 50 years, FEV_1 and PEF < 50% predicted Major exclusions: fever; history of chronic cough; heart, liver, renal or other disease; pregnancy Baseline FEV_1% mean (SD): treatment 24.9 (10.8), control 25.1 (9.0)
Interventions	Setting: ED of a hospital in Montevideo, Uruguay Intervention: this study had 3 treatment arms. Group 1 received fluticasone 1000 µg, albuterol 400 µg, and ipratropium 84 µg every 10 min by MDI with spacer for 3 h. Group 2 received albuterol 400 µg and ipratropium 84 µg every 10 min by MDI with spacer for 3 h. Group 3 received fluticasone 1000 µg and albuterol 400 µg every 10 min by MDI with spacer for 3 h. For this review, group 1 was included as the treatment group (received ICS) and group 2 was included as the control group (did not receive ICS, but identical other treatments) Standard of care: systemic corticosteroids were withheld until discharge or admission to hospital. Discharged patients received prednisone 60 mg daily for 7 days, admitted patients received IV corticosteroids. Oxygen was administered if oxygen saturations were < 92%
Outcomes	Primary outcome was admission to hospital and improvement in PFTs. Admission was determined by senior ED staff without knowledge of the treatment allocation Other outcomes included vital signs and side effects
Notes	This trial was included in July 2005. The author was not contacted. ICS versus placebo comparison

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated by random number table
Allocation concealment (selection bias)	Low risk	Opaque envelopes containing identical canisters
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	Unclear risk	2 patients were withdrawn early from the ICS group, and 3 from the control group, because they did not meet the inclusion criteria

Rodrigo 2003 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Rodrigo 2005

Methods	Design: randomised, double-blind, placebo-controlled trial Method of randomisation: random number table Means of allocation concealment: opaque envelopes containing identical canisters and syringes Withdrawals/drop-outs: 8 patients in the ICS treatment group, and 7 patients in the IV hydrocortisone group were withdrawn early because they did not meet the inclusion criteria
Participants	Eligible: unclear Randomised: 60/61 Completed: 52/54 Age (mean (SD)) (years): ICS 33.9 (8.8), IV hydrocortisone: 33.2 (8.8) Sex (M/F): ICS 16/36, IV hydrocortisone 15/39 Asthma diagnosis: diagnostic criteria of acute asthma of the Global Strategy of Asthma Management and prevention report Inclusion criteria: aged 18 to 50 years, PEF or FEV_1 < 50% predicted Major exclusions: fever, history of other significant medical diseases, pregnancy Baseline PEF (%): ICS 32.9 (8.2), IV hydrocortisone 33.8 (7.2)
Interventions	Setting: ED of a hospital in Montevideo, Uruguay Intervention 1: fluticasone by MDI with spacer, 500 µg every 10 min for 3 h (total dose 9000 µg) Intervention 2: hydrocortisone 500 mg IV at start of trial Both groups received albuterol by MDI with spacer 600 µg every 10 min for 3 h, and Ipratropium bromide 84 µg every 10 min for 3 h. Systemic corticosteroids were withheld until patients were discharged from the ED, at the end of the study, when all patients were started on prednisone 60 mg orally every day for 7 days
Outcomes	Primary outcomes were hospital admissions and PFTs. Need for admission was determined by senior ED staff at 180 min, without knowledge of the treatment group Other outcomes included a clinical score and symptoms
Notes	This trial was included in July 2005. The author was not contacted. ICS versus systemic corticosteroid comparison

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated by random number table
Allocation concealment (selection bias)	Low risk	Opaque envelopes containing identical canisters and syringes
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

Rodrigo 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8 patients in the ICS treatment group, and 7 patients in the IV hydrocortisone group were withdrawn early because they did not meet the inclusion criteria
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Sari 2004

Methods	Design: randomised controlled trial
Participants	Patients with severe asthma Randomised: nebulised fluticasone 38, IV methylprednisolone 38
Interventions	Intervention: combination nebulised fluticasone 0.5 mg plus salbutamol 2.5 mg Control: methylprednisolone IV 125 mg plus nebulised salbutamol 2.5 mg
Outcomes	PEF and symptom scores for 6 h
Notes	ICS versus systemic corticosteroid comparison Trial added in 2012 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear – conference abstract with very limited information in report
Allocation concealment (selection bias)	Unclear risk	Unclear – conference abstract with very limited information in report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear – conference abstract with very limited information in report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear – conference abstract with very limited information in report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear – conference abstract with very limited information in report
Selective reporting (reporting bias)	Unclear risk	Unclear – conference abstract with very limited information in report

Scarfone 1995

Methods	Design: randomised controlled trial

Scarfone 1995 *(Continued)*

	Method of randomisation: computer generated, blocks of 10 Means of allocation concealment: allocation list kept by pharmacy, who provided study drugs according to the list Blinding: double-blind, double-dummy Withdrawal/drop-outs: 17 patients were excluded after randomisation: pneumonia (7), missing scheduled albuterol treatment (3), vomiting study medication (5), parental withdrawal (1) or equipment failure (1)
Participants	Eligible: unclear; convenience sample Randomised: 62/66 Completed: 56/55 Age (mean (SD)) (months): dexamethasone 64 (39), prednisone 55 (36). Range: 1 to 17 Sex (M/F): dexamethasone 57%/43%, prednisone 62%/38% Asthma diagnosis: 1 prior episode wheezing, doctor's diagnosis Inclusion criteria: moderate exacerbation, defined by PIS > 8 Major exclusions: severe exacerbation, defined by PIS > 13 or oxygen saturation < 88%, inhaled or systemic corticosteroids use in the preceding 72 h, vomiting oral study drug x 2, requiring more frequent albuterol than every 30 min or deteriorating status or missing a scheduled albuterol dose by > 10 min, previous enrolment, pneumonia, bronchiolitis or croup Baseline PIS (median): dexamethasone 10, prednisone 11
Interventions	Setting: ED at a Children's Hospital in US Intervention 1: nebulised dexamethasone 1.5 mg/kg x 1 Intervention 2: oral prednisone 2 mg/kg x 1 Both groups received nebulised albuterol 15 mg/kg every 30 min x 3 doses then every 40 min as needed to a maximum of 6 doses, and supplemental oxygen to keep O_2 saturation > 92%. On discharge all patients were given a prescription for prednisone 2 mg/kg in 2 divided doses for 5 days, and oral or inhaled albuterol 3 times per day for 7 days. Co-interventions such as extra doses of beta$_2$-agonists, theophylline or ipratropium bromide were not permitted
Outcomes	Hospital admissions, change in PIS, time to discharge, vomiting and relapse to additional care after discharge PIS calculated from scoring RR, wheezing, inspiratory/expiratory ratio, accessory muscle use and oxygen saturation
Notes	This trial was only included in the secondary analysis comparing ICS versus systemic corticosteroids. The author was contacted and provided additional information about the study design; however, the data were not available for further analysis

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	Allocation list kept by pharmacy, who provided study drugs according to the list
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

Scarfone 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17 patients were excluded after randomisation: pneumonia (7), missing scheduled albuterol treatment (3), vomiting study medication (5), parental withdrawal (1) or equipment failure (1)
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Schuh 2000

Methods	Design: randomised controlled trial Method of randomisation: blocked randomisation code from computer-generated list Means of allocation concealment: sealed sequential packets Blinding: double-blind, double-dummy Withdrawal/drop-outs: 1 in fluticasone group (FEV_1% too high after 1 treatment), 2 from prednisone group (1 because of repeated vomiting of oral drug, 1 became acutely ill within 1 h after treatment with prednisone)
Participants	Eligible: 148 Randomised: 103 (52/51) Completed: 100 (51/49) Age (mean (SD)) (years): fluticasone 9.3 (3.3), prednisone 9.5 (3.2) Sex (M/F): fluticasone 49%/51%, prednisone 69%/31% Asthma diagnosis: prior episodes of wheezing, baseline FEV_1% < 60% predicted Inclusion criteria: age ≥ 5, FEV_1 < 60% predicted, presentation between 8 AM and 5 PM, ability to use inhaler and do PFTs reliably Major exclusions: requiring immediate IV corticosteroids or intubation, use of oral corticosteroids within 7 days, or current use of moderate or high dose ICS Baseline FEV_1% mean (SD): fluticasone 35.8 (8.5), prednisone 34.4 (9.8)
Interventions	Setting: ED at a Children's hospital in Canada Intervention: fluticasone group received 2 mg fluticasone by MDI with spacer at start of study and oral placebo; prednisone group received 2 mg/kg prednisone orally and placebo by MDI Standard of care: both groups received nebulised albuterol 0.15 mg/kg at time -20, 0, 20, 40, 60, 80 and 140 min, and 250 µg nebulised ipratropium bromide at time = 0. Oxygen was given at 6 to 7 L/min with treatments
Outcomes	Primary outcome was the change in % predicted FEV_1. Other outcomes included other PFT results, hospital admission, clinical response, asthma relapse and vital signs
Notes	This trial was included in the ICS versus systemic corticosteroid comparison in September 2000; the author was not contacted

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	Sealed sequential packets
Blinding of participants and personnel (performance bias)	Low risk	Trial reported as double-blind, double-dummy

Schuh 2000 *(Continued)*
All outcomes

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	Unclear risk	1 patient in fluticasone group (FEV_1% too high after 1 treatment), 2 from prednisone group (1 because of repeated vomiting of oral drug, 1 became acutely ill within 1 h after treatment with prednisone)
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Schuh 2006

Methods	Design: randomised controlled trial
Participants	Children with mild to moderate asthma Randomised: fluticasone 35, placebo 34 Age (mean (SD)) (years): fluticasone 9.0 (2.6), placebo 9.2 (3.4) Sex (M/F): fluticasone 25/10, placebo 20/14 Baseline lung function; mean % predicted FEV_1 (SD): fluticasone 63.0 (10.8), placebo 61.5 (10.7) Inclusion criteria: children aged 5 to 17 years, diagnosed with acute asthma by the ED paediatrician, with FEV_1 50% to 79% predicted on ED presentation Exclusion criteria: children presenting with a first episode of wheezing, persistent vomiting, airway instability, those who had received oral corticosteroids within 7 days, co-existent cardiopulmonary/neuromuscular disease, varicella contact within 21 days of the study entry, previous intensive care unit treatment for asthma, inability to communicate in English
Interventions	Intervention: fluticasone propionate 2 mg (8 inhalations, 250 µg each) via MDI/VHC with a mouthpiece and prednisolone placebo syrup in the ED Control: 8 inhalations of fluticasone placebo and 2 mg/kg (maximum 60 mg) of active prednisolone syrup Co-interventions: all children received nebulised albuterol (dose of 0.15 mg/kg in first 10 patients, then decreased to 0.075 mg/kg because of tremor and tachycardia noted in the first 10 patients attributed to the high-efficiency nebuliser) and ipratropium bromide, 250 µg per dose, with a mouthpiece 20 min before the experimental therapy, immediately after the initial dose of the experimental therapy (0 min), and at 60, 120, 180 and 240 min
Outcomes	Change in % predicted FEV_1 from baseline to 240 min and 48 h in the 2 groups, RR and oxygen saturation, hospital admissions, adverse events
Notes	ICS versus systemic corticosteroid subgroup Trial added in 2012 update

Schuh 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme, random block sizes of 10
Allocation concealment (selection bias)	Low risk	The research pharmacist supplied the corresponding MDI/syrup in a double-dummy setup to the study nurses who enrolled participants and delivered the experimental therapy. Randomisation codes were secured in the pharmacy until enrolment and analysis decisions had been completed. The study nurses were unable to determine which intervention a given patient had received
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	60 children performed spirometry at 240 min, 30 in the intervention group and 30 in the control group (of 35 and 34 enrolled) 1 parent changed her mind regarding participation at 120 min, 5 children vomited the syrup and were too nauseated for FEV_1 assessment, and 3 children were too sleepy to cooperate with FEV_1 assessment
Selective reporting (reporting bias)	Unclear risk	No apparent indication of selective reporting bias

Sekerel 2005

Methods	Design: randomised controlled trial
Participants	Children with mild to moderate asthma Randomised: budesonide 33, placebo 34 Age (mean (SD)) (years): budesonide 10.0 (1.72), placebo 10.5 (2.33) Sex (M/F): budesonide 24/9, placebo 21/13 Baseline lung function mean (SD) % predicted FEV_1: budesonide 77.7 (6.89), placebo 81.7 (9.91) Inclusion criteria: children with asthma exacerbations (defined as the presence of all of the following: 1) increased frequency of cough, wheeze and/or dyspnoea; 2) at least 2-fold increase in mean daily bronchodilator use for > 24 h; and 3) > 15% decrease in FEV_1 if spirometric evaluation was possible at baseline) and an FEV_1 between 70% to 90% of personal best after 3 nebulised salbutamol doses. They also had to have had their FEV_1 measured during the past 6 months when they were well Exclusion criteria: current use of ICS exceeding 800 mg/day or any change in their dose of ICS in the prior 2 months, any systemic corticosteroid in the past 6 months, any hospitalisation within 1 year, hy-

Sekerel 2005 *(Continued)*

	poxia (documented oxygen saturation of < 90%), presence of concurrent pulmonary disease, history of non-compliance
Interventions	All participants received nebulised salbutamol (0.15 mg/kg, maximum 5 mg) every 20 min for 3 doses prior to enrolment. FEV_1 was performed 20 min after the third dose of salbutamol to determine eligibility for enrolment Intervention: budesonide (1 mg/2mL) with salbutamol (0.15 mg/kg/ dose, maximum 5 mg) every hour for 3 h Control: normal saline (2 mL) as well as salbutamol every hour for 3 doses
Outcomes	The primary outcome measure was the proportion of children requiring systemic corticosteroid intervention The secondary outcome measures were FEV_1, PEF, rescue $beta_2$-agonist use and hospitalisations
Notes	ICS versus placebo comparison Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A unit nurse, who was not involved in the study design and analysis, randomised children using a table of random numbers (blocks of 6)
Allocation concealment (selection bias)	Low risk	Identical numbered plastic syringes were provided, each covered with aluminium foil and containing either budesonide (1 mg/2 mL) or preservative-free normal saline (2 mL), which served as a placebo. The content of the 2 types of syringes appeared identical. The investigators and the patients were unaware of group assignments and syringe contents The randomisation list was concealed in sealed opaque envelopes until data analysis was performed
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	Unclear risk	No patients were reported as being withdrawn
Selective reporting (reporting bias)	Unclear risk	No indication of reporting bias

Sharma 2003

Methods	Design: randomised controlled trial Method of randomisation: not stated Means of allocation concealment: not stated

Sharma 2003 *(Continued)*

	Withdrawals/drop-outs: not stated Blinding: none
Participants	Eligible: not stated Randomised: 57 (group 1: 14, group 2: 14, group 3: 15, group 4: 14) Completed: 57 Age range (years): 5 to 12 Sex (M/F): 29/28 Asthma diagnosis: unclear Inclusion criteria: history of cough, breathlessness with wheezing, RR > 30 per min, in ED for asthma Major exclusions: tuberculosis, history suggestive of tuberculosis Baseline PEF mean (SD): treatment 92 (48), control 92 (35)
Interventions	Setting: patients attending outpatient or casualty department for acute asthma at a hospital in India Patients were randomised to 1 of 4 groups: group 1: BDP 100 µg plus salbutamol 200 µg via MDI plus spacer; group 2: BDP 100 µg plus salbutamol 200 µg via MDI; group 3: salbutamol 200 µg via MDI plus spacer; group 4: salbutamol via MDI. The treatment was repeated every 20 min for a total of 3 treatments as needed
Outcomes	Clinical parameters recorded included PEF, HR, RR, blood pressure, wheezing and retractions. Laboratory parameters recorded included serum glucose, sodium, potassium and arterial blood gases
Notes	This trial was added in July 2005; the author was not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Trial not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No indication of patients being withdrawn from trial
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Singhi 1999

Methods	Design: randomised, double-blind, placebo-controlled study Method of randomisation: not described Concealment: identical drug packages, but concealment not described

Singhi 1999 *(Continued)*

Participants	Eligible: unclear; convenience sample Randomised: 60/60 Completed: 60/60 Age (mean (SD)) (years): budesonide 7.8 (2.5), placebo 8.1 (2.9) Sex (M/F): budesonide 19/11, placebo 20/10 Asthma diagnosis: at least 1 prior attack of asthma within the past 6 months Major exclusions: severe asthma; patients who had received corticosteroids in the preceding 72 h; and those with pneumonia, pertussis, measles, suspected foreign body, or any other chronic disease Baseline PEF mean (SD) (%): budesonide group 55 (26), placebo group 53 (20)
Interventions	Setting: ED at a Children's Hospital in India Intervention 1: 400 µg budesonide x 3 doses through MDI and spacer Intervention 2: placebo through MDI and spacer Both groups received nebulised salbutamol 0.15 mg/kg every 30 min x 3 doses then every 30 min as needed, and supplemental oxygen. If there was an inadequate response, co-interventions such as extra doses of $beta_2$-agonists, theophylline or corticosteroids were given while blinding was maintained
Outcomes	Change in RR, oxygen saturation, % predicted PEF (in those who could perform it), respiratory distress score, and respiratory distress grade (mild, moderate, severe)
Notes	New reference in 2003. The author was not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
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	Unclear risk	No indication of patients being withdrawn from the trial but baseline PEF was available for only 28 in the intervention group and 28 patients in the control group
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Starobin 2008

Methods	Design: randomised controlled trial, 3 arms
Participants	Randomised: nebulised fluticasone 24, IV methylprednisolone 23, combined 26 Age (mean ± SD) (years): nebulised fluticasone 37.9 ± 16.8, IV methylprednisolone 47 ± 14.6, combined 48.2 ± 17.2

Starobin 2008 *(Continued)*

	Sex (M/F): nebulised fluticasone 11/13, IV methylprednisolone 9/14, combined 15/11 Baseline PEF mean ± SD (% predicted): nebulised fluticasone 42 ± 27.5, IV methylprednisolone 35.2 ± 21.3, combined 38.9 ± 18.0 Inclusion criteria: ED patients aged 18 to 75 years with acute asthma, history of atopic or idiosyncratic asthma with any grade of severity Exclusion criteria: chronic use of systemic corticosteroids for severe asthma; history of severe cardiac, renal or liver disease; tracheostomy; requiring mechanical ventilation
Interventions	Group 1 patients (Flixotide group) received inhalation of Flixotide Nebules® (fluticasone propionate) (Glaxo Wellcome, Australia) 2 mL (0.5 mg) Group 2 patients (the Solumedrol® group) received IV infusion of Solumedrol (methylprednisolone) 125 mg within the first 30 min after admission Group 3 patients (combined group) were treated by both routes of corticosteroids All patient received oxygen at a rate of 5 L/min, salbutamol 0.5 mL plus ipratropium bromide 1 mg plus 2 mL of normal saline 0.9% every 20 min during the first hour of ED treatment Decisions regarding admission to the internal medicine ward, intensive care unit or discharge, as well as additional treatment decisions were made independently by the local ED staff
Outcomes	Primary outcome: hospital admissions. Other outcomes included PEF, oxygen saturation, HR and dyspnoea score, measured before and 2 h after ED treatment was initiated. Corticosteroids were continued for 1 week following the ED visit according to the protocol arm, and hospital admission/discharge rate, ED re-admissions in the week after enrolment and other major events related to asthma were recorded. (Only the 0- and 2-h outcomes contribute to this review) It is stated there were no serious adverse event, although 1 patient (treatment group not stated) required mechanical ventilation and 1 patient from group 3 (both ICS and systemic corticosteroid) returned to the ED during the first week of the study
Notes	ICS versus systemic corticosteroid subgroup, and ICS versus placebo (systemic corticosteroid in both groups) Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Reported as "random consecutive case fashion to one of three protocol arms"
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias)	Unclear risk	Unclear

Starobin 2008 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Sung 1998

Methods	Design: randomised controlled trial Method of randomisation: block randomisation in groups of 4 to 6 stratified by age (6 months to < 5 years, and > 5 years) and by concurrent use of ICS Means of allocation concealment: randomisation sequence concealed to all study personnel, identical drug packages Blinding: double-blind, identical packages of study drugs made indistinguishable from each other and identified only by a study number Withdrawal/drop-outs: all subjects accounted for
Participants	Eligible: 82 referred. 38 excluded for: PIS < 5 (32), declined (2), congenital heart disease (1), chicken pox exposure (1), assessed too late (1), ICS use (1) Randomised: 44 (24/20) Completed: 44 Age (mean) (years): study group 4.4, control group 3.5. Range: 6 months to 18 years Sex (M/F): 80%/20% Asthma diagnosis: wheezing on at least 2 prior occasions Inclusion criteria: PIS ≥ 5 and ≤ 11 Major exclusion criteria: acute exacerbation ≤ 2 weeks prior, use of systemic glucocorticoids < 1 month prior, previous enrolment, presence of any underlying disease that could affect the patient's cardiopulmonary status Baseline PIS median (range): budesonide 7 (6 to 8.8), placebo 7 (6 to 8)
Interventions	Setting: tertiary care paediatric hospital in Canada Study group received nebulised budesonide 2 mg x 1 dose Control group received normal saline placebo Both groups were given oral prednisone 1 mg/kg (maximum 50 mg) x 1 dose and salbutamol 0.15 mg/kg x 3 doses then every hour x 4 h. Supplemental oxygen was given as needed to maintain O_2 saturation > 92%
Outcomes	Primary outcome was PIS, which was correlated with FEV_1/FVC in asthmatic children > 6 years. Secondary outcomes included oxygen saturation, HR and co-interventions including the use of extra doses of salbutamol, ipratropium bromide use and IV glucocorticoid use. Other outcomes included admission, length of hospitalisation and relapse of wheezing
Notes	The author was contacted and provided additional data from the study. ICS versus placebo, both groups received systemic corticosteroid

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of how the random sequence was generated are not available in the trial report. Block randomisation in groups of 4 to 6 stratified by age (6 months to < 5 years, and > 5 years) and by concurrent use of ICS
Allocation concealment (selection bias)	Low risk	Randomisation sequence concealed to all study personnel, identical drug packages

Sung 1998 *(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	Unclear risk	No indication of patients being withdrawn from trial
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Tsai 2001

Methods	Design: randomised controlled trial Method of randomisation: random number allocation Means of allocation concealment: not stated Blinding: double-blind, double-dummy Withdrawals/drop-outs: 4 patients excluded because the ambient nitric oxide levels were too high (the primary outcome), 2 patients were excluded because of disease deterioration
Participants	Eligible: unclear Randomised: 30 Completed: 24 (12/12) Sex: not stated Asthma diagnosis: previous diagnosis of allergic asthma Inclusion criteria: age 6 to 17 years, allergic asthma Exclusion criteria: acute febrile respiratory infection, on corticosteroids or leukotriene D4 receptor agonists within 4 weeks Baseline PEF: treatment group 110 L/min, control group 89 L/min
Interventions	Setting: ED at a Children's Hospital in Taiwan Intervention group was given nebulised terbutaline 0.1 mg/kg per dose at 0 a 6 h plus budesonide 0.05 mg/kg, maximum 2 mg, at 0 h, while the control group received the same dose of terbutaline plus nebulised placebo
Outcomes	Outcomes evaluated included exhaled nitric oxide levels, PIS, PEF and blood pressure
Notes	This trial was added in July 2002. ICS versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number allocation but unclear from trial report whether the sequence was produced by computer or tables
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported

Tsai 2001 *(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	Unclear risk	4 patients excluded because the ambient nitric oxide levels were too high (the primary outcome), 2 patients were excluded because of disease deterioration
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Upham 2011

Methods	Design: randomised controlled trial
Participants	Randomised: budesonide 91, placebo 89 Age (mean (range)) (years): budesonide 6.2 (5.4 to 7.0), placebo 6.3 (5.5 to 7.1) Sex (M/F): budesonide 64/27, placebo 54/35 Reported as: "116 patients (64%) presented in the moderate severity range (asthma score 8–11), and 62 patients (34%) presented in the severe (12–15) range." General point. Reported as: "Baseline demographic and clinical characteristics were similar between treatment groups (Table 2). BUD subjects had a slightly higher rate of prior hospitalisation and number of nebulized albuterol treatments prior to ED arrival" Inclusion criteria: children 2 to 18 years of age, with a history of asthma defined by at least 2 prior episodes of treatment with bronchodilators, and an asthma score of ≥ 8 who were prescribed systemic corticosteroid were eligible for inclusion. Screening was limited to patients triaged to the highest 2 acuity categories of a 4-level triage system. The asthma score used was reported by Qureshi et al (Qureshi 1998), and was chosen due to its similarity to the PIS, age-specific RR and excellent inter-rater reliability Exclusion criteria: any use of systemic corticosteroid in the prior 30 days; chronic lung disease, sickle cell anaemia, immunodeficiency, cardiac disease requiring surgery or medications, known renal or hepatic dysfunction, impending respiratory failure, altered level of consciousness, exposure to varicella in the prior 21 days, suspected foreign body or croup; had been enrolled in the study previously; or had an adverse drug reaction or allergy to the study drugs
Interventions	Intervention: budesonide inhalation suspension 2 mg, nebulised Control: placebo All patients received standard acute asthma therapy while consent was being obtained, which included albuterol (3.75 mg for patients weighing 10 to 20 kg, 5 mg for those > 20 kg); ipratropium bromide (500 µg); and prednisolone, prednisone, or methylprednisolone (2 mg/kg to a maximum of 60 mg)
Outcomes	Primary outcome: difference in median asthma scores between study groups 2 h after intervention Secondary outcomes: hospital admissions to an inpatient floor or observation unit, HR, RR and oxygen saturation
Notes	Include - ICS versus placebo (systemic corticosteroid in both groups)

Upham 2011 *(Continued)*

	Trial added in 2012 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were stratified by age category (2 to 8 and 9 to 18 years) and use of ICS at study entry. Enrolment occurred in each strata until that strata was filled
Allocation concealment (selection bias)	Low risk	Opaque envelopes that were pre-randomised in variable-sized blocks
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study medication was prepared by a respiratory therapist out of sight of other staff, the patient, and the patient's family, and was placed into a shielded nebulisation chamber. Nebulised medications were administered by a respiratory therapist not involved in asthma scoring, treatment decisions or disposition decisions. The investigators recorded which treatment the study physicians felt the patient received at the time of the patient's final disposition, and they did not seem to be able to distinguish between the
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators recorded which treatment the study physicians felt the patient received at the time of the patient's final disposition, and they did not seem to be able to distinguish between the 2
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All 91 patients randomised to budesonide received budesonide, and 89 were evaluable for the primary outcome (1 patient was discharged before the 2-h evaluation, and 1 did not have a 2-h score). 88 of 89 patients randomised to normal sterile saline placebo received normal sterile saline placebo (1 patient was inadvertently started on standard therapy without placebo), and 81 of those 89 patients were evaluable for the primary outcome. 2 patients in the normal sterile saline group withdrew from the study: 1 for feeling "jittery" and 1 for unspecified reasons at the guardian's request. 5 additional patients in the normal sterile saline group could not be evaluated for the primary outcome because they were admitted to the inpatient ward before the 2-h evaluation. 2 patients in the budesonide group and 4 patients in the normal sterile saline group were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

Volovitz 1998

Methods	Design: randomised controlled trial Method of randomisation: computer generated Means of allocation concealment: sealed envelopes Blinding: double-blind, double-dummy Withdrawal/drop-outs: 1 patient excluded because of pneumonia, and another for non-compliance
Participants	Eligible: unclear Randomised: 24 Completed: 11/11 Sex (M/F): intervention 73%/37%, control 64%/46% Asthma diagnosis: moderately severe attack with PEF1 35-75% predicted and PIS 8 to 13 Inclusion criteria: PEF 35-75% and PIS 8 to 13, aged 6 to 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%: FEV_1 not done

Volovitz 1998 *(Continued)*

	Baseline PEF% mean (SD): budesonide 54.40 (10.25), prednisolone 61.67 (10.73) Baseline PIS mean (SD): budesonide 8.75 (1.22), prednisolone 8.67 (1.12)
Interventions	Interventions: ED at a paediatric Hospital in Israel Intervention 1: single-dose budesonide 1600 µg by Turbohaler Intervention 2: prednisolone 2 mg/kg orally Both groups received terbutaline 5 mg by nebuliser or 0.5 mg by Turbohaler at 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 x 2 weeks Intervention 2 group was discharged on prednisolone 2 mg/kg/day, reduced by 25% every second day, and placebo Turbohaler
Outcomes	Outcomes evaluated in the ED included PEF, PIS and vital signs
Notes	This trial was only included in the secondary analysis comparing ICS versus systemic corticosteroid. The author was contacted and provided additional data from the study

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	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	Unclear risk	1 patient excluded because of pneumonia, and 1 for non-compliance
Selective reporting (reporting bias)	Unclear risk	No apparent indication of reporting bias

BDP: beclomethasone dipropionate; COPD: chronic obstructive pulmonary disease; ED: emergency department; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; HR: heart rate; ICS: inhaled corticosteroid; IM: intramuscular; IV: intravenous; LABA: long-acting $beta_2$-agonist; M/F: male/female; MDI: metered-dose inhaler; MPIS: modified pulmonary index score; PEF: peak expiratory flow; PEF: peak expiratory flow rate; PFT: pulmonary function test; PIS: Pulmonary Index Score; RR: respiratory rate; SD: standard deviation; VHC: valved holding chamber.

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

Study	Reason for exclusion
Agarwal 2010	Study compared combination therapy with inhaled corticosteroids + long-acting beta$_2$-agonists versus placebo
Balanag 2003	RCT comparing combination therapy with budesonide plus formoterol versus salbutamol alone
Balanag 2006	Study compared combination therapy with a long-acting beta$_2$-agonist + ICS versus a short-acting beta$_2$-agonist alone
Bilancia 1998	Study included only hospitalised patients
Brenner 2000	Study compared ICS versus placebo, with both groups receiving systemic corticosteroids, in the treatment of acute asthma after ED discharge
Camargo 2000	Study compared ICS versus placebo, with both groups receiving systemic corticosteroids, in the treatment of asthma exacerbations after ED discharge
Chhabra 1994	Study compared sequential treatment with beta$_2$-agonists alone with beta$_2$-agonists plus ICS in chronic asthma
Clarke 2007	Study involved only patients with chronic asthma
Connett 1994	RCT of systemic corticosteroids versus placebo
Crain 1998	Review of the study by Pauwels 1997
Cueva 1975	Study investigated the effects of chronic beclomethasone use on pulmonary function tests and adrenal function in chronic asthma
Curtis 1995	Study involved only hospitalised patients
da Silva 2007	Study involved children under 3 years of age hospitalised with episodes of wheezing, who did not have a clear diagnosis of asthma
Decimo 2009	Study compared fluticasone versus budesonide in the outpatient treatment of asthma exacerbations in children, with no placebo group
Di Franco 2006	Study randomised clinic patients with an asthma exacerbation to outpatient treatment with ICS versus oral corticosteroids
Ediger 2001	RCT including patients with asthma and COPD, who were all admitted to hospital
Ediger 2006	Study randomised outpatients with asthma exacerbations at a clinic to treatment with ICS alone, ICS plus systemic corticosteroid, or systemic corticosteroid alone
Fitzgerald 2000	Study comparing ICS versus systemic corticosteroid in the treatment of asthma exacerbations after ED discharge
Francis 1997	Study investigated the outpatient treatment of asthma exacerbations with ICS versus systemic corticosteroid in children under 4 years of age
Frye 1988	Letter regarding intravenous corticosteroid use in acute asthma
Higenbottam 2000	Study included only patients admitted to hospital
Joubert 1985	Study used patients with chronic asthma with simulated acute attacks

Study	Reason for exclusion
La Rosa 1997	Study compared ICS versus placebo in the outpatient treatment of acute asthma. Systemic corticosteroids were withheld from both treatment groups
Lai 2005	All patients in this study were hospitalised
Latysheva 1996	Non-randomised study that compared betamethasone with dexamethasone in asthma and other allergic conditions
Lee-Wong 2002	All the patients in this study were hospitalised
Leuppi 2002	Study investigated the use of single high dose of budesonide versus doubling of standard dose budesonide in induced asthma exacerbations, with no placebo group
Lim 1996	Study included only hospitalised patients
Lin 1999	RCT of systemic corticosteroids versus placebo
Lipworth 1997	Review article on acute asthma
Littenberg 1986	RCT of systemic corticosteroids versus placebo
Manjra 2000	Study investigated the use of ICS versus systemic corticosteroid in the outpatient treatment of acute asthma
Mannan 2008	Study investigated patient initiated increase in the baseline dose of inhaled corticosteroids to prevent ED visits and oral corticosteroid use
Matthews 1999	Study involved only children who were hospitalised with acute asthma
McEvoy 1977	All patients in this study were hospitalised, and were enrolled after 2 days of hospitalisation if they had not responded satisfactorily to intravenous aminophylline and $beta_2$-agonists
Mendes 2008	Study included outpatients with mild stable asthma
Mitchell 1995	Study involved only hospitalised patients
Nana 1998a	Study compared budesonide and prednisolone in the treatment of asthma exacerbations after ED discharge
Nuhoglu 2001	Study compared high-dose ICS versus medium-dose ICS plus systemic corticosteroid in the outpatient treatment of asthma exacerbations
Pauwels 1997	Study involved long acting $beta_2$-agonists and budesonide use in chronic asthma
Pierson 1974	Study investigated the use of ICS in acute asthma
Postma 2006	Study included outpatients with asthma exacerbations induced by withdrawal of ICS
Razi 2008	Trial compared different methods of giving ICS, but all patients received ICS
Rivera 1999	Not a clinical trial
Rodrigo 1994	RCT of systemic corticosteroids versus placebo
Salmeron 1989	Study compared the use of ICS versus placebo in chronic asthma

Study	Reason for exclusion
Sano 2000	Study included only children less than 24 months old admitted to hospital for wheezing episodes
Scarfone 1993	RCT of systemic corticosteroids versus placebo
Schneider 1988	RCT of systemic corticosteroids versus placebo
Sereda 2004	Study included only admitted patients
Singhi 1995	Review of the study by Scarfone 1995
Stein 1990	RCT of systemic corticosteroids versus placebo
Storr 1987	RCT of systemic corticosteroids versus placebo
Tal 1990	RCT of systemic corticosteroids versus placebo
Verona 1998	Study compared ICS versus systemic corticosteroid in the outpatient treatment of asthma exacerbations
Wen 2008	Not a randomised trial, and involved children hospitalised with asthma
Wendel 1996	All of the patients randomised in this study were all admitted to hospital
Winter 1997	All of the patients included in this study were hospitalised
Wolfson 1994	RCT of systemic corticosteroids versus placebo
Yang 2000	All of the patients included in this study were all admitted to hospital
Yashina 2001	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	Study recruited patients both from the ED and hospitalised patients with acute asthma
Zhen 2003	Not an RCT. Allocation was by order of administration
Zhou 2000	This study investigated the use of a spacer in the delivery of beclomethasone in chronic asthma therapy

COPD: chronic obstructive pulmonary disease; ED: emergency department; ICS: inhaled corticosteroid; RCT: randomised controlled trial.

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

Acun 2003

Methods	Randomised controlled trial
Participants	42 children with moderately severe asthma. Aged 6 months and 15 years (total sample). The baseline characteristics of the 2 groups were reported as similar
Interventions	Intervention: on first and second days: nebulised budesonide 2000 µg/day. On third and fourth days: 1000 µg/day Control: on first and second days: prednisolone 2 mg/kg/day. On third and fourth days: 1 mg/kg/day

Acun 2003 *(Continued)*

	Both groups received salbutamol 1.2 mg/kg/day on first day, and on the second day 0.6 mg/kg/day. On the third and fourth days and on both groups received 0.3 mg/kg/day
Outcomes	Hospital length of stay. PIS (pre- and post-treatment), heart rate and oxygen saturation levels
Notes	Unclear whether patients were hospitalised

Agarwal 2003

Methods	Randomised controlled trial
Participants	114 patients, 15 and 45 years of age with acute moderate exacerbations of asthma
Interventions	budesonide 800 µg with MDI and spacer versus placebo at 30-min intervals for 3 doses
Outcomes	PEF, length of stay
Notes	Study reported as conference abstract. Unclear whether patients were hospitalised. Awaiting further clarification from author

Agarwal 2005

Methods	Randomised controlled trial
Participants	90 patients, 15 and 45 years of age with acute moderate exacerbations of asthma
Interventions	Fluticasone 500 µg with MDI and spacer versus placebo at 30-min intervals for 3 doses
Outcomes	PEF, length of stay
Notes	Study reported as conference abstract. Unclear whether all patients were hospitalised. Awaiting further clarification from author

Agarwal 2009

Methods	Randomised controlled trial
Participants	70 patients, 15 and 45 years of age with acute moderate exacerbations of asthma
Interventions	Fluticasone 500 µg + salmeterol 50 µg with MDI and spacer versus placebo at 30-min intervals for 3 doses
Outcomes	PEF, length of stay
Notes	Study reported as conference abstract. Unclear whether all patients were hospitalised. Awaiting further clarification from author

Akhtaruzzaman 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Alangari 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Ambrosio 1997

Methods	Randomised controlled trial
Participants	Adults with acute exacerbations of asthma
Interventions	Terbutaline + budesonide versus terbutaline alone given through nebulisation at 15-min intervals for 3 doses
Outcomes	Admissions, PEF, adverse effects and vital signs
Notes	Trial report unobtainable

Arulparithi 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Chen 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Demirca 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Jerez 2002

Methods	Randomised controlled trial
Participants	15 patients, mean age 38 years with acute asthma
Interventions	Fluticasone 4000 µg versus oral prednisolone 30 mg
Outcomes	FEV_1 and eosinophils in differential cell counts
Notes	Unclear whether all patients were hospitalised

Ndeezi 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Razi 2017
Methods
Participants
Interventions
Outcomes
Notes

Sampayo 2017
Methods
Participants
Interventions
Outcomes
Notes

Silverman 2010
Methods
Participants
Interventions
Outcomes
Notes

FEV_1: forced expiratory volume in 1 second; MDI: metered-dose inhaler; PEF: peak expiratory flow rate; PIS: Pulmonary Index Score.

DATA AND ANALYSES

Comparison 1. ICS versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admission to hospital	12	960	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.31, 0.62]
1.1 ICS + systemic corticosteroids vs. systemic corticosteroids	5	433	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.36, 0.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 ICS vs. placebo	7	527	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.14, 0.52]
2 FEV_1 at 1 hour	4	248	Mean Difference (IV, Random, 95% CI)	0.28 [-0.22, 0.77]
2.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Random, 95% CI)	0.0 [-0.34, 0.34]
2.2 ICS vs. placebo	3	188	Mean Difference (IV, Random, 95% CI)	0.37 [-0.32, 1.07]
3 FEV_1 at 2 hours	3	203	Mean Difference (IV, Random, 95% CI)	0.05 [-0.23, 0.33]
3.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.45, 0.25]
3.2 ICS vs. placebo	2	143	Mean Difference (IV, Random, 95% CI)	0.10 [-0.27, 0.48]
4 FEV_1 at 3 to 4 hours	4	319	Mean Difference (IV, Random, 95% CI)	0.15 [-0.09, 0.39]
4.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.46, 0.26]
4.2 ICS vs. placebo	3	259	Mean Difference (IV, Random, 95% CI)	0.23 [-0.01, 0.47]
5 FEV_1 at 5 to 6 hours	2	106	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.42, 0.16]
5.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.49, 0.29]
5.2 ICS vs. placebo	1	49	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.59, 0.27]
6 FEV_1 (% predicted) at 1 hour	4	324	Mean Difference (IV, Fixed, 95% CI)	2.13 [-1.10, 5.36]
6.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Fixed, 95% CI)	3.30 [-6.73, 13.33]
6.2 ICS vs. placebo	3	264	Mean Difference (IV, Fixed, 95% CI)	1.99 [-1.42, 5.41]
7 FEV_1 (% predicted) at 2 hours	4	319	Mean Difference (IV, Fixed, 95% CI)	3.81 [0.28, 7.33]
7.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Fixed, 95% CI)	2.0 [-8.23, 12.23]
7.2 ICS vs. placebo	3	259	Mean Difference (IV, Fixed, 95% CI)	4.05 [0.30, 7.80]

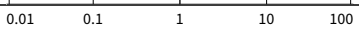
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 FEV_1 (% predicted) at 3 to 4 hours	4	319	Mean Difference (IV, Fixed, 95% CI)	5.93 [2.11, 9.75]
8.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Fixed, 95% CI)	3.0 [-7.95, 13.95]
8.2 ICS vs. placebo	3	259	Mean Difference (IV, Fixed, 95% CI)	6.34 [2.26, 10.42]
9 FEV_1 (% predicted) at 5 to 6 hours	2	106	Mean Difference (IV, Fixed, 95% CI)	1.43 [-5.67, 8.53]
9.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	57	Mean Difference (IV, Fixed, 95% CI)	1.0 [-10.49, 12.49]
9.2 ICS vs. placebo	1	49	Mean Difference (IV, Fixed, 95% CI)	1.70 [-7.33, 10.73]
10 PEF at 1 hour	5	289	Mean Difference (IV, Fixed, 95% CI)	10.22 [-6.13, 26.57]
10.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Fixed, 95% CI)	-23.5 [-95.66, 48.66]
10.2 ICS vs. placebo	4	200	Mean Difference (IV, Fixed, 95% CI)	14.50 [-4.15, 33.15]
10.3 ICS vs. placebo without spacer	1	29	Mean Difference (IV, Fixed, 95% CI)	1.57 [-36.95, 40.09]
11 PEF at 2 hours	3	208	Mean Difference (IV, Random, 95% CI)	14.32 [-33.54, 62.18]
11.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Random, 95% CI)	-22.90 [-94.11, 48.31]
11.2 ICS vs. placebo	2	148	Mean Difference (IV, Random, 95% CI)	27.21 [-26.83, 81.26]
12 PEF at 5 to 6 hours	3	135	Mean Difference (IV, Random, 95% CI)	0.83 [-62.87, 64.53]
12.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	57	Mean Difference (IV, Random, 95% CI)	-30.70 [-106.40, 45.00]
12.2 ICS vs. placebo	2	78	Mean Difference (IV, Random, 95% CI)	12.19 [-72.49, 96.87]
13 PEF at 3 to 4 hours	5	348	Mean Difference (IV, Random, 95% CI)	26.07 [-1.17, 53.31]
13.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Random, 95% CI)	-39.80 [-108.45, 28.85]

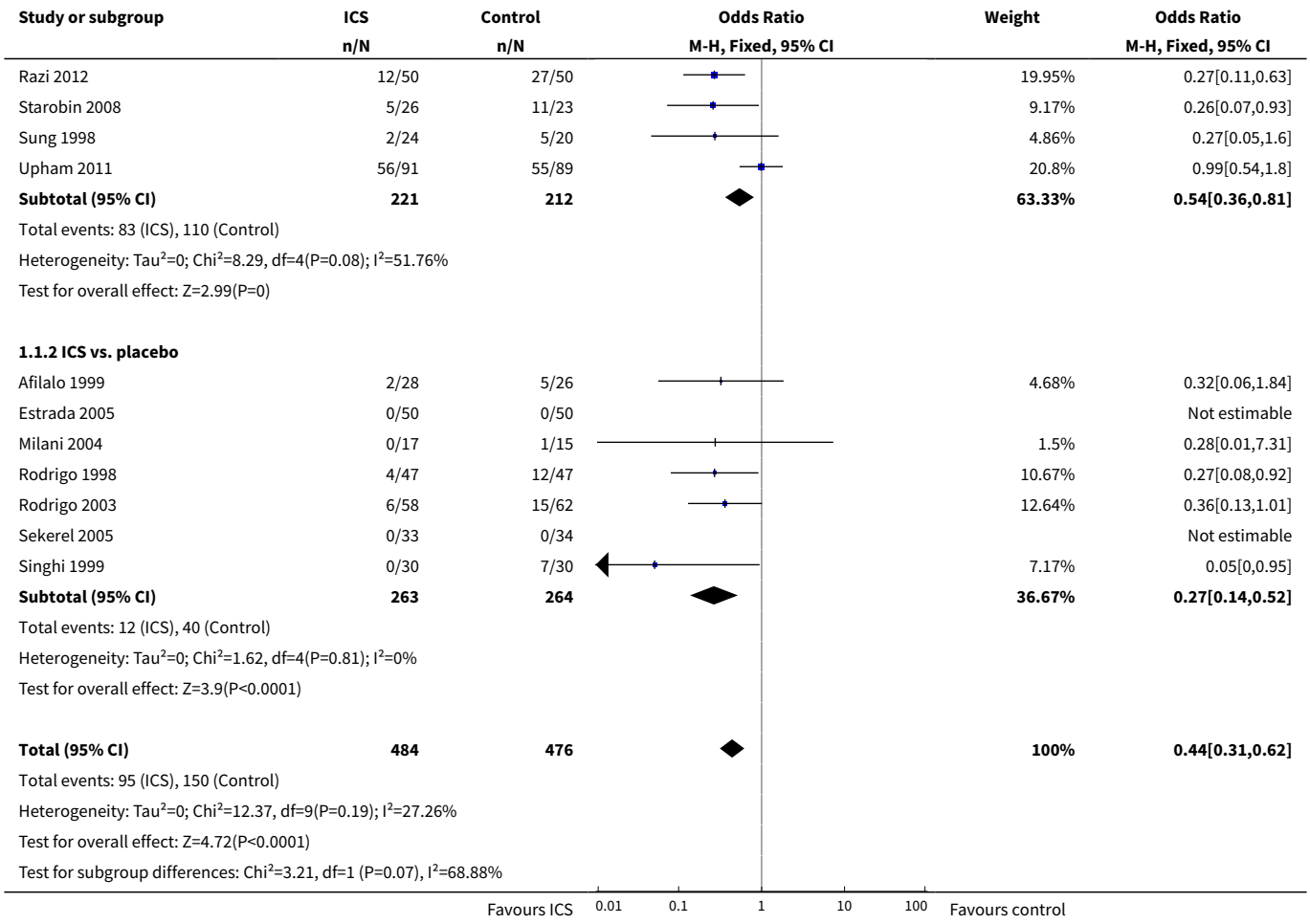
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 ICS vs. placebo	4	288	Mean Difference (IV, Random, 95% CI)	37.44 [16.92, 57.96]
14 PEF (% predicted) at 1 hour	4	324	Mean Difference (IV, Fixed, 95% CI)	5.66 [2.01, 9.32]
14.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Fixed, 95% CI)	-2.13 [-17.08, 12.82]
14.2 ICS vs. placebo	3	264	Mean Difference (IV, Fixed, 95% CI)	6.16 [2.39, 9.93]
15 PEF (% predicted) at 2 hours	5	384	Mean Difference (IV, Fixed, 95% CI)	7.46 [3.77, 11.15]
15.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-16.56, 12.96]
15.2 ICS vs. placebo	4	324	Mean Difference (IV, Fixed, 95% CI)	8.07 [4.27, 11.88]
16 PEF (% predicted) at 3 to 4 hours	4	324	Mean Difference (IV, Fixed, 95% CI)	7.19 [3.05, 11.33]
16.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Fixed, 95% CI)	-5.27 [-19.80, 9.26]
16.2 ICS vs. placebo	3	264	Mean Difference (IV, Fixed, 95% CI)	8.29 [3.97, 12.61]
17 PEF (% predicted) at 5 to 6 hours	2	114	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-10.59, 8.84]
17.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	60	Mean Difference (IV, Fixed, 95% CI)	-3.20 [-18.49, 12.09]
17.2 ICS vs. placebo	1	54	Mean Difference (IV, Fixed, 95% CI)	0.70 [-11.88, 13.28]
18 Clinical score at 1 to 2 hours	4	176	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.59, 0.01]
18.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-1.16, 0.40]
18.2 ICS vs. placebo	3	150	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.66, 0.16]
19 Clinical score at 3 to 4 hours	4	194	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.62, -0.05]
19.1 ICS + systemic corticosteroids vs. systemic corticosteroids	1	44	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.74, 0.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 ICS vs. placebo	3	150	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.73, -0.02]
20 Vital signs	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.1 Respiratory rate	3	198	Mean Difference (IV, Random, 95% CI)	0.57 [-1.69, 2.83]
20.2 Heart rate	5	363	Mean Difference (IV, Random, 95% CI)	3.99 [0.59, 7.39]
20.3 Oxygen saturation	5	301	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.66, 0.31]
20.4 Systolic blood pressure	3	128	Mean Difference (IV, Random, 95% CI)	-0.32 [-4.00, 5.36]
21 Adverse effects	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 Nausea/vomiting	1	94	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.18]
21.2 *Tremor	3	309	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.84, 2.45]
22 Admission to hospital sub-grouped children vs. adults	12	960	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.31, 0.62]
22.1 Adults	5	377	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.20, 0.60]
22.2 Children	7	583	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.33, 0.80]
23 Admission to hospital sub-grouped high vs. low dose	12	960	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.31, 0.62]
23.1 High dose	8	775	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.35, 0.74]
23.2 Low dose	4	185	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.08, 0.49]
24 Admission to hospital sub-grouped by delivery devices	11	906	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.32, 0.63]
24.1 Nebuliser	7	572	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.35, 0.82]
24.2 MDI and spacer	4	334	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.18, 0.59]

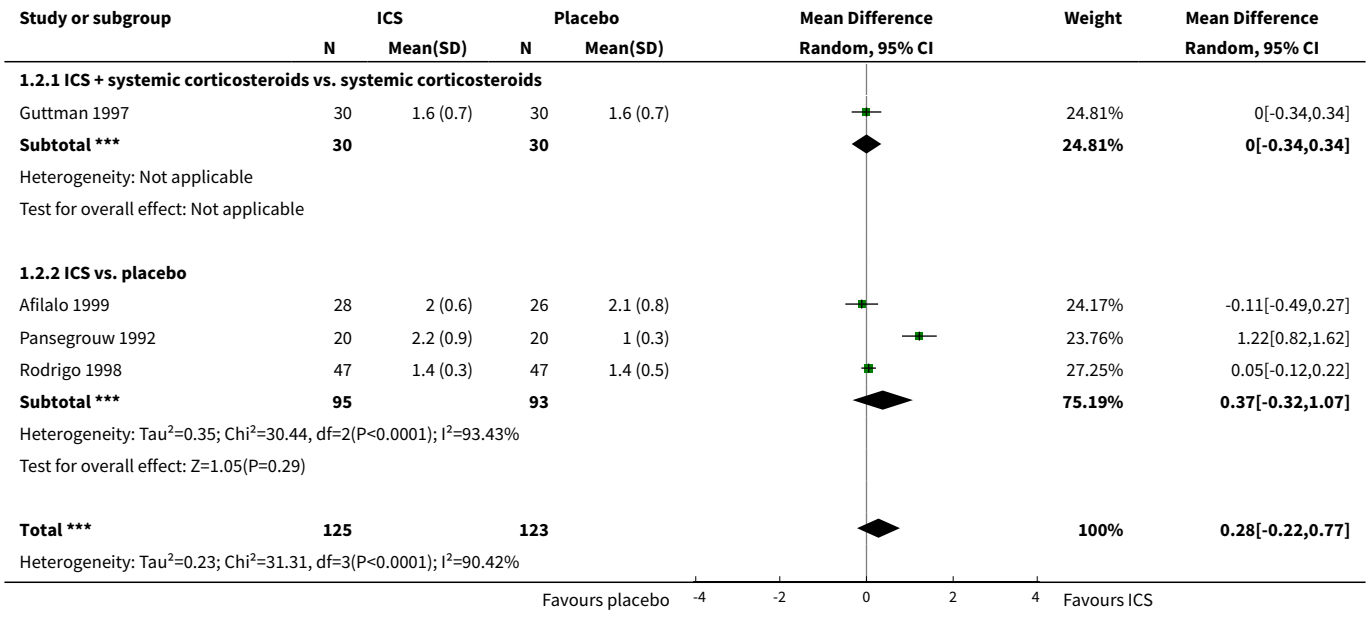
Analysis 1.1. Comparison 1 ICS versus placebo, Outcome 1 Admission to hospital.

Study or subgroup	ICS n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 ICS + systemic corticosteroids vs. systemic corticosteroids					
Guttman 1997	8/30	12/30		8.56%	0.55[0.18,1.62]





Analysis 1.2. Comparison 1 ICS versus placebo, Outcome 2 FEV_1 at 1 hour.



Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=1.1(P=0.27)							
Test for subgroup differences: Chi²=0.89, df=1 (P=0.34), I²=0%							

Favours placebo -4 -2 0 2 4 Favours ICS

Analysis 1.3. Comparison 1 ICS versus placebo, Outcome 3 FEV_1 at 2 hours.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.3.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Guttman 1997	30	1.7 (0.6)	30	1.8 (0.7)		29.88%	-0.1[-0.45,0.25]
Subtotal ***	**30**		**30**			**29.88%**	**-0.1[-0.45,0.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.56(P=0.57)							
1.3.2 ICS vs. placebo							
Afilalo 1999	26	2.1 (0.6)	23	2.2 (0.8)		26.53%	-0.13[-0.52,0.26]
Rodrigo 1998	47	1.6 (0.5)	47	1.4 (0.5)		43.59%	0.26[0.07,0.45]
Subtotal ***	**73**		**70**			**70.12%**	**0.1[-0.27,0.48]**
Heterogeneity: Tau²=0.05; Chi²=3.05, df=1(P=0.08); I²=67.2%							
Test for overall effect: Z=0.54(P=0.59)							
Total ***	**103**		**100**			**100%**	**0.05[-0.23,0.33]**
Heterogeneity: Tau²=0.04; Chi²=5.09, df=2(P=0.08); I²=60.72%							
Test for overall effect: Z=0.34(P=0.73)							
Test for subgroup differences: Chi²=0.61, df=1 (P=0.43), I²=0%							

Favours placebo -4 -2 0 2 4 Favours ICS

Analysis 1.4. Comparison 1 ICS versus placebo, Outcome 4 FEV_1 at 3 to 4 hours.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.4.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Guttman 1997	30	1.7 (0.7)	30	1.8 (0.8)		21.36%	-0.1[-0.46,0.26]
Subtotal ***	**30**		**30**			**21.36%**	**-0.1[-0.46,0.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.55(P=0.58)							
1.4.2 ICS vs. placebo							
Afilalo 1999	26	2 (0.7)	23	2.2 (0.8)		17.77%	-0.17[-0.59,0.25]
Rodrigo 1998	47	1.8 (0.6)	47	1.4 (0.5)		30.77%	0.36[0.15,0.57]
Rodrigo 2003	56	2.1 (0.6)	60	1.8 (0.6)		30.1%	0.3[0.08,0.52]
Subtotal ***	**129**		**130**			**78.64%**	**0.23[-0.01,0.47]**
Heterogeneity: Tau²=0.03; Chi²=4.9, df=2(P=0.09); I²=59.18%							
Test for overall effect: Z=1.86(P=0.06)							
Total ***	**159**		**160**			**100%**	**0.15[-0.09,0.39]**

Favours placebo -4 -2 0 2 4 Favours ICS

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=0.04; Chi²=8.59, df=3(P=0.04); I²=65.09%							
Test for overall effect: Z=1.22(P=0.22)							
Test for subgroup differences: Chi²=2.25, df=1 (P=0.13), I²=55.48%							

Favours placebo -4 -2 0 2 4 Favours ICS

Analysis 1.5. Comparison 1 ICS versus placebo, Outcome 5 FEV_1 at 5 to 6 hours.

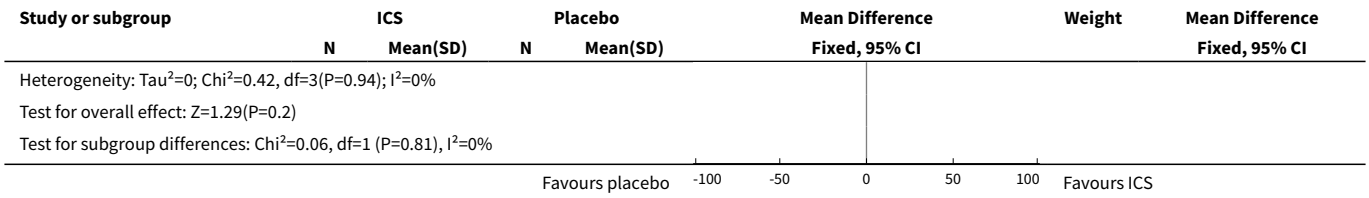
Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Guttman 1997	28	1.8 (0.7)	29	1.9 (0.8)		54.51%	-0.1[-0.49,0.29]
Subtotal ***	**28**		**29**			**54.51%**	**-0.1[-0.49,0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.5(P=0.62)							
1.5.2 ICS vs. placebo							
Afilalo 1999	26	2.1 (0.7)	23	2.2 (0.9)		45.49%	-0.16[-0.59,0.27]
Subtotal ***	**26**		**23**			**45.49%**	**-0.16[-0.59,0.27]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.47)							
Total ***	**54**		**52**			**100%**	**-0.13[-0.42,0.16]**
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%							
Test for overall effect: Z=0.86(P=0.39)							
Test for subgroup differences: Chi²=0.04, df=1 (P=0.84), I²=0%							

Favours placebo -4 -2 0 2 4 Favours ICS

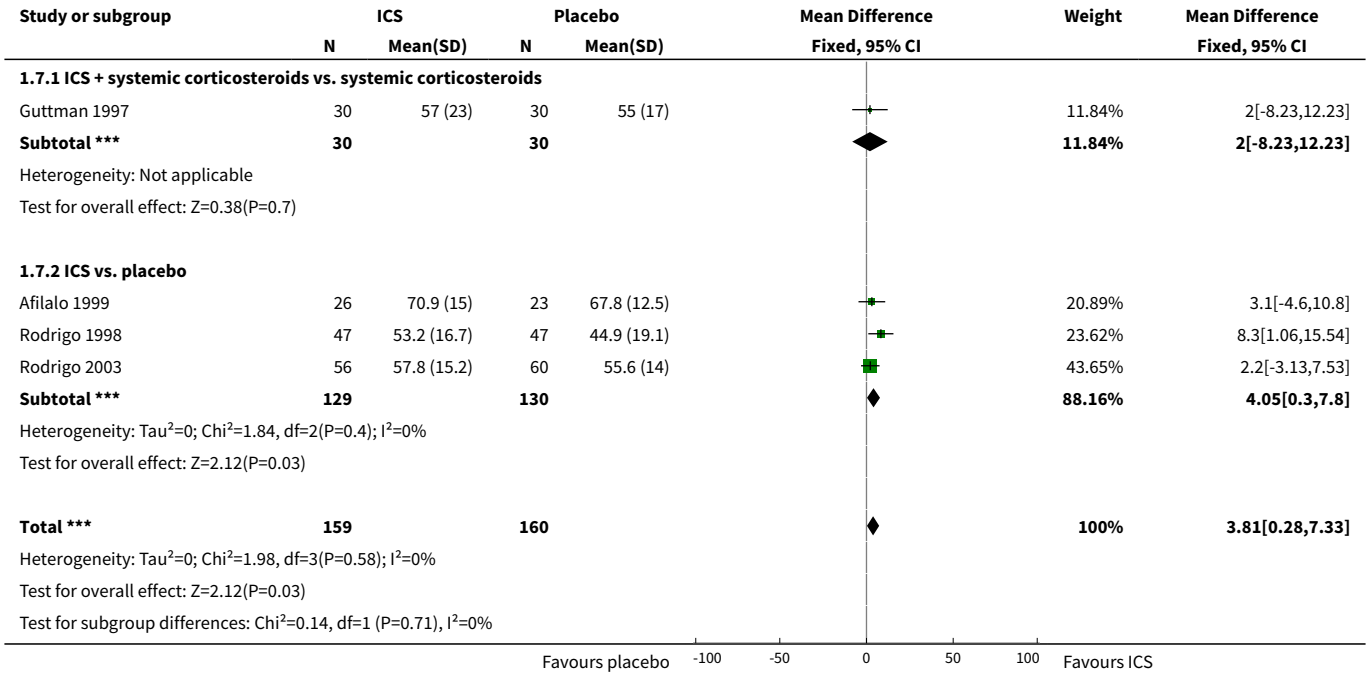
Analysis 1.6. Comparison 1 ICS versus placebo, Outcome 6 FEV_1 (% predicted) at 1 hour.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Guttman 1997	30	54 (23)	30	50.7 (16)		10.4%	3.3[-6.73,13.33]
Subtotal ***	**30**		**30**			**10.4%**	**3.3[-6.73,13.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.65(P=0.52)							
1.6.2 ICS vs. placebo							
Afilalo 1999	28	69 (13)	26	65.5 (14.2)		19.72%	3.5[-3.78,10.78]
Rodrigo 1998	47	46 (14.8)	47	43.4 (17.2)		24.8%	2.6[-3.89,9.09]
Rodrigo 2003	56	53 (13.6)	60	52 (12.8)		45.08%	1[-3.81,5.81]
Subtotal ***	**131**		**133**			**89.6%**	**1.99[-1.42,5.41]**
Heterogeneity: Tau²=0; Chi²=0.36, df=2(P=0.83); I²=0%							
Test for overall effect: Z=1.14(P=0.25)							
Total ***	**161**		**163**			**100%**	**2.13[-1.1,5.36]**

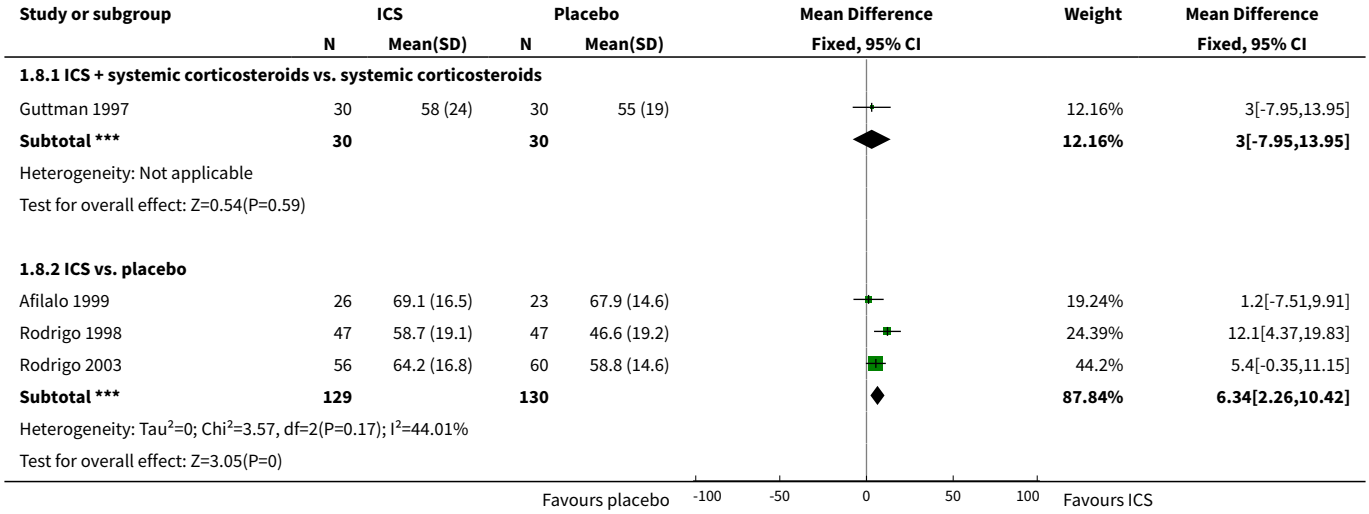
Favours placebo -100 -50 0 50 100 Favours ICS

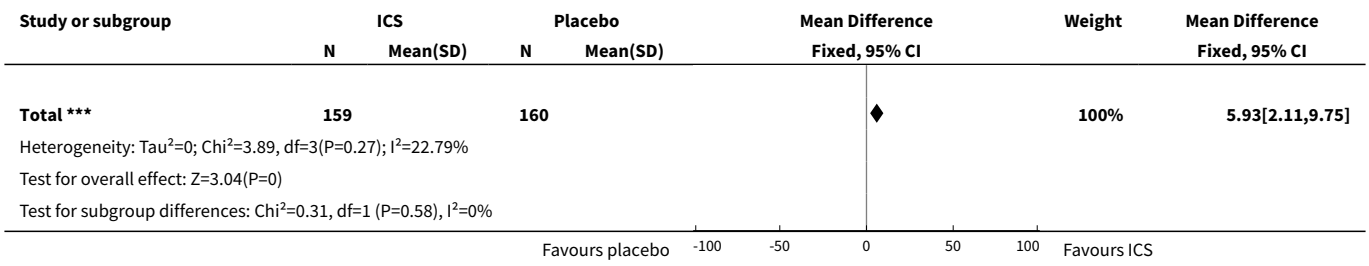


Analysis 1.7. Comparison 1 ICS versus placebo, Outcome 7 FEV_1 (% predicted) at 2 hours.

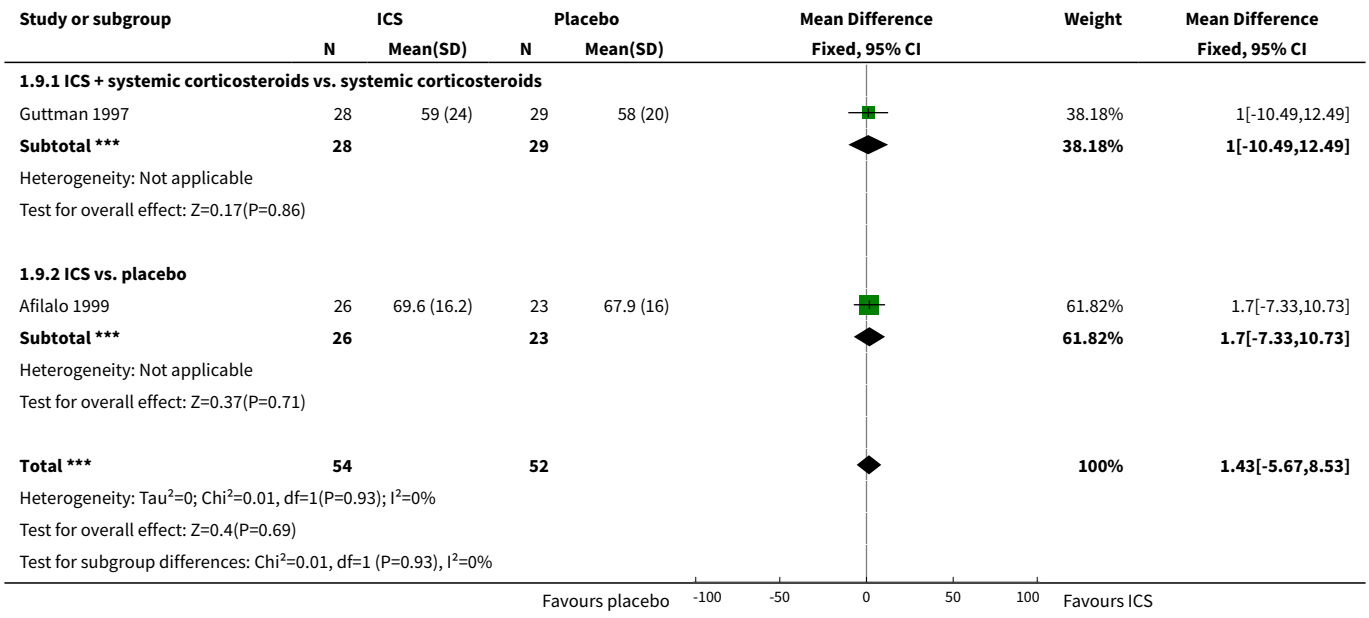


Analysis 1.8. Comparison 1 ICS versus placebo, Outcome 8 FEV_1 (% predicted) at 3 to 4 hours.

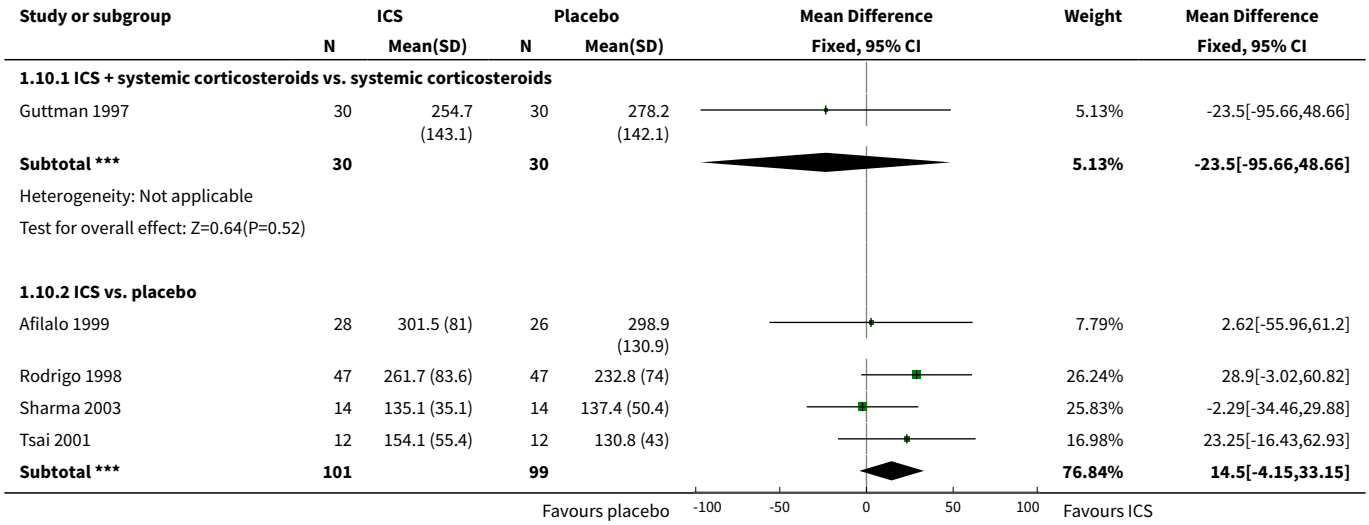


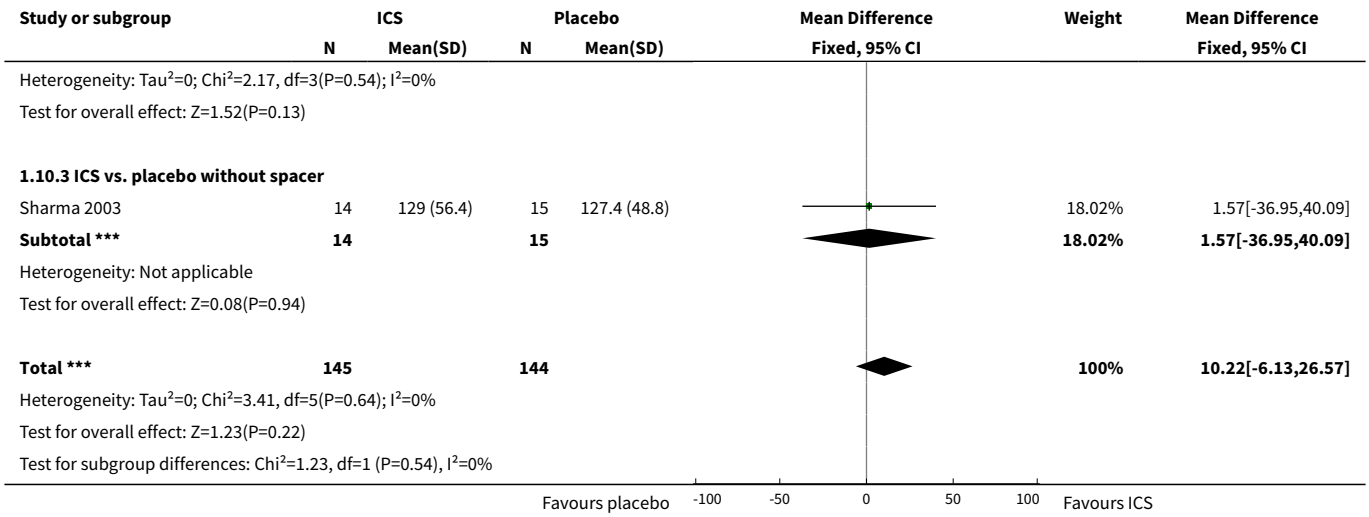


Analysis 1.9. Comparison 1 ICS versus placebo, Outcome 9 FEV_1 (% predicted) at 5 to 6 hours.

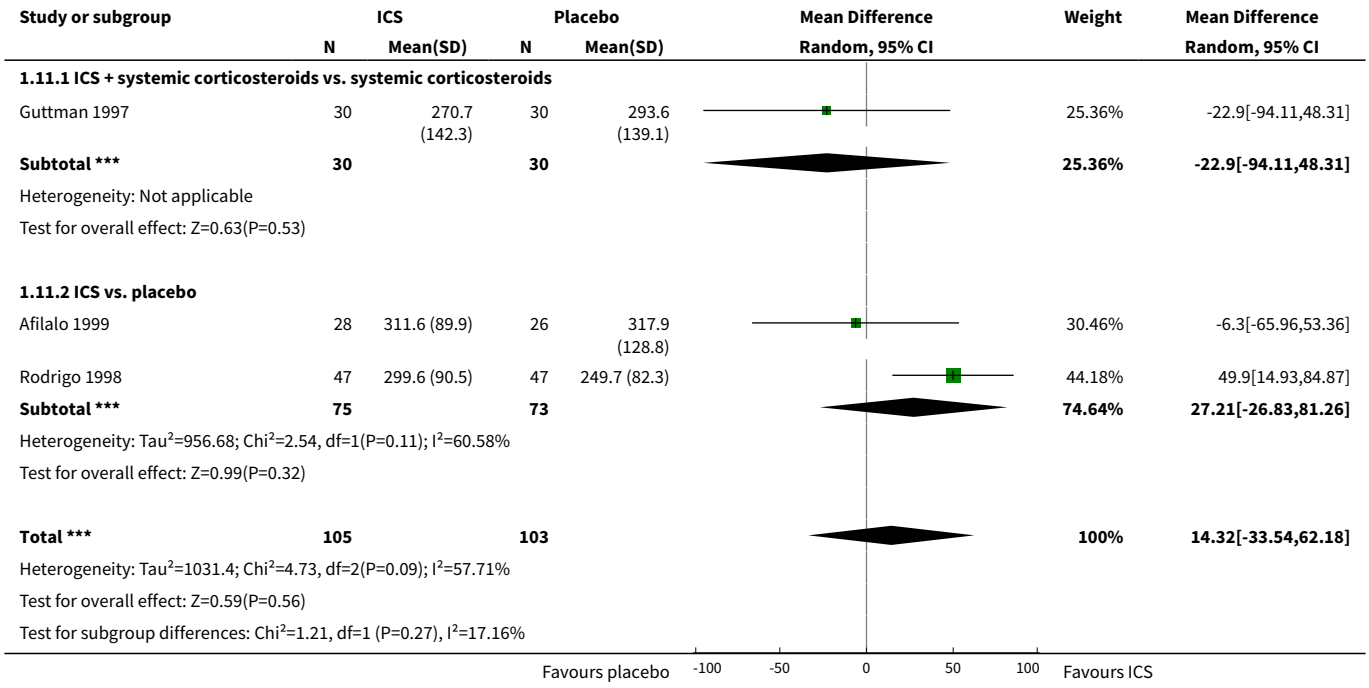


Analysis 1.10. Comparison 1 ICS versus placebo, Outcome 10 PEF at 1 hour.

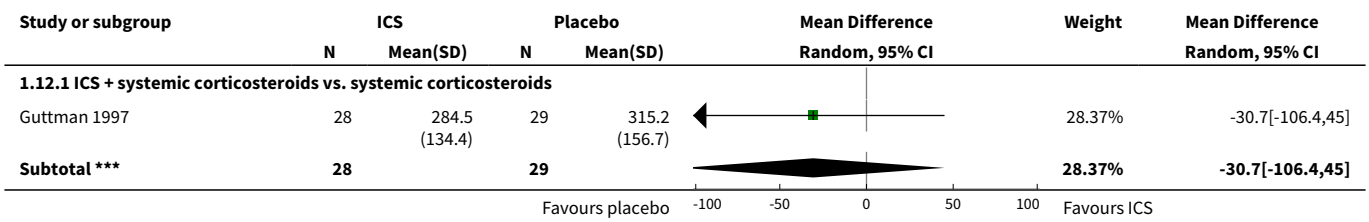


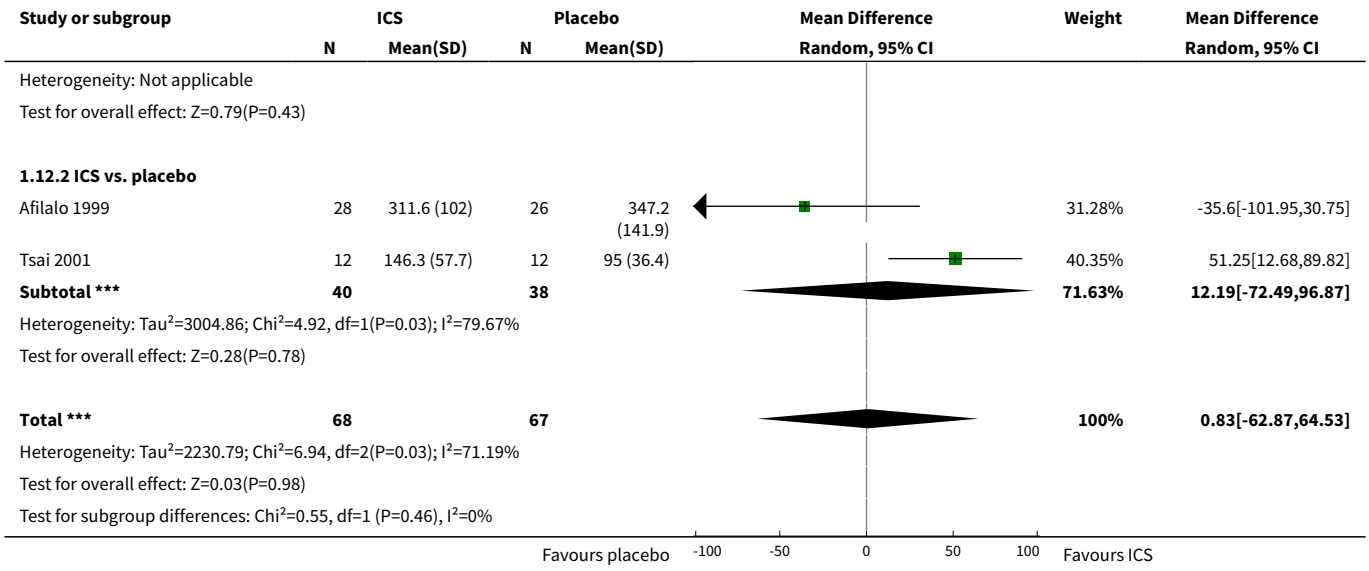


Analysis 1.11. Comparison 1 ICS versus placebo, Outcome 11 PEF at 2 hours.

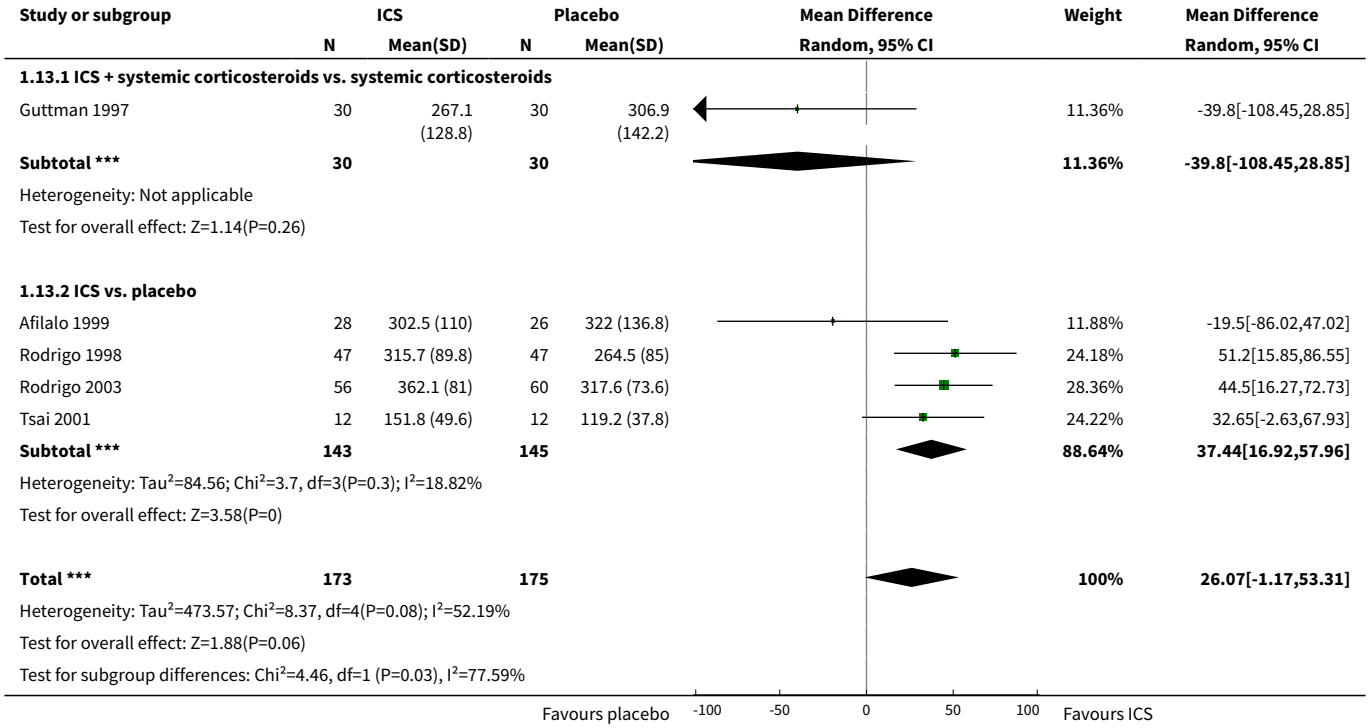


Analysis 1.12. Comparison 1 ICS versus placebo, Outcome 12 PEF at 5 to 6 hours.



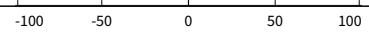


Analysis 1.13. Comparison 1 ICS versus placebo, Outcome 13 PEF at 3 to 4 hours.



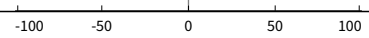
Analysis 1.14. Comparison 1 ICS versus placebo, Outcome 14 PEF (% predicted) at 1 hour.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.14.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Guttman 1997	30	58.3 (30.6)	30	60.4 (28.4)		5.98%	-2.13[-17.08,12.82]
Subtotal ***	**30**		**30**			**5.98%**	**-2.13[-17.08,12.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.28(P=0.78)							
1.14.2 ICS vs. placebo							
Afilalo 1999	28	74.3 (16.9)	26	65 (20.7)		13.04%	9.28[-0.84,19.4]
Rodrigo 1998	47	52.1 (17.2)	47	46.8 (14.3)		32.67%	5.3[-1.09,11.69]
Rodrigo 2003	56	60.8 (15.1)	60	54.9 (13.7)		48.31%	5.9[0.64,11.16]
Subtotal ***	**131**		**133**			**94.02%**	**6.16[2.39,9.93]**
Heterogeneity: Tau^2=0; Chi^2=0.44, df=2(P=0.8); I^2=0%							
Test for overall effect: Z=3.2(P=0)							
Total ***	**161**		**163**			**100%**	**5.66[2.01,9.32]**
Heterogeneity: Tau^2=0; Chi^2=1.55, df=3(P=0.67); I^2=0%							
Test for overall effect: Z=3.04(P=0)							
Test for subgroup differences: Chi^2=1.11, df=1 (P=0.29), I^2=9.97%							



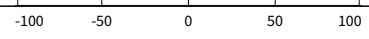
Analysis 1.15. Comparison 1 ICS versus placebo, Outcome 15 PEF (% predicted) at 2 hours.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.15.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Guttman 1997	30	62.1 (31)	30	63.9 (27.3)		6.24%	-1.8[-16.56,12.96]
Subtotal ***	**30**		**30**			**6.24%**	**-1.8[-16.56,12.96]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.24(P=0.81)							
1.15.2 ICS vs. placebo							
Afilalo 1999	28	76.9 (17.5)	26	70 (23.3)		11.11%	6.93[-4.13,17.99]
Rodrigo 1998	47	59.9 (17.7)	47	49.8 (14.7)		31.43%	10.1[3.52,16.68]
Rodrigo 2003	56	66.7 (16.5)	60	59.6 (14.9)		41.35%	7.1[1.37,12.83]
Singhi 1999	30	80 (26)	30	73 (20)		9.87%	7[-4.74,18.74]
Subtotal ***	**161**		**163**			**93.76%**	**8.07[4.27,11.88]**
Heterogeneity: Tau^2=0; Chi^2=0.55, df=3(P=0.91); I^2=0%							
Test for overall effect: Z=4.16(P<0.0001)							
Total ***	**191**		**193**			**100%**	**7.46[3.77,11.15]**
Heterogeneity: Tau^2=0; Chi^2=2.16, df=4(P=0.71); I^2=0%							
Test for overall effect: Z=3.96(P<0.0001)							
Test for subgroup differences: Chi^2=1.61, df=1 (P=0.2), I^2=37.98%							



Analysis 1.16. Comparison 1 ICS versus placebo, Outcome 16 PEF (% predicted) at 3 to 4 hours.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.16.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Guttman 1997	30	61.6 (28.6)	30	66.9 (28.8)		8.12%	-5.27[-19.8,9.26]
Subtotal ***	**30**		**30**			**8.12%**	**-5.27[-19.8,9.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.71(P=0.48)							
1.16.2 ICS vs. placebo							
Afilalo 1999	28	74.4 (23.2)	26	69.8 (22.9)		11.3%	4.59[-7.73,16.91]
Rodrigo 1998	47	64 (18.7)	47	52.5 (16.7)		33.37%	11.5[4.33,18.67]
Rodrigo 2003	56	70.4 (17.3)	60	63.5 (15.7)		47.21%	6.9[0.87,12.93]
Subtotal ***	**131**		**133**			**91.88%**	**8.29[3.97,12.61]**
Heterogeneity: Tau^2=0; Chi^2=1.32, df=2(P=0.52); I^2=0%							
Test for overall effect: Z=3.76(P=0)							
Total ***	**161**		**163**			**100%**	**7.19[3.05,11.33]**
Heterogeneity: Tau^2=0; Chi^2=4.39, df=3(P=0.22); I^2=31.71%							
Test for overall effect: Z=3.4(P=0)							
Test for subgroup differences: Chi^2=3.07, df=1 (P=0.08), I^2=67.45%							



Analysis 1.17. Comparison 1 ICS versus placebo, Outcome 17 PEF (% predicted) at 5 to 6 hours.

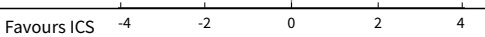
Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.17.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Guttman 1997	30	65.3 (29.6)	30	68.5 (30.8)		40.37%	-3.2[-18.49,12.09]
Subtotal ***	**30**		**30**			**40.37%**	**-3.2[-18.49,12.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.41(P=0.68)							
1.17.2 ICS vs. placebo							
Afilalo 1999	28	76.9 (21.8)	26	76.2 (25.1)		59.63%	0.7[-11.88,13.28]
Subtotal ***	**28**		**26**			**59.63%**	**0.7[-11.88,13.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.11(P=0.91)							
Total ***	**58**		**56**			**100%**	**-0.87[-10.59,8.84]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%							
Test for overall effect: Z=0.18(P=0.86)							
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%							

Analysis 1.18. Comparison 1 ICS versus placebo, Outcome 18 Clinical score at 1 to 2 hours.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.18.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Nuhoglu 2005	12	2.3 (0.9)	14	2.7 (1.4)		14.7%	-0.38[-1.16,0.4]
Subtotal ***	**12**		**14**			**14.7%**	**-0.38[-1.16,0.4]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.95(P=0.34)							
1.18.2 ICS vs. placebo							
Milani 2004	17	6.2 (2.2)	15	5.6 (2.4)		18.37%	0.24[-0.46,0.93]
Rodrigo 1998	47	0.3 (0.4)	47	0.5 (0.6)		53.61%	-0.38[-0.78,0.03]
Tsai 2001	12	5.1 (1.8)	12	6 (1.4)		13.31%	-0.56[-1.38,0.26]
Subtotal ***	**76**		**74**			**85.3%**	**-0.25[-0.66,0.16]**
Heterogeneity: Tau^2=0.04; Chi^2=2.79, df=2(P=0.25); I^2=28.27%							
Test for overall effect: Z=1.2(P=0.23)							
Total ***	**88**		**88**			**100%**	**-0.29[-0.59,0.01]**
Heterogeneity: Tau^2=0; Chi^2=2.85, df=3(P=0.42); I^2=0%							
Test for overall effect: Z=1.89(P=0.06)							
Test for subgroup differences: Chi^2=0.08, df=1 (P=0.78), I^2=0%							

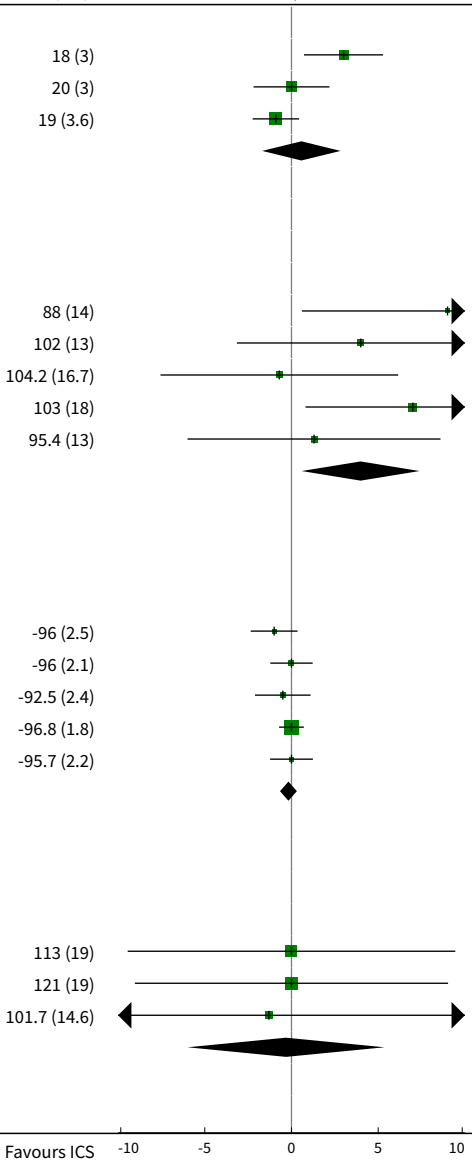
Analysis 1.19. Comparison 1 ICS versus placebo, Outcome 19 Clinical score at 3 to 4 hours.

Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.19.1 ICS + systemic corticosteroids vs. systemic corticosteroids							
Sung 1998	24	3.3 (2)	20	3.6 (2.1)		22.98%	-0.15[-0.74,0.45]
Subtotal ***	**24**		**20**			**22.98%**	**-0.15[-0.74,0.45]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.49(P=0.63)							
1.19.2 ICS vs. placebo							
Milani 2004	17	5.6 (2.7)	15	5.4 (2.6)		16.82%	0.07[-0.62,0.77]
Rodrigo 1998	47	0.1 (0.3)	47	0.4 (0.5)		47.84%	-0.54[-0.95,-0.13]
Tsai 2001	12	4.6 (1.7)	12	5.5 (2.2)		12.35%	-0.42[-1.23,0.39]
Subtotal ***	**76**		**74**			**77.02%**	**-0.37[-0.73,-0.02]**
Heterogeneity: Tau^2=0.01; Chi^2=2.22, df=2(P=0.33); I^2=9.81%							
Test for overall effect: Z=2.07(P=0.04)							
Total ***	**100**		**94**			**100%**	**-0.33[-0.62,-0.05]**
Heterogeneity: Tau^2=0; Chi^2=2.69, df=3(P=0.44); I^2=0%							
Test for overall effect: Z=2.28(P=0.02)							
Test for subgroup differences: Chi^2=0.41, df=1 (P=0.52), I^2=0%							



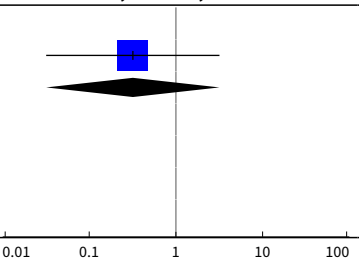
Analysis 1.20. Comparison 1 ICS versus placebo, Outcome 20 Vital signs.

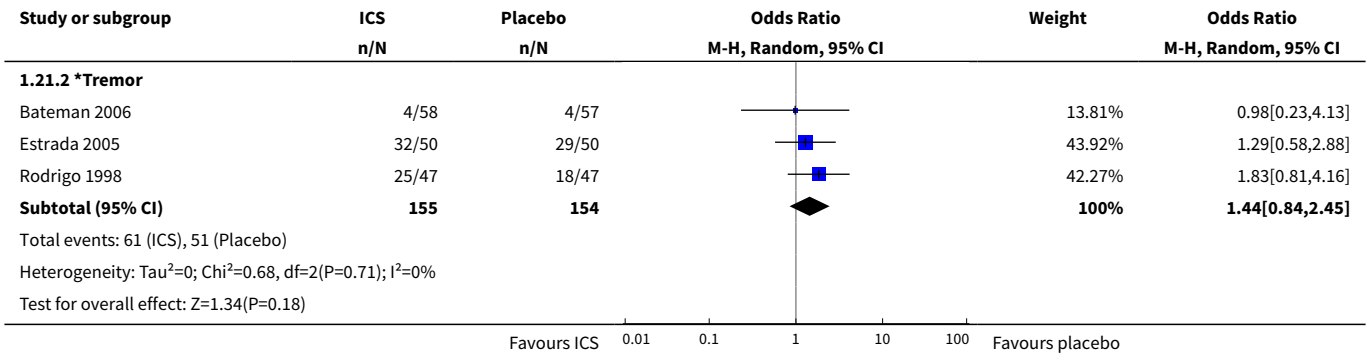
Study or subgroup	ICS N	ICS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.20.1 Respiratory rate							
Afilalo 1999	26	21 (5)	23	18 (3)		30.49%	3[0.72,5.28]
Guttman 1997	27	20 (5)	28	20 (3)		31.25%	0[-2.19,2.19]
Rodrigo 1998	47	18.1 (3)	47	19 (3.6)		38.26%	-0.9[-2.24,0.44]
Subtotal ***	**100**		**98**			**100%**	**0.57[-1.69,2.83]**
Heterogeneity: Tau^2=3.01; Chi^2=8.36, df=2(P=0.02); I^2=76.09%							
Test for overall effect: Z=0.49(P=0.62)							
1.20.2 Heart rate							
Afilalo 1999	26	97 (16)	23	88 (14)		14.8%	9[0.6,17.4]
Guttman 1997	27	106 (14)	28	102 (13)		19.73%	4[-3.15,11.15]
Rodrigo 1998	47	103.5 (17.2)	47	104.2 (16.7)		21.21%	-0.7[-7.55,6.15]
Rodrigo 2003	56	110 (16)	60	103 (18)		25.22%	7[0.81,13.19]
Starobin 2008	26	96.7 (13)	23	95.4 (13)		19.04%	1.3[-5.99,8.59]
Subtotal ***	**182**		**181**			**100%**	**3.99[0.59,7.39]**
Heterogeneity: Tau^2=1.96; Chi^2=4.6, df=4(P=0.33); I^2=12.98%							
Test for overall effect: Z=2.3(P=0.02)							
1.20.3 Oxygen saturation							
Afilalo 1999	26	-97 (2.3)	23	-96 (2.5)		12.97%	-1[-2.35,0.35]
Guttman 1997	27	-96 (2.5)	28	-96 (2.1)		15.84%	0[-1.22,1.22]
Milani 2004	17	-93 (2.2)	15	-92.5 (2.4)		9.22%	-0.5[-2.1,1.1]
Rodrigo 2003	56	-96.8 (2.1)	60	-96.8 (1.8)		46.43%	0[-0.71,0.71]
Starobin 2008	26	-95.7 (2.2)	23	-95.7 (2.2)		15.54%	0[-1.23,1.23]
Subtotal ***	**152**		**149**			**100%**	**-0.18[-0.66,0.31]**
Heterogeneity: Tau^2=0; Chi^2=1.98, df=4(P=0.74); I^2=0%							
Test for overall effect: Z=0.71(P=0.48)							
1.20.4 Systolic blood pressure							
Afilalo 1999	26	113 (14)	23	113 (19)		36.14%	0[-9.45,9.45]
Guttman 1997	27	121 (15)	28	121 (19)		39.56%	0[-9.03,9.03]
Tsai 2001	12	100.4 (14.2)	12	101.7 (14.6)		24.29%	-1.3[-12.82,10.22]
Subtotal ***	**65**		**63**			**100%**	**-0.32[-6,5.36]**
Heterogeneity: Tau^2=0; Chi^2=0.04, df=2(P=0.98); I^2=0%							
Test for overall effect: Z=0.11(P=0.91)							



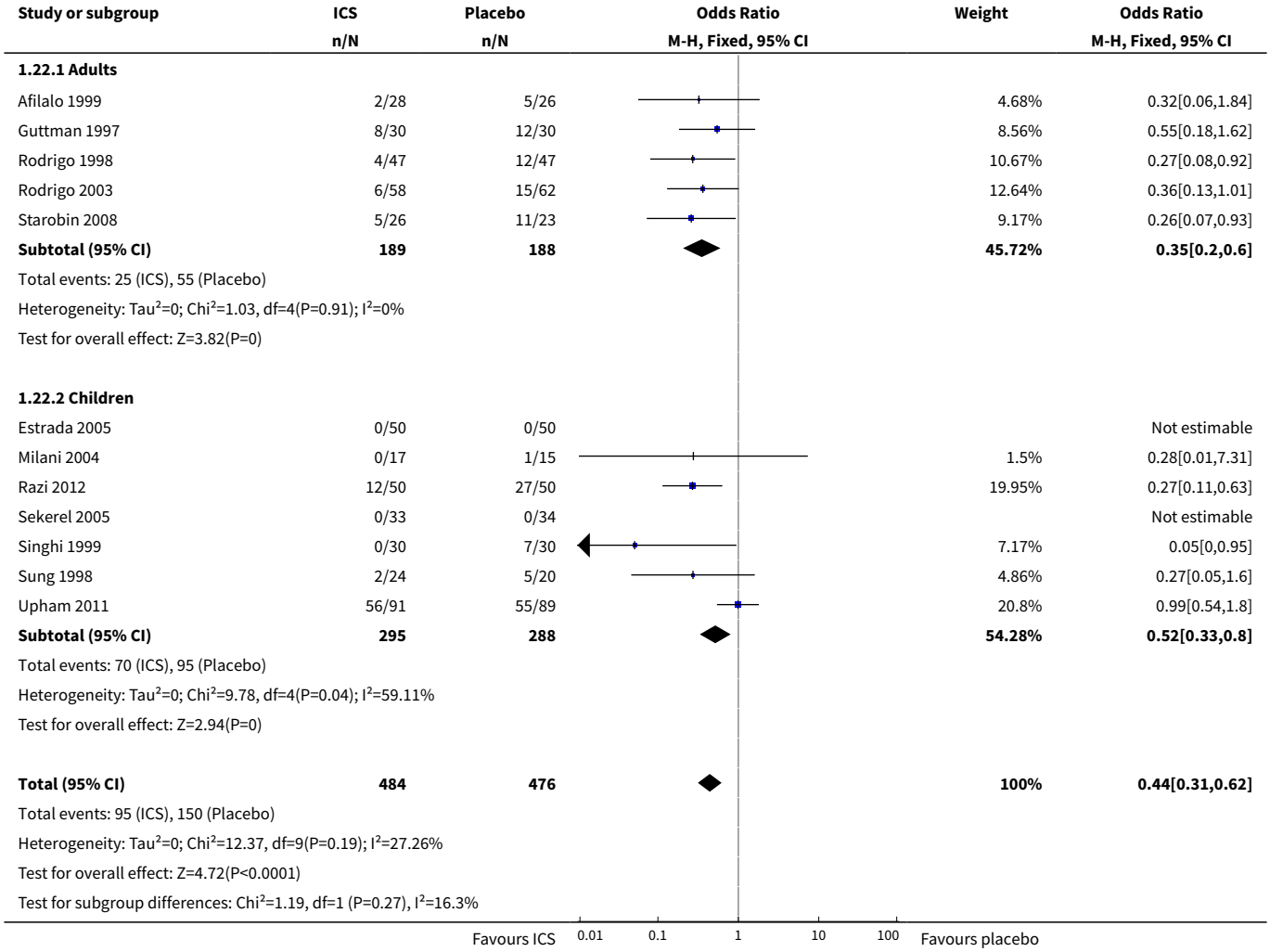
Analysis 1.21. Comparison 1 ICS versus placebo, Outcome 21 Adverse effects.

Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.21.1 Nausea/vomiting					
Rodrigo 1998	1/47	3/47		100%	0.32[0.03,3.18]
Subtotal (95% CI)	**47**	**47**		**100%**	**0.32[0.03,3.18]**
Total events: 1 (ICS), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					





Analysis 1.22. Comparison 1 ICS versus placebo, Outcome 22 Admission to hospital subgrouped children vs. adults.

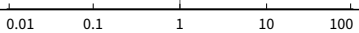


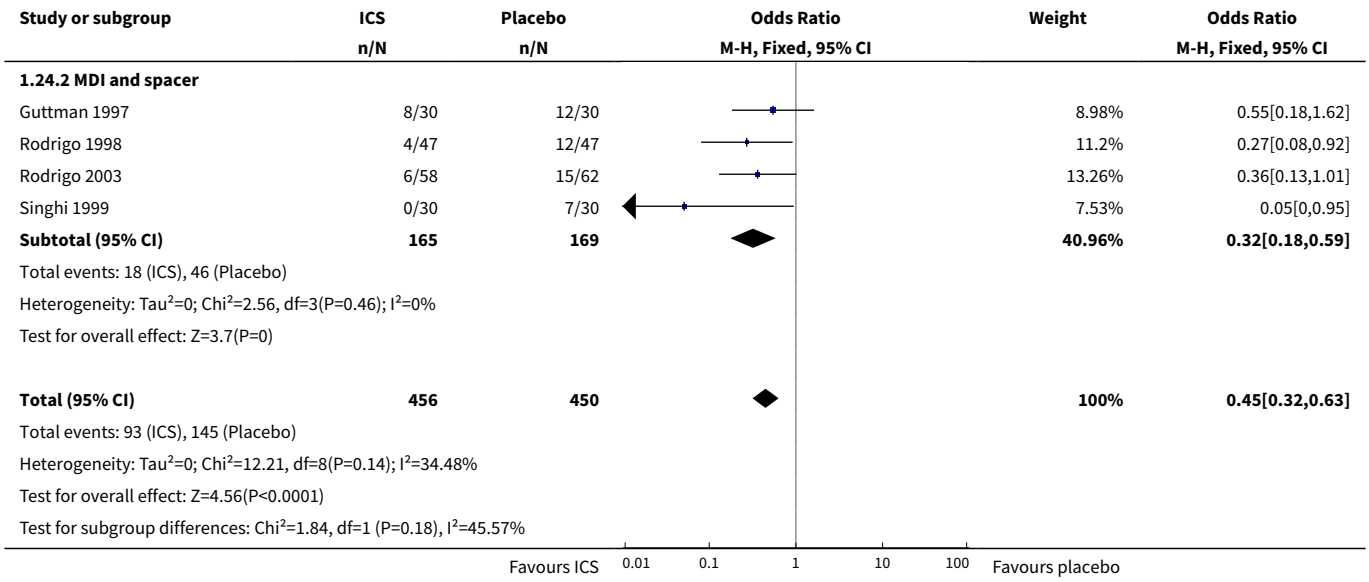
Analysis 1.23. Comparison 1 ICS versus placebo, Outcome 23 Admission to hospital subgrouped high vs. low dose.

Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.23.1 High dose					
Afilalo 1999	2/28	5/26		4.68%	0.32[0.06,1.84]
Estrada 2005	0/50	0/50			Not estimable
Guttman 1997	8/30	12/30		8.56%	0.55[0.18,1.62]
Razi 2012	12/50	27/50		19.95%	0.27[0.11,0.63]
Rodrigo 1998	4/47	12/47		10.67%	0.27[0.08,0.92]
Rodrigo 2003	6/58	15/62		12.64%	0.36[0.13,1.01]
Sekerel 2005	0/33	0/34			Not estimable
Upham 2011	56/91	55/89		20.8%	0.99[0.54,1.8]
Subtotal (95% CI)	**387**	**388**		**77.3%**	**0.51[0.35,0.74]**
Total events: 88 (ICS), 126 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.56, df=5(P=0.13); I^2=41.6%					
Test for overall effect: Z=3.54(P=0)					
1.23.2 Low dose					
Milani 2004	0/17	1/15		1.5%	0.28[0.01,7.31]
Singhi 1999	0/30	7/30		7.17%	0.05[0,0.95]
Starobin 2008	5/26	11/23		9.17%	0.26[0.07,0.93]
Sung 1998	2/24	5/20		4.86%	0.27[0.05,1.6]
Subtotal (95% CI)	**97**	**88**		**22.7%**	**0.2[0.08,0.49]**
Total events: 7 (ICS), 24 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.17, df=3(P=0.76); I^2=0%					
Test for overall effect: Z=3.49(P=0)					
Total (95% CI)	**484**	**476**		**100%**	**0.44[0.31,0.62]**
Total events: 95 (ICS), 150 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=12.37, df=9(P=0.19); I^2=27.26%					
Test for overall effect: Z=4.72(P<0.0001)					
Test for subgroup differences: Chi^2=3.61, df=1 (P=0.06), I^2=72.29%					

Analysis 1.24. Comparison 1 ICS versus placebo, Outcome 24 Admission to hospital subgrouped by delivery devices.

Study or subgroup	ICS n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.24.1 Nebuliser					
Estrada 2005	0/50	0/50			Not estimable
Milani 2004	0/17	1/15		1.57%	0.28[0.01,7.31]
Razi 2012	12/50	27/50		20.93%	0.27[0.11,0.63]
Sekerel 2005	0/33	0/34			Not estimable
Starobin 2008	5/26	11/23		9.62%	0.26[0.07,0.93]
Sung 1998	2/24	5/20		5.1%	0.27[0.05,1.6]
Upham 2011	56/91	55/89		21.82%	0.99[0.54,1.8]
Subtotal (95% CI)	**291**	**281**		**59.04%**	**0.53[0.35,0.82]**
Total events: 75 (ICS), 99 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.46, df=4(P=0.08); I^2=52.7%					
Test for overall effect: Z=2.87(P=0)					

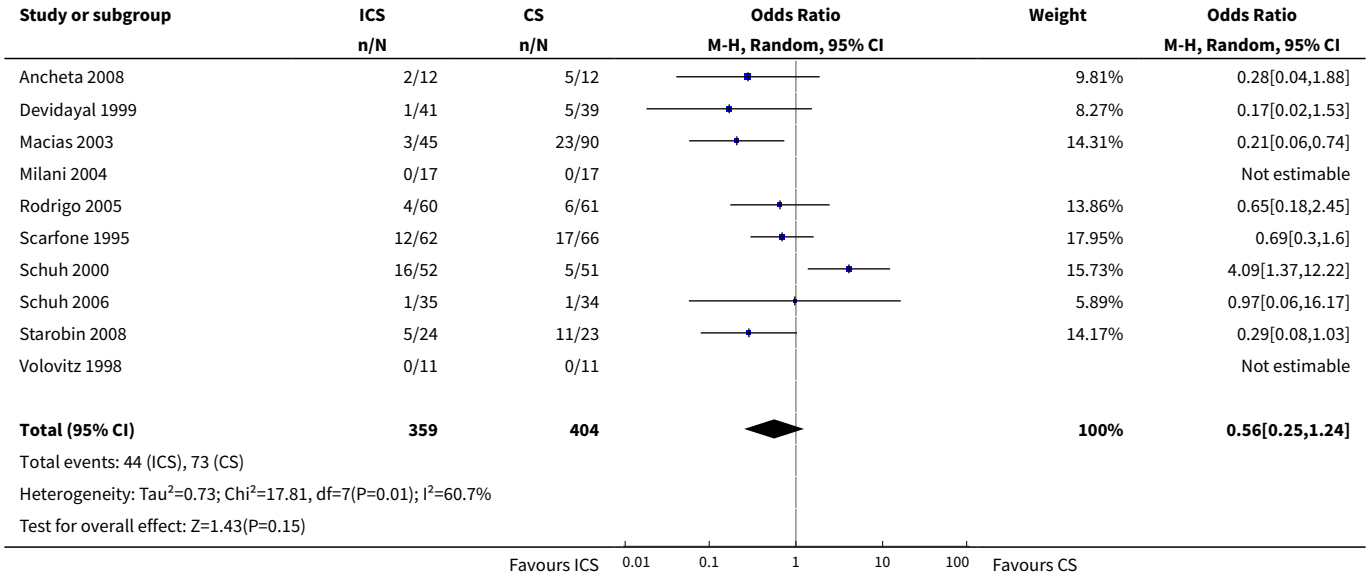




Comparison 2. ICS versus systemic steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admission to hospital	10	763	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.25, 1.24]

Analysis 2.1. Comparison 2 ICS versus systemic steroids, Outcome 1 Admission to hospital.



ADDITIONAL TABLES

Table 1. Summary of included trials: ICS versus placebo, both groups receiving oral corticosteroids

Study	N on ICS	N on placebo	Age group	Delivery device	ICS dose	Hospital admissions reported?
Bateman 2006	58	57	Adults	*	Budesonide 320 µg/puff 2 puffs q 5 min x 2; total dose 1280 µg; LOW	N
Guttman 1997	30	30	Adults	MDI plus chamber	Beclomethasone dipropionate 1 mg at 0, 30 min, 1, 2, 4, 6, 8 h; total dose 7 mg; HIGH	Y
Nuhoglu 2005	12	14	Children	Nebuliser	Budesonide 1 mg; LOW	N
Razi 2012	50	50	Children	Nebuliser	Budesonide 1 mg q 20 min x 3; total dose 3 mg; HIGH	Y
Starobin 2008	26	23	Adults	Nebuliser	Fluticasone 0.5 mg; LOW	Y
Sung 1998	24	20	Children	Nebuliser	Budesonide 2 mg; HIGH	Y
Upham 2011	91	89	Children	Nebuliser	Budesonide 2 mg; HIGH	Y

* Denotes uncertainty.
Dose equivalency used: high ≥ beclomethasone dipropionate 2 mg (e.g. budesonide 1.5 mg, fluticasone 1.5 mg, triamcinolone 5 mg).

Table 2. Summary of included trials: ICS versus placebo, systemic corticosteroids withheld from both treatment groups

Study	N on ICS	N on placebo	Age group	Delivery device	ICS dose	Hospital admissions reported?
Afilalo 1999	28	26	Adults	MDI	Beclomethasone 1 mg at 0, 30 min, 1, 2, 4 h; total dose 5 mg; HIGH	Y
Blandon 2004	40	46	Children	Nebuliser	Budesonide 550 µg x 1 dose; LOW	N
Bautista 1994	*	*	30 Children	*	Dose not stated	N
Estrada 2005	50	50	Children	Nebuliser	Fluticasone 500 µg/dose x 3 doses; total dose 1500 µg; HIGH	Y
Milani 2004	17	15	Children	Nebuliser	Budesonide 2 mg; HIGH	Y
Olaivar 1999	33	32	Children	Nebuliser	Budesonide 0.5 mg q 20 min x 3; total dose 1.5 mg; HIGH	N
Pansegrouw 1992	20	20	Adults	MDI	Beclomethasone 200 µg; LOW	N

Table 2. Summary of included trials: ICS versus placebo, systemic corticosteroids withheld from both treatment groups *(Continued)*

Rodrigo 1998	47	47	Adults	MDI+spacer	Flunisolide 1 mg q 10 min x 3 hours; total dose 18 mg; HIGH	Y
Rodrigo 2003	58	62	Adults	MDI+spacer	Fluticasone 1 mg q 10 min x 3 hours; total dose 18 mg; HIGH	Y
Sekerel 2005	33	34	Children	Nebuliser	Budesonide 1 mg q 1 h x 3; total dose 3 mg; HIGH	Y
Sharma 2003	28	29	Children	MDI+spacer	Beclomethasone 100 µg q 20 min x 3 prn; total dose 300 µg; LOW	N
Singhi 1999	30	30	Children	MDI+spacer	Budesonide 400 µg q 30 min x 3; total dose 1200 µg; LOW	Y
Tsai 2001	12	12	Children	Nebuliser	Budesonide 0.05 mg/kg, maximum 2 mg; HIGH	N

* Denotes uncertainty.
Dose equivalency used: high ≥ beclomethasone dipropionate 2 mg (e.g. budesonide mg, fluticasone 1.5 mg, triamcinolone 5 mg).

Table 3. Summary of included studies: ICS versus systemic corticosteroids

Study	N on ICS	N on oral corticosteroids	Age group	Delivery device	ICS dose	Systemic corticosteroid dose and mode of delivery	Hospital admissions reported?
Ancheta 2008	12	12	Children	MDI+spacer	Fluticasone 125 µg/puff 4 puffs q 20 min x 3; total dose 1500 µg; HIGH	Hydrocortisone 4 mg/kg to maximum 200 mg; IV	Y
Belda 2007	19	20	Adults	MDI	Fluticasone 16 puffs; total dose 4000 µg; HIGH	Prednisone 30 mg; oral	N
Devidayal 1999	41	39	Children	Nebuliser	Budesonide 800 µg x 3 doses; total dose 2400 µg; HIGH	Prednisolone 2 mg/kg; oral	Y
Go 2010	16	17	Adults	Nebuliser	Dose not stated	Hydrocortisone 250 mg; IV	N
Macias 2003	45	90	Children	MDI+spacer	Triamcinolone 600 µg; LOW	Prednisone 2 mg/kg; oral	Y
Milani 2004	17	17	Children	Nebuliser	Budesonide 2 mg; HIGH	Prednisone 1 mg/kg; oral	Y
Rahman 2008	*	*	100 Adults	MDI+spacer	Budesonide 3000 µg/h x 2 hours; total dose 6000 µg; HIGH	"systemic corticosteroid" 500 mg; IV	N
Rodrigo 2005	60	61	Adults	MDI+spacer	Fluticasone 500 µg q10 min x 3 hours; total dose 9000 µg; HIGH	Hydrocortisone 500 mg; IV	Y
Sari 2004	38	38	Adults	Nebuliser	Fluticasone 500 µg; LOW	Methylprednisolone 125 mg; IV	N
Scarfone 1995	62	66	Children	Nebuliser	Dexamethasone 1.5 mg/kg; HIGH*	Prednisone 2 mg/kg; oral	Y
Schuh 2000	52	51	Children	MDI+spacer	Fluticasone 2000 µg	Prednisolone syrup 2 mg/kg to maximum 60 mg; oral	Y
Schuh 2006	35	34	Children	MDI+spacer	Fluticasone 2000 µg; HIGH	Prednisolone syrup 2 mg/kg to maximum 60 mg; oral	Y
Starobin 2008	24	23	Adults	Nebuliser	Fluticasone 500 µg; LOW	Methylprednisolone 125 mg; IV	Y
Volovitz 1998	11	11	Children	Turbohaler	Budesonide 1600 µg; HIGH	Prednisolone 2 mg/kg; oral	Y

* Denotes uncertainty.
Dose equivalency used: high ≥ beclomethasone dipropionate 2 mg (e.g. budesonide 1.5 mg, fluticasone 1.5 mg, triamcinolone 5 mg).

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. (randomised 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 searches pre-2005

The Cochrane Airways Group Asthma and Wheez* register was searched using 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]

Appendix 3. Database search strategies 2005-2012

Cochrane Airways Group Register (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*))

[Search was limited to records coded as 'asthma']

Clinicaltrials.gov

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

WHAT'S NEW

Date	Event	Description
13 August 2018	Amended	Nine trials identified from an update search of the Cochrane Airways Group Register of trials as being potentially eligible for inclusion in a future update. Studies added to Studies awaiting classification.

HISTORY

Review first published: Issue 3, 2000

Date	Event	Description
28 September 2012	New search has been performed	Update. Ten new studies were added to the primary analysis, which now shows a clear benefit of ICS use in the ED treatment of asthma.
28 September 2012	New citation required and conclusions have changed	Clear benefit of inhaled steroids in the ED treatment of acute asthma.
23 July 2008	Amended	Converted to new review format.
13 September 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

In the original version of the review:

Edmonds ML: initiated the review, wrote the protocol, performed searches, performed quality assessments, entered data and performed analysis, and primary author of review and updated versions.
Camargo CA Jr: protocol development, methodological input, statistical support and assumed major editorial role.
Pollack CV 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 ARG.

In the 2012 revision of this review:
Milan SJ and Edmonds M independently selected trials for inclusion from initial searches.
Edmonds M and Milan SJ 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.
Milan SJ updated the results section and this was checked by Edmonds M. Milan SJ and Edmonds M jointly completed the restructuring of the remaining areas of the review and in updated the text.
Rowe BH: review and in updated the text, assigned editor for ARG.

DECLARATIONS OF INTEREST

The review authors who have been involved in this review have done so without any known conflicts of interest. They are not involved with the primary studies. Drs. Camargo, Pollack have received unrestricted educational grants for research from AstraZeneca, Boehringer-Ingelheim, Forest, GlaxoSmithKline, Merck and Sepracor. In the past three years, Dr. Rowe has participated in trials sponsored by GSK and MedImmune Inc. None of the authors, however, are considered paid consultants by any pharmaceutical company that produces ICS agents.

SOURCES OF SUPPORT

Internal sources

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

External sources

- National Institutes of Health (HL-03533) Bethesda, MD (Dr. 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 the I^2 statistic. Risk of bias is assessed in accordance with Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A post-hoc subgroup analysis comparing delivery with nebuliser and MDI with spacer was performed following the suggestion of a peer reviewer.

INDEX TERMS

Medical Subject Headings (MeSH)

*Emergency Service, Hospital; Acute Disease; Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Hospitalization [statistics & numerical data]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans