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Early emergency department treatment of acute asthma with systemic corticosteroids (Review)

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[Intervention Review]

Early emergency department treatment of acute asthma with systemic corticosteroids

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ABSTRACT

Background

The airway edema and secretions associated with acute asthma are most effectively treated with anti-inflammatories such as corticosteroids delivered by inhaled, oral, intravenous or intra-muscular routes. There is an unresolved debate about the use of systemic corticosteroids in the early treatment of acute asthma for emergency department patients.

Objectives

To determine the benefit of treating patients with acute asthma with systemic corticosteroids within an hour of presenting to the emergency department (ED).

Search methods

Randomised controlled trials were identified from the Cochrane Airways Group Asthma Register. Primary authors and content experts were contacted to identify eligible studies. Bibliographies from included studies and known reviews were searched.

Selection criteria

Only randomised controlled trials (RCTs) or quasi-randomised trials were eligible for inclusion. Studies were included if patients presenting to the ED with acute asthma were treated with IV/IM or oral corticosteroids (CS) versus placebo within 1 hour of arrival and either admission rate or pulmonary function results were reported.

Data collection and analysis

Trial selection, data extraction and quality assessment were carried out independently by two reviewers, and confirmed with corresponding authors.

Main results

Twelve studies involving 863 patients (435 corticosteroids; 428 placebo) were included. Early use of CS for acute asthma in the ED significantly reduced admission rates (N = 11; pooled OR: 0.40, 95% CI: 0.21 to 0.78). This would correspond with a number needed to treat of 8 (95% CI: 5 to 21). This benefit was more pronounced for those not receiving systemic CS prior to ED presentation (N = 7; OR: 0.37, 95% CI: 0.19 to 0.70) and those with more severe asthma (N = 7; OR: 0.35, 95% CI: 0.21 to 0.59). Oral CS therapy in children was particularly effective (N = 3; OR: 0.24, 95% CI: 0.11 to 0.53); no trials in adults used the oral route. Side effects were not significantly different between corticosteroid treatments and placebo.

An update search conducted in September 2002 did not yield any further trials.

Authors' conclusions

Use of corticosteroids within 1 hour of presentation to an ED significantly reduces the need for hospital admission in patients with acute asthma. Benefits appear greatest in patients with more severe asthma, and those not currently receiving steroids. Children appear to respond well to oral steroids.

PLAIN LANGUAGE SUMMARY

Early emergency department treatment of acute asthma with systemic corticosteroids

In an asthma attack, the airways (passages to the lungs) narrow from muscle spasms and swelling (inflammation). Bronchodilators (reliever inhalers to open up the lungs and airways) can be used for the spasms, and corticosteroids for the swelling. Corticosteroids can be inhaled, or taken by mouth (orally) or through a drip into the veins (intravenously). The review of trials found that systemic (oral or intravenous) corticosteroids reduce the need for people with asthma attacks to stay in hospital, with few adverse effects.

BACKGROUND

Acute asthma is a common presenting complaint to emergency departments (ED). In the United States alone, acute asthma accounts for almost 2 million ED visits per year (Mannino 1998). Approximately 10-20% of these patients will require admission to the hospital, and, of those discharged from the ED after apparently successful treatment, approximately 10-20% will relapse within the subsequent two weeks (Camargo 1998a; Camargo 1998b). These results depend closely on the treatments prescribed in the ED and at discharge (Rowe 1997; Rowe 1999). Many asthmatics experience a poor quality of life for weeks following acute asthma during which they are particularly prone to repeat exacerbations (Fitzgerald 1990; Camargo 1998b).

Emergency treatment is based on the pathophysiology of acute asthma. Bronchospasm can generally be relieved with bronchodilators. The first treatment agents include beta 2-agonists which specifically target b-adrenergic receptors (Cates 2006). In some studies, quaternium agents administered in conjunction with beta 2-agonists have been shown to potentially increase the magnitude and duration of bronchodilation over that achieved with beta 2-agonists alone. A Cochrane review examined this therapy in children (Plotnik 1998). The airway edema and secretions associated with acute asthma are best treated with anti-inflammatories such as corticosteroids (CS) delivered by inhaled, oral, intravenous or intra-muscular routes. However, the timing, route, dose, and target population for CS treatment may vary markedly. The potential role of other agents in the initial management of acute asthma is still unclear.

Despite this general consensus, treatment approaches vary between and within emergency departments, perhaps because of the lack of evidence-based summaries of the research pertinent to this field. For example, there is an unresolved debate about the use of corticosteroids in the early treatment of acute asthma for ED patients (Engel 1991; Rowe 1992). Although previous overviews (Engel 1991; Rowe 1992; Rowe 1997) have attempted to clarify the evidence, several new trials have been completed since their publication; an update of the available evidence is needed.

OBJECTIVES

The objective of this review was to determine the effect (on admission rate, pulmonary functions [PFTs], physiologic measures, etc.) of any form of systemic corticosteroids (intravenous [IV], intramuscular [IM], oral [OCS]) administered early in the course of treatment for patients presenting to the ED with acute asthma.

Specific Aims: To quantify the effect of the combination of corticosteroids with other agents compared to the effect of these other agents alone.
The specific outcomes include:

- the effect of CS therapy on admission (e.g., time to decision, % admission);
- the effect of CS therapy on pulmonary functions; and
- the effect of CS therapy on side effects and vital signs (e.g., heart rate, respiratory rate, and blood pressure).

METHODS

Criteria for considering studies for this review

Types of studies

To be considered, studies had to be randomised controlled trials (RCT) or quasi RCTs (allocation on days of the week, or some other method).

Types of participants

Studies including patients of any age (adults, children > 2 years or combined) presenting to an ED were considered for inclusion. If a trial also recruited patients from other settings who could be removed easily from the study (for example if stratified randomisation was employed) the data would be included.

Types of interventions

The target intervention was the administration of IV, IM, or oral corticosteroids early (< 1 hour) in the ED treatment. Studies in which patients were admitted to the hospital and later given corticosteroids were excluded. The control intervention was the administration of placebo. Comparison of doses, delivery systems, or agents were included only if a placebo arm was incorporated. Details of co-interventions were recorded.

Types of outcome measures

(Yes/No). Attempts were made to contact the primary investigators of included studies to obtain individual patient data, however this was unsuccessful.

Primary outcomes

The primary outcome was admission to hospital.

Secondary outcomes

Lung function

Symptoms

Adverse events

Search methods for identification of studies

Electronic searches

The Cochrane Airways Review Group (ARG) has developed an "Asthma and Wheez* RCT" register through a comprehensive search of EMBASE, MEDLINE, and CINAHL. Hand searching of 20 common respiratory care journals has been completed and relevant RCTs have been added to this register. It is updated regularly with searches of CENTRAL, the Cochrane Collaboration's RCT register. Search of the ARG register was completed using the following terms:

- Corticosteroid* OR steroid* OR glucocorticoid* OR prednis* OR solumedrol OR medrol OR dexamethasone OR methylpred* OR solucortef OR decadron AND Emerg* AND Discharge OR admi* OR hospit*.

We did not exclude trials on the basis of language. The current overview includes ARG register updates to January 1999.

Searching other resources

Randomised controlled trials were identified in the register using the following search strategy: placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study. Additional efforts to locate potential trials were as follows:

- Reference lists of all available primary studies 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.
- Structured searches of CENTRAL using Corticosteroids AND Asthma.
- Personal contact with colleagues, collaborators and other trialists working in the field of asthma was made to identify potentially relevant studies.
- Screening the reference lists of both review articles (Engel 1991; Rowe 1992).

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, two reviewers (BR, JB) independently reviewed literature searches to identify potentially relevant trials for full review. From the full text, using specific criteria, two reviewers (CS, FD) independently selected trials for inclusion in this review. Agreement was measured using kappa statistics. Disagreement was resolved by consensus or third party adjudication (BR).

Data extraction and management

Data for the trials were extracted by two reviewers (BR, JB) and entered into the Cochrane Collaboration software program (Review Manager). Primary study authors were requested to confirm data extraction and provide additional clarification and information for the review. In some cases, point estimates were obtained from expansions of graphic reproductions and calculations from other data presented in the paper.

Assessment of risk of bias in included studies

Methodological quality assessment was performed independently by two reviewers using two methods. The first method used the Cochrane approach to assessment of allocation concealment (Grade A: adequate concealment; Grade B: uncertain concealment; Grade C: clearly inadequate concealment). In the second method, each study was assessed independently by two reviewers for validity using a ordinal scale (0-5) described by Jadad (Jadad 1996). One point is allocated for randomisation, blinding and description of withdrawals and drop-outs; an extra point can be added for methods of randomisation and blinding that are well described and adequate. Studies which use a clearly inadequate method of randomisation or blinding (such as alternating patients) lose the point allocated. The maximum score is five points and studies scoring below three points are usually regarded as being of low methodological quality. For both methods, inter-rater reliability was measured by kappa and weighted kappa statistics, and disagreement was resolved by third party adjudication.

Assessment of heterogeneity

For pooled effects, heterogeneity was tested using the Breslow-Day test; $p < 0.05$ was be considered statistically significant. Results are reported using a random effects model. In most cases, the results for fixed and random effects model were similar, except where there was significant heterogeneity.

Data synthesis

Trial data were combined using Review Manager. For continuous variables, a random effects weighted mean difference (WMD) or standardised mean difference (SMD) and 95% confidence interval (CI) was calculated for each study. All similar studies were pooled using random effects WMD or SMD and 95% CIs. For dichotomous variables, a random effects odds ratio (OR) with 95% confidence intervals (95% CI) was calculated for individual studies. All similar studies were pooled using random effects OR and 95% CIs.

Subgroup analysis and investigation of heterogeneity

Since significant heterogeneity existed, a series of subgroup analyses were performed (Oxman 1992). A priori, these studies were divided on the following basis:

- Age: pediatric versus adult (<18 pediatric);
- Steroid use: previous steroid use vs. no previous steroid use;
- Severity: severity was based on admission rates in placebo group (severe if admission = or > 40% in the placebo arm or non-severe if admission rate < 40% in the placebo arm);
- Outcome: assessment scores and time of outcome assessment (2, 4, 6 hours);
- Intervention: route of administration (IV vs. PO).

Sensitivity analysis

In addition, sensitivity analyses were conducted on fixed effect versus random effects modelling, and methodological quality (high versus low).

RESULTS

Description of studies

Results of the search

Eighteen articles were identified by one or both of the reviewers as being potentially relevant. All of these articles were recovered and provided to two different reviewers for independent decision on inclusion. A total of 9 articles were included (kappa: 0.78). Following communication with authors, one additional article was identified (Connett 1994a), and one article was excluded because it dealt with in-hospital treatment (Deshpande 1986). This search was updated in 1999 and three additional trials were identified (Lin 1997; Lin 1999; McFadden 1976). An update search conducted in September 2002 did not yield any further trials.

Included studies

For descriptions of the design of each included study see Characteristics of included studies.

The evidence that corticosteroids prevent admissions when used in early ED asthma care has been the result of research produced within the past 15 years. Since the previous overviews (Rowe 1992; Engel 1991), 6 additional studies have been published (Scarfone

1993; Connett 1994a; Wolfson 1994; Rodrigo 1994; Lin 1997; Lin 1999) and 1 additional study was identified (Deshpande 1986).

Populations: Six (55%) publications specifically examined the use of corticosteroids in adult patients and 5 (45%) involved pediatric patients. Most studies included patients if they exhibited clinical criteria for acute asthma and did not have known chronic medical conditions. Patients receiving systemic corticosteroids prior to the exacerbation were excluded from five studies (Littenberg 1986; Storr 1987; Tal 1990; Scarfone 1993; Connett 1994a; Wolfson 1994) and sub-grouped in another (Schneider 1988). Exclusions for current inhaled corticosteroid use were less frequently reported, and sub-group analyses could not be performed based on this population separation.

The severity of asthma at presentation was poorly documented, but by inference would be considered "severe". For example, most studies (N = 7; 64%) had placebo arm admissions rates of > 40%. In addition, most studies excluded patients presenting for prescription refills, or with mild asthma. The range of admission rates in the placebo groups was 10 to 97%.

Interventions: The drug type, route of administration and dose varied across studies. Studies examined the use of oral (N = 3), intravenous (N = 7), or intramuscular (N = 1) steroids as a single therapy early in the ED. No studies specifically compared inhaled steroids to a placebo agent; however, two studies which added inhaled steroids to the systemic CS without a placebo arm were excluded (Scarfone 1995; Guttman 1997).

While the dose of steroids varied, all protocols required the corticosteroids to be administered "early" (between 30-45 minutes post arrival). In adults, solucortef (N = 1) or solumedrol (N = 5) was used in doses of 500 mg and 125 mg intravenously, respectively. Oral therapy only occurred in children, and consisted of doses of 1-2 mg/kg of prednisone or prednisolone. All doses would be considered "high" (Manser 1998).

Co-interventions: Different co-interventions were provided. Variable approaches to beta2-agonist delivery were reported; most patients received nebulised therapy, but one study did use MDI + spacer (Rodrigo 1994). Studies permitted flexible (N = 2: Littenberg 1986; Wolfson 1994) or insisted on rigorous (N = 9) dosing schedules for the in-ED beta2-agonists and other co-interventions. Theophylline use was routine in two studies (Littenberg 1986 - IV; Stein 1990 - oral) and administered to "failures" in one study (Schneider 1988). The use of anticholinergic agents in addition to beta2-agonists was rarely reported (Lin 1999).

Outcomes: A variety of outcome measures were reported. Hospital discharge or admission were the most common (11/12 studies); however, the criteria for admission/discharge and timing of decision varied considerably. In addition, several pulmonary function test outcomes (PEFR, FEV-1, FVC, % predicted PEFR, % predicted FEV-1, etc) were used to measure treatment effect but there was no consistent format for reporting. A pooled estimate was obtained using the final study measurement for % PEFR and PEFR using an SMD. Infrequently, symptom scores were reported as outcomes. Due to the variation in scales and scores used, no pooled analysis was possible for symptoms. Finally, side-effects (e.g., nausea, headache, tremor) were occasionally reported also.

Confirmation of data: We attempted to contact all authors to request confirmation of methods and data extraction and provide additional clarification and information for the review. While many authors responded, unfortunately, most could not access their original data source to perform supplemental analyses. Wherever possible, expansions of graphic reproductions and estimations were used.

Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

Many of the studies were double-blind, all were placebo controlled, demonstrated an appreciation of the need for concealment of allocation, and reported a sufficient number of outcomes. The methodological quality of all studies, using the Jadad method, was rated as "high" (scores => 3). Using the Cochrane method, 5 studies (Littenberg 1986; Schneider 1988; Tal 1990; Connett 1994a; Wolfson 1994) were rated as having blinded allocation and 7 studies (McFadden 1976; Storr 1987; Stein 1990; Scarfone 1993; Rodrigo 1994; Lin 1997; Lin 1999) were rated as having unclear allocation concealment.

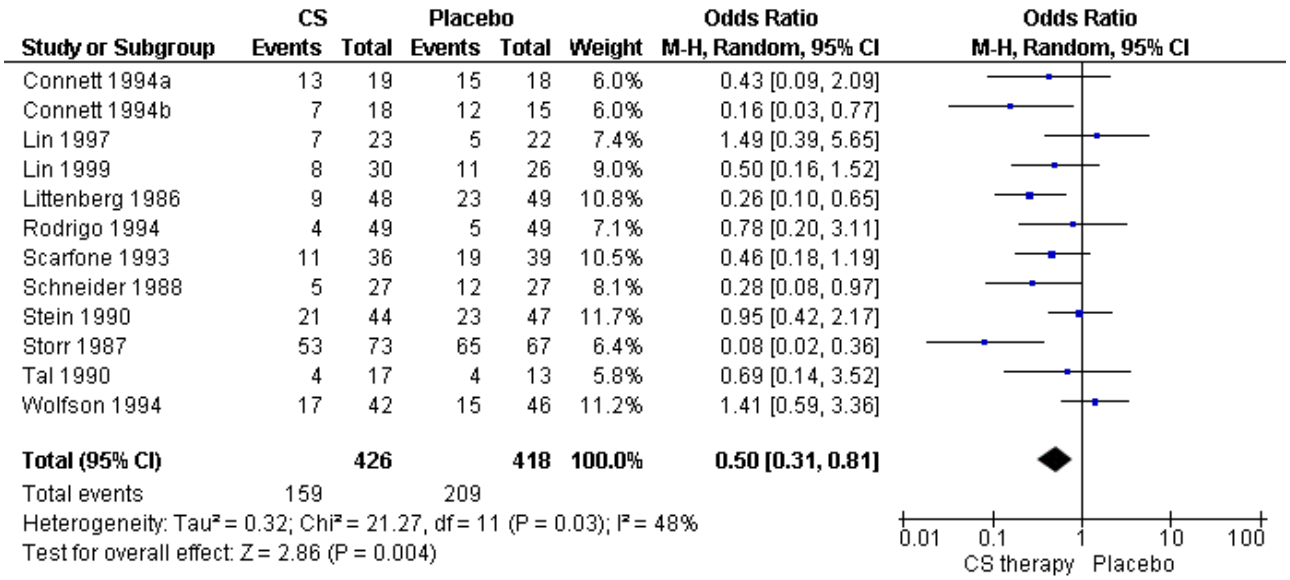
Effects of interventions

Pooling of data was carried out because the populations, interventions and outcomes were similar. Despite this, significant heterogeneity was identified in the pooled analyses so results are presented with the pooled data followed by subgroup analyses.

Main Comparison: Corticosteroids versus Placebo

Eleven of the 12 included studies provided sufficient information for pooling hospital admission rates. Most studies (9/11) provided a point estimate in favor of treatment with CS. Four studies demonstrated a statistically significant difference in favor of CS treatment, while no studies demonstrated a benefit with placebo treatment. Using a random effects model, the overall result suggests a significant reduction in admission following the early use of corticosteroids in ED asthma treatment (n = 11; pooled OR: 0.50, 95% CI: 0.31, 0.81, Figure 1). This would correspond with a number needed to treat (NNT) of 8 (95% CI: 5 to 21). However, heterogeneity was demonstrated in this pooled estimate (chi square = 21.3; df = 11; $p < 0.05$). As planned, the following subgroup analyses were performed to identify the source of the heterogeneity.

Figure 1. Forest plot of comparison: 1 Any steroid (po, IM, IV, inhaled) vs placebo, outcome: 1.1 Admitted to hospital (all times).



Subgroup Analyses

Use of Systemic Steroids: Because the regular use of systemic corticosteroids in the days and weeks preceding the index visit could be a potential confounder, a subgroup analysis based on previous CS therapy was completed. When only studies involving patients not receiving systemic CS prior to ED presentation were considered, early ED CS therapy appeared effective (N = 7; OR: 0.37, 95% CI: 0.19 to 0.70). This would correspond with a number needed to treat of 6 (95% CI: 4 to 11). However, heterogeneity existed in this pooled analysis (chi square = 15.21; df = 7; p < 0.05). In studies with mixed populations the early use of CS in the ED appeared to be less effective (N = 5; OR: 0.82; 95% CI: 0.48 to 1.4), without significant heterogeneity (chi square = 3.53; df = 4; p > 0.1).

Severity of Disease: In the absence of any consistent application of PFT results to determine disease severity, the rate of admission in the placebo group was used as a proxy severity measure. Most studies (N = 7; 64%) had admission rates > 40%. When trials were stratified using this cut-off, trials with a high baseline admission rates experienced a significant reduction in admissions following early CS use (N = 7; OR: 0.35, 95% CI: 0.21 to 0.59) compared to those studies with lower severity (N = 4; OR: 1.21, 95% CI: 0.66 to 2.22). The pooled results were homogeneous for both the severe (chi square = 11.2; df = 7; p > 0.1) and non-severe (chi square = 1.4; df = 3; p > 0.1) groups. These results would correspond with a number needed to treat of 5 (95% CI: 4 to 7) in the severe group.

Age Subgroup: There did not appear to be any difference in the magnitude of the reduction in admission rate due to early CS use between studies of children (n = 5; OR: 0.40, 95% CI: 0.17 to 0.94) or adults (n = 6; OR: 0.58, 95% CI: 0.32 to 1.07). The pooled results were homogeneous for adults but not for children (chi square = 13.65; df = 5; p < 0.025).

Sensitivity analyse

Timing of Outcome Assessment: Since steroids are believed to exert their effect over hours rather than minutes, one would expect a greater reduction in admission rate with longer ED treatment times. The sensitivity analysis confirmed this theory. However, few trialists could provide additional time data, and these results should be interpreted cautiously. The early outcomes (<= 2 hours) were not significant (N = 2; OR: 1.38, 95% CI: 0.41 to 4.67), whereas a benefit with CS therapy was demonstrated at 4 hours (n = 5; OR: 0.48, 95% CI: 0.24 to 0.97) and 6 hours (N = 7; OR: 0.28, 95% CI: 0.09 to 0.84) after administration. Significant heterogeneity (chi square = 17.7; df = 6; p < 0.01) was demonstrated for the 6 hour pooled results.

Route of Administration: Although no direct comparison of routes of administration could be made, the magnitude of the reduction in admission rates appeared greater with the oral routes (N = 3; OR: 0.24, 95% CI: 0.11 to 0.53) than IV (N = 7; OR: 0.68, 95% CI: 0.39 to 1.21) routes. The oral corticosteroid analysis did not demonstrate heterogeneity (p > 0.1) while the IV analysis did (chi square = 11.9; df = 6; p < 0.1). Whilst these results suggest at first sight that oral therapy may be more effective, it should be recalled that this route was only used in the treatment of children, whereas IV therapy was used in children and adults.

Other Outcomes

Pulmonary Functions: The most commonly and consistently reported pulmonary function data were PEFR and % predicted PEFR. The PEFR data were pooled using a SMD for the trials reporting end-of treatment results. The analysis indicated a moderate effect of corticosteroids on PEFR (N = 7; SMD: 0.54; 95% CI: 0.01 to 1.1) with persistent heterogeneity (chi square = 49.25; df = 7; p < 0.001).

Adverse Reactions: Side effect monitoring was uncommon in these studies, and few adverse events were reported. Nausea (N = 2; OR = 0.48; 95% CI: 0.1 to 2.4), tremor (N = 4; OR = 0.82; 95% CI: 0.45 to 1.48), and headache (N = 2; OR = 1.04; 95% CI: 0.26 to 4.2) were similar in frequency; all pooled side effect results demonstrated homogeneity. An insufficient number of studies were available to provide meaningful sensitivity comparisons.

DISCUSSION

This systematic review summarises the latest evidence derived from randomised controlled trials for the early use of corticosteroids in the treatment of acute asthma in the ED setting. Overall, the results of this review indicate that patients who were treated with systemic corticosteroids within one hour of presentation to the emergency department were significantly less likely to be admitted to hospital. This benefit was not apparent for the first two hours of therapy and maximal at 6 hours. Thus, there appears to be benefit in delaying a decision to admit until 4-6 hours after CS therapy. Subgroup analysis suggests that patients with a greater likelihood of admission (i.e. the more severe) and those not recently treated with oral CS appeared to benefit most.

Oral therapy appears to be effective in children and in a comparison in children, oral and IV therapy were found to be equally effective (Barnett 1997). It is not possible to comment on the efficacy of oral steroids used in adults, since all trials in this age group used the IV route. Similarly, no conclusions can be drawn about dose-response effects, since all steroid doses were high.

Secondary analyses from pulmonary function data suggest that the benefit of corticosteroids is demonstrable by the measurement of the final PEFR or % predicted PEFR. The benefit represents a range of possible improvements in PFT, which also appears to be a clinically important improvement (Tiffany 1993).

Within the time course of this study, these doses of steroids did not appear to cause more tremor, headache or nausea than placebo.

The number needed to treat (NNT) with corticosteroids compared to placebo to prevent one admission is 5 (95% CI: 4 to 7) for an admission rate of > 40% in the placebo arm. Alternatively, the NNT is higher and not statistically significant if the admission rate is low (< 20%) in the placebo arm. Since corticosteroids are inexpensive, readily available, and their safety in single-dose or short term therapy is accepted, early treatment using these drugs for most asthmatics would be prudent. This recommendation is in keeping with that provided by the Canadian Association of Emergency Physicians (CAEP; Beveridge 1996), national asthma plan in the US (NAEPP 1997), and British Thoracic Society (BTS; BTS 1997); all of whom recommend systemic corticosteroids for patients with acute asthma.

Methodological Limitations
Due to the heterogeneity of the pooled results in this meta-analysis and the overall small number of patients upon which the subgroup results are based, subgroup analyses need to be interpreted with caution (Oxman 1992). However, the overall findings would seem to apply to all patients with acute asthma presenting to the ED setting.

There is a possibility of publication bias or study selection bias in this meta-analysis. For example, by not identifying unpublished negative trials we may be over-estimating the effect of corticosteroid treatment. A comprehensive search of the published literature for potentially relevant studies was conducted, using a systematic strategy and objective inclusion criteria to avoid such biases. This was followed by attempts to contact corresponding and first authors. No unpublished or negative trials were uncovered, however we recognise that they may exist. In addition, examination of the funnel plots (OR vs. Sample size/weight) indicates symmetry, thus suggesting publication bias was unlikely.

Several other methodological issues limit the applicability of the results of this review. The admission rate for the placebo arms of these trials varied from 10% to 97%; 7 trials had admission rates above 40%. These rates are higher than expected and certainly higher than the 10 to 20% quoted in large multicenter studies in US and Canada (Camargo 1998a; Camargo 1998b). Since the subgroup analyses suggested a possible effect of severity on response to CS, this is an important area for future research. While the criteria for admission were variable or poorly documented, this does appear to be a clinically valuable measure of asthma outcome. Rigorous standardisation of this outcome would improve study comparability. For now, the results of this review apply to patients with severe asthma.

Evaluation of pulmonary function data was complicated by a lack of standardised reporting and changing analyses within the reports. For example, PFT analyses often changed from comparisons of treatment vs. control at the start of the study, to comparisons between admitted and non-admitted groups at the end. This precluded more formal evaluation of the effects of the interventions based on PFTs and also the effects of the intervention on PFTs at follow-up.

AUTHORS' CONCLUSIONS

Implications for practice

This overview reconfirms evidence from earlier systematic reviews (Rowe 1992; Engel 1991) and supports the use of steroids for treatment of emergency department patients assessed with acute asthma. Therapy with high dose systemic steroids should be commenced within one hour of presentation to the emergency department. Unless the patients failed to respond to early therapy, deteriorated or gave other reasons for concern, a decision whether to admit may be usefully delayed until 6 hours after treatment. In children, oral therapy appears to be very effective, although there are no data to provide guidance as to the efficacy of oral therapy for adults in this setting.

Implications for research

Further studies in this area will need to consider the results of the subgroup analyses. Studies which stratify patients into those recently receiving oral steroids vs those receiving maintenance inhaled steroids would seem appropriate. Documentation of asthma severity at presentation needs to be standardised to permit generalisability of trial results. Standardised assessment times would also be useful. A better description of admission criteria is required.

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CHARACTERISTICS OF STUDIES

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

Connett 1994a

Methods	Randomisation: Treatments were numbered by a pharmacist in random order before the start of the study using a random numbers table. Blinding: double-blind. Number excluded: documented (26%). Withdrawals: 8 documented. Baseline characteristics: imbalances demonstrated; no adjusted analyses.
Participants	Location: Children's Hospital in Brighton, UK. Participants: age > 18 mo. with acute asthma requiring admission (after 5 mg nebulised salbutamol and re-assessment in 30 minutes) if study investigator available. Asthma definition and severity: "severe". severe asthma requiring admission Exclusion criteria: Mild asthma, croup, corticosteroids within the past 2 weeks.
Interventions	Intervention: 2 mg/kg oral prednisolone Control: identical placebo Co-interventions: 5 mg nebulized salbutamol q 1-4 hrs x 3 hrs. Supplemental oxygen was used for nebulisation.
Outcomes	Admission: based on history, physical findings, and response to therapy (at 4 hours). Pulmonary functions: PEFR and % predicted PEFR Adverse effects: tremor, hyperactivity, vomiting, headache. Vital signs: pulse rate, saturation, Symptoms: scale from 0-6. Lab: not reported. Timing of assessment: 0, q 30 minutes, 4 hours.
Notes	Jadad score:

Connett 1994a *(Continued)*

	Author correspondence successful, but unable to provide data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Treatments were numbered by a pharmacist in random order before the start of the study using a random numbers table.

Connett 1994b

Methods	Randomisation: Treatments were numbered by a pharmacist in random order before the start of the study using a random numbers table. Blinding: double-blind. Number excluded: documented (26%). Withdrawals: 8 documented. Baseline characteristics: imbalances demonstrated; no adjusted analyses.
Participants	Location: Children's Hospital in Brighton, UK. Participants: age > 18 mo., with acute asthma requiring admission (after 5 mg nebulised salbutamol and re-assessment in 30 minutes) if study investigator available. Asthma definition and severity: "severe". severe asthma requiring admission Exclusion criteria: Mild asthma, croup, corticosteroids within the past 2 weeks.
Interventions	Intervention: 2 mg/kg soluble prednisolone (oral agent). Control: identical oral placebo. Co-interventions: After corticosteroid treatment children were treated with 0.15 mg/kg q 30 min x 3 hrs. Supplemental oxygen was used for nebulisation.
Outcomes	Admission: based on history, physical findings, and response to therapy (at 4 hours). Pulmonary functions: PEFR and % predicted PEFR Adverse effects: tremor, hyperactivity, vomiting, headache. Vital signs: pulse rate, saturation, Symptoms: scale from 0-6. Lab: not reported. Timing of assessment: 0, q 30 minutes, 4 hours.
Notes	Jadad score:

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Treatments were numbered by a pharmacist in random order before the start of the study using a random numbers table.

Lin 1997

Methods	Randomisation: non-study nurse allocated treatment and provided a filled syringe with either saline or active drug. Blinding: "double blinded" - similar appearing medication Number excluded: convenience sample of 48 patients, exclusions not reported. Withdrawals: 3 (repeat entry) Baseline characteristics: no imbalances demonstrated; adjusted analyses performed.

Lin 1997 *(Continued)*

Participants	Location: New York City hospital ED. Participants: adults (> 17 yrs), acute asthma (clinical definition: prior diagnosis of asthma and history of improvement with B-agonists). Asthma definition and severity: < 200 L/min PEFR Exclusion criteria: age < 18, smoking history of > 20 pack years, pregnancy, received nebulised B-agonists from EM personnel prior to the study.
Interventions	Treatment: 125 mg methylprednisolone (MP) IV Conrol: equivolume IV saline Co-interventions in both groups: 2.5 mg albuterol with 0.5 mg ipratropium bromide, then q 20 min X 2 (2.5 mg albuterol), and 30 minutes later 2.5 mg albuterol. Supplemental oxygen was used for nebulisation and between treatments. Cross-over: treating physicians were permitted to administer 125 mg of MP if response was deemed inadequate.
Outcomes	Admission: accessory muscle use, RR > 24/min, ABG PCO2 > 44 mm Hg or PO2 < 70 mm Hg, pneumonia or T > 38.8 C, or failure to improve after 5-6 hours AND associated fatigue and shortness of breath. Pulmonary functions: PEFR and % predicted PEFR Adverse effects: agitation, tremor. Vital signs: pulse rate. Symptoms: none reported. Lab: not reported. Timing of assessment: 0, 20, 40, 60 minutes
Notes	Jadad score: Author correspondence pending.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Non-study nurse allocated treatment and provided a filled syringe with either saline or active drug.

Lin 1999

Methods	Randomisation: sealed opaque envelopes, non-study physician read allocation, and filled syringe with either saline or active drug. Blinding: "double blinded" Number excluded: convenience sample of 60 patients, exclusions not reported. Withdrawals: 4 (repeat entry) Baseline characteristics: imbalance demonstrated. No adjusted analyses.
Participants	Location: New York City hospital ED. Participants: adults (> 18 yrs), acute asthma (clinical definition: history, response to B-agonists, past prescription for B-agonists). Asthma definition and severity: < 50% predicted PEFR after single nebulised 2.5 mg salbutamol. Exclusion criteria: age < 18, smoking history of > 20 pack years, pregnancy, inability to perform PEFR.
Interventions	Treatment: 125 mg methylprednisolone (MP) IV . Conrol: equivolume IV saline . Co-interventions in both groups: 2.5 mg albuterol with 0.5 mg ipratropium bromide, then q 20 min X 3 - 2.5 mg albuterol, and 30 minutes later 2.5 mg albuterol. Supplemental oxygen was used for nebulisation and between treatments. Cross-over: treating physicians were permitted to administer 125 mg of MP if response was deemed inadequate.

Lin 1999 *(Continued)*

Outcomes	Admission: accessory muscle use, RR > 24/min, ABG PCO2 > 44 mm Hg or PO2 < 70 mm Hg, pneumonia or T > 38.8 degrees C, or failure to improve after 5-6 hours AND associated fatigue and shortness of breath. Pulmonary functions: PEFR and % predicted PEFR Adverse effects: tremor. Vital signs: pulse rate. Symptoms:"symptomatic complaints" Lab: not reported Timing of assessment: 0, 20, 40, 60, 90 minutes
Notes	Jadad score: Author correspondence pending.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Sealed opaque envelopes, non-study physician read allocation, and filled syringe with either saline or active drug.

Littenberg 1986

Methods	Randomisation: The vials were filled by a pharmacist at a remote site according to random sequence. Blinding: "double blinded" - similar appearance of treatment and placebo. Number excluded: not reported. Withdrawals: not reported. Baseline characteristics: no imbalances demonstrated.
Participants	Location: Adult ED in Hartford, USA. Participants: Patients =>18 ys, acute exacerbation of asthma, no underlying medical conditions Asthma definition and severity: hetereogenous population. Exclusion criteria: Patients using steroid medication within 2 weeks of presentation, ED MD diagnosis of chronic bronchitis or emphysema.
Interventions	Intervention: within 30 minutes of arrival, 125 mg of IV methylprednisolone (MP) diluted to 3 ml with saline. Control: Identical 3 ml of saline IV. Co-interventions: Each patient was treated as indicated, with subcutaneous epinephrine or terbutaline, oxygen, metaproterenol sulfate (administered as an aerosol), and intravenous aminophylline. Cross-over: not permitted.
Outcomes	Admission: no criteria; physician determined. Symptom scores: mild, moderate, severe. PEFRs: FVC, FEV-1. Adverse effects: "toxicity" but not defined. Timing: assessment made at 4 hours. Follow-up: relapse at 1 week.
Notes	Jadad score: No response from the author.

Risk of bias

Bias	Authors' judgement	Support for judgement

Littenberg 1986 *(Continued)*

Allocation concealment?	Low risk	The vials were filled by a pharmacist at a remote site according to random sequence.

McFadden 1976

Methods	Randomisation: Not reported. Blinding: "double blinded" - no report of method. Number excluded: not reported. Withdrawals: not reported. Baseline characteristics: description of patients limited; no adjusted analyses.
Participants	Location: EDs in Boston and Galveston, USA. Participants: adults (16-44 yr), acute allergic or intrinsic asthma . Asthma definition and severity: severe (% predicted FEV-1 < 30.1 %). Exclusion criteria: use of corticosteroids within a month of ED presentation; no others reported.
Interventions	Intervention: 0.25, 0.5, or 1.0 gm of hydrocortisone upon completion of interview (? time). Control: similar appearing saline solution. Co-interventions: 30 minutes after corticosteroid treatment, nebulised isopreterenol (0.5 ml) by positive pressure breathing. This was "repeated" variable times over the course of the care in the ED.
Outcomes	Admission: not reported. Pulmonary functions: FEV-1 and % predicted FEV-1; airway resistance and conductance. Adverse effects: not reported. Vital signs: not reported. Symptoms: subjective dyspnea rating. Lab: not reported Timing of assessment: 0, 30, 60 minutes; minimum of 6 hours.
Notes	Jadad score: No data could be extracted for use in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Rodrigo 1994

Methods	Randomisation: Random number allocation was used to randomise the patients. Blinding: "double blinded" - similar appearing agents. Number excluded: not reported. Withdrawals: not reported. Baseline characteristics: no imbalances demonstrated.
Participants	Location: Military hospital in Montevideo, Uruguay. Participants: 98 adults (18 - 50 yrs), with bronchial asthma. Asthma definition and severity: PEFR and FEV-1 <50% of predicted value. Exclusion criteria: Hx of chronic cough, chronic sputum production; cardiac, hepatic, renal, or other medical disease.
Interventions	Intervention: 500 mg of IV hydrocortisone as 3 ml solution immediately after arrival to the ED. Control: placebo of 3 ml of normal saline

Rodrigo 1994 *(Continued)*

	Co-interventions: salbutamol by MDI + spacer , 4 puffs actuated in rapid succession (100 micrograms per actuation), q 10 min. Hospitalization was mandatory if treatment time was greater than 6 hours. Prednisone 40 mg x 5 days tapered dose was prescribed to those patients discharged from the ED. Cross-over: not permitted.
Outcomes	Admission: discharged after 6 hours if met the following criteria: free of dyspnea, no accessory muscles use at rest, and no wheezing. Pulmonary functions: PEF, FEV-1, FVC (absolute and % predicted). Adverse effects: tremor, headache, anxiety, palpitations, and nausea. Vital signs: . Heart rate, respiratory rate, blood pressure. Symptoms: 0-3 scale (mild, moderate, severe); accessory muscle use, dyspnea and wheezing were assessed throughout the patient's stay in the ER. Lab: theophylline levels. Timing of assessment: q 30 minutes. Follow-up: phone call to discharged patients to determine relapse rates. A retrospective chart review was also done in order to identify any patients returning to the ED.
Notes	Jadad score: Authors corresponded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Scarfone 1993

Methods	Randomisation: Randomisation of drug or placebo preparation was done by ED physicians who were not involved with the study. Randomisation was accomplished using a random numbers table. Blinding: "double blinded" Number excluded: not stated. Withdrawals: 6 (5 steroids; 1 placebo). Baseline characteristics: no imbalances demonstrated. No adjusted analyses.
Participants	Location: Children's Hospital in Philadelphia, USA. Participants: 75 children (1-17 yrs), exacerbation of asthma with at least one prior episode of wheezing, and initial PIS > 8. Asthma definition and severity: "moderate" as described by author. Subgroup: PIS > 10 vs PIS < 10 Exclusion criteria: use of inhaled or systemic steroids within the previous 72 hours, other serious medical condition, pneumonia, vomited study drug within 15 minutes of administration
Interventions	Intervention: 2 mg/kg of oral prednisone after first albuterol treatment. Placebo: similar appearing placebo capsule. If unable to swallow, capsule was mixed with 5 ml of juice; patients who vomited within 15 minutes, were given a repeat dose. Co-intervention: Patients in each group were then treated with an identical regimen of frequent aerosolized albuterol, for a maximum of 4 hours. Cross-over: not permitted.
Outcomes	Admission: Determined at 4 hours by blinded physician. Based on oxygen saturation of < 92%, poor aeration by auscultation, or continued significant retractions. Pulmonary functions: PEFR and % predicted PEFR. Since 2/3 of patients < 6 yrs, PFT collection abandoned early in the study. Admission to hospital at 2 hours was provided by the author. Adverse effects: not reported. Vital signs: respiratory rate, oxygen saturation, respiratory rate. Symptoms: pulmonary index score.

Scarfone 1993 *(Continued)*

	Lab: not reported Timing of assessment: 2 and 4 hours. Follow-up: relapse rates for those discharged from ED
Notes	Jadad score: Dr. Scarfone responded to correspondence and provided additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Schneider 1988

Methods	Randomisation: Patients were randomised using computer-generated random numbers and randomised separately according to chronic steroid dependency. Blinding: double blinded - similar appearing Number excluded: Withdrawals: 2 (1 pneumonia: MP; 1 tachycardia: placebo) Baseline characteristics: limited reporting; no adjusted analyses.
Participants	Location: Montefiore Hospital in Pittsburgh, USA. Participants: 56 adults, Dx of asthma, acute bronchospasm and dyspnea, Asthma definition and severity: FEV-1 < 70% predicted. No severity subgroups. Exclusion criteria: TB, pregnancy, diabetes mellitus, pneumonia or congestive heart failure Subgroups: Patients were considered non-steroid dependent if they had used no steroid treatment within the past 14 days.
Interventions	Intervention: methylprednisolone (MP: 30 mg/kg) infused over 30 min. Control: saline placebo Co-interventions: Treatment begun with epinephrine, 0.3 ml sub-Q in patients < 35 yrs or isoetharine 0.5 ml (updraft nebulization, followed by the inhalation of albuterol). If subsequent FEV-1 showed improvement > 20%, the patient received beta-agonist q 30 min until improvement ceased, or discharge criteria met. Patients failing to improve received IV aminophylline in addition to the beta-agonists.
Outcomes	Admission: hospitalized if failed to improve during initial or any subsequent 60 minute period of combined aminophylline maintenance infusion and beta-agonist therapy. Discharged if clinical signs and symptoms of bronchospasm had cleared and the FEV-1 =>70% of predicted or previous best. Pulmonary functions: FEV-1 and % predicted FEV-1. Adverse effects: none. Vital signs: none. Symptoms: none. Lab: not reported. Timing of assessment: entry, q 30 minutes Follow-up: Patients were considered treatment failures if they required hospitalization within 7 days after being successfully treated. Relapses were determined by chart audits as all patients were likely to return to the same hospital.
Notes	Jadad score: Dr. Schneider responded to correspondence, and was able to provide additional information including the data.

Risk of bias

Bias	Authors' judgement	Support for judgement

Schneider 1988 *(Continued)*

Allocation concealment?	Low risk	Patients were randomised using computer-generated random numbers and randomised separately according to chronic steroid dependency.

Stein 1990

Methods	Randomisation: Random numbers table. Drug prepared by ED physician not involved in recruitment. Blinding: double blinded - similar appearing Number excluded: not reported. Withdrawals: 13 (%) of 104 visits. Described, but not reported in groups allocated. Baseline characteristics: no imbalances demonstrated. No adjusted analyses.
Participants	Location: ED, Presbyterian Hospital, NY, USA. Participants: 81 adults (91 visits) (18-45 yrs), acute bronchial asthma. Corticosteroid use permitted. Asthma definition and severity: not reported. Exclusion criteria: serious underlying medical illness (sickle cell, HIV, cancer, heart disease), pneumonia, pregnancy, or temperature >38.3 C. Patients could be entered >1.
Interventions	Intervention: 125 mg IV methylprednisolone (MP; 3 ml) 30 minutes after initial treatment. Control: IV normal saline Co-interventions: 3 aerosolized metaproterenol (q 30 min X 2 hrs) and oral theophylline therapy.
Outcomes	Admission: At discretion of treating physician, no specific criteria: relief of wheezing, clear chest examinations, or minimal wheezing. Six hours after study entry, remaining patients were treated with 40mg IV MP. Hospitalization was mandatory if total treatment time was greater than 12 hours. Pulmonary functions: PEFR. Adverse effects: not reported. Vital signs: temperature, pulse rate, respiratory rate, and blood pressure. Symptoms: 0-3 (none, mild, moderate, severe). Lab: theophylline levels, complete lymphocyte level, electrolytes, . Timing of assessment: entry, 30 minutes, and 2, 4, 6 hours. Duration in the ED: measured. Relapse: 2 and 7 day follow-up of discharged patients.
Notes	Jadad score: Author provided 6 hour admission data for this analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available

Storr 1987

Methods	Randomisation: Hospital pharmacy using random numbers table Blinding: double blinded - similar appearing and tasting (grapefruit-flavoured mixture) Number excluded: well described. Withdrawals: described, and based on allocation (prednisone = 2; placebo = 2). Baseline characteristics: no imbalances demonstrated. No adjusted analyses.
Participants	Location: Children's Hospital, Brighton, UK. Participants: 140 children, moderate-severe acute asthma. Information on the subgroup of patients receiving inhaled steroids at the study enrolment was available. Asthma definition and severity: moderate-severe

Storr 1987 *(Continued)*

	Exclusion criteria: croup, pneumonia, pertussis, congenital heart disease, mental retardation. Any child receiving a steroid within the previous 48 hours was excluded, as well as any child vomiting the study medication within 1 hour of ingestion.
Interventions	Intervention: Children < 5 given 30 mg of oral prednisone, =>5 received 60 mg . Control: identical placebo. Co-interventions: nebulised salbutamol 5 mg in 2 ml saline on admission and three or more times daily when needed.
Outcomes	Admission: At six hours, by treating MD, no specific criteria. Pulmonary functions: PEFR and % predicted. Adverse effects: none Vital signs: none. Symptoms: 0 -10 scale (0 = good, 10 = poor). Lab: not reported Timing of assessment: entry, 30 minutes, and 4 hours. Administrative data: times of admission, length of hospital stay.
Notes	Jadad score: Dr. Storr responded to correspondence and provided additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Hospital pharmacy using random numbers table

Tal 1990

Methods	Randomisation: Central pharmacy prepared solution using a random numbers table. Blinding: double blinded - similar appearance - all delivered by IM injection. Number excluded: not reported. Withdrawals: 2 (described). Baseline characteristics: minimal imbalance demonstrated. No adjusted analyses.
Participants	Location: ED at Children's Hospital in Beer Sheva, Isreal. Participants: 75 children (6-60 mo), acute asthma. at least 3 prior episodes of wheezing. Only the sub-group of patients between 25-54 months were used in this analysis Asthma definition and severity: moderate (PIS: 6-8) and severe (PIS: 9-11). Exclusion criteria: pneumonia, cystic fibrosis, foreign body aspiration, broncho-pulmonary dysplasia, or other respiratory illness. Corticosteroids within 1 month prior to presentation. PIS < 5 and > 11.
Interventions	Intervention: single dose of IM methylprednisolone (MP: 4mg/kg). Control: single dose of IM saline placebo. Co-interventions: salbutamol nebulisation at presentation and q 30 min following intervention. Oxygen was used to drive delivery.
Outcomes	Admission: decision made at 3 hours based on clinical criteria at the discretion of the senior resident. Pulmonary functions: PFTs were not recorded due to the young age of the sample. Adverse effects: not recorded. Vital signs: no. Symptoms: 0 - 12. Pulmonary index score (PIS). Lab: not routine (at discretion of MD). Timing of assessment: entry, 30 minutes and 3 hours. All made by same physician. Relapse: Telephone contact at 5 days to determine relapse.
Notes	Jadad score:

Tal 1990 *(Continued)*

	Dr. Tal responded and provided supplemental information in addition to data extraction verification. A matched pairs design (matched on the basis of age group and disease severity) was employed and the analyses in the paper are more robust than the ones employed for this meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Wolfson 1994

Methods	Randomisation: A predetermined random sequence established by the pharmacist to allocated treatment; vials were prepared daily by a pharmacist. Blinding: double blinded - similar appearance Number excluded: not reported. Withdrawals: none reported. Baseline characteristics: no imbalances demonstrated. No adjusted analyses.
Participants	Location: ED Children's Hospital, Chicago, USA. Participants: 88 children, (4 - 18 yrs), Dx of asthma, acute asthma, without other serious medical problems Exclusion criteria: First-time episodes of wheezing, fever > 38.5 C, patients who had taken systemic corticosteroids within 2 weeks of presentation. Asthma definition and severity: none. No child enrolled > once
Interventions	Intervention: Maximum 125 mg IV methylprednisolone (MP: 2 mg/kg) within 45 minutes of arrival. Control: equivalent volume (2 ml) saline placebo Co-interventions: usual ED management of their acute exacerbation including subcutaneous epinephrine, IV access, oxygen, and B-agonists (at the discretion of the treating MD).
Outcomes	Admission: at 3 hours, clinical decision (lack of resolution of wheezing) made by non-treating MD. Pulmonary functions: PEFR (discontinued at some time during the study due to technical difficulties). Adverse effects: none. Vital signs: "recorded". Symptoms: 0 - 10 (Woods-Downes Asthma Score). Lab: not reported Timing of assessment: entry and discharge or admission (mean of 2.8 hours - CS group; 3.0 hours - placebo group). Administrative: time to disposition, length of stay. Follow-up: 24 hours for discharged patients.
Notes	Jadad score: Dr. Wolfson responded to correspondence, but was unable to provide additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A predetermined random sequence established by the pharmacist to allocated treatment; vials were prepared daily by a pharmacist.

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

Study	Reason for exclusion
Afilalo 1999	RCT of inhaled corticosteroids vs standard care in ED.
Arnaud 1982	RCT of in-patients receiving corticosteroids.
Barnett 1997	IV vs oral corticosteroid in ED prevention of admission. No placebo arm.
Deshpande 1986	Home-based, out-patient treatment with corticosteroids (correspondence with authors).
Fanta 1983	In-patient treatment protocol.
Guttman 1997	RCT of inhaled corticosteroids vs standard care in ED. No placebo arm
Klig 1997	IV vs oral corticosteroids for out-patient care. No placebo arm
Morray 1995	Not an RCT.
Ogirala 1991	Patients were experiencing chronic asthma, as opposed to an acute exacerbation.
Pansegrouw 1992	RCT of inhaled corticosteroids vs standard care in ED. No placebo arm
Rodrigo 1998	RCT of inhaled corticosteroids vs standard care in ED. No placebo arm
Scarfone 1995	RCT comparing two different delivery systems (oral vs nebulization), doses, and therapeutic agents (prednisone vs dexamethasone) for the treatment of acute asthma. Admission rates were reported, but no placebo arm was documented.
Schuckerman 1998	IV vs oral RCT in out-patient setting. No placebo arm
Shapiro 1983	RCT of oral steroids as out-patients after discharge from the acute care setting.
Sung 1997	RCT of inhaled corticosteroids vs standard care in ED.
Volovitz 1998	RCT of inhaled corticosteroids vs standard care in ED.

DATA AND ANALYSES

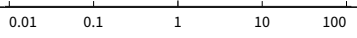
Comparison 1. Any steroid (po, IM, IV, inhaled) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admitted to hospital (all times)	12	844	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.31, 0.81]
2 Admitted to hospital (1-2 hours)	2	126	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.41, 4.67]
3 Admitted to hospital (3-4 hours)	6	366	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.24, 0.91]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 Admitted to hospital (5-6 hours)	7	606	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.15, 0.64]

Analysis 1.1. Comparison 1 Any steroid (po, IM, IV, inhaled) vs placebo, Outcome 1 Admitted to hospital (all times).

Study or subgroup	CS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Connett 1994a	13/19	15/18		6.03%	0.43[0.09,2.09]
Connett 1994b	7/18	12/15		5.99%	0.16[0.03,0.77]
Lin 1997	7/23	5/22		7.41%	1.49[0.39,5.65]
Lin 1999	8/30	11/26		8.96%	0.5[0.16,1.52]
Littenberg 1986	9/48	23/49		10.77%	0.26[0.1,0.65]
Rodrigo 1994	4/49	5/49		7.13%	0.78[0.2,3.11]
Scarfone 1993	11/36	19/39		10.49%	0.46[0.18,1.19]
Schneider 1988	5/27	12/27		8.12%	0.28[0.08,0.97]
Stein 1990	21/44	23/47		11.69%	0.95[0.42,2.17]
Storr 1987	53/73	65/67		6.43%	0.08[0.02,0.36]
Tal 1990	4/17	4/13		5.77%	0.69[0.14,3.52]
Wolfson 1994	17/42	15/46		11.21%	1.41[0.59,3.36]
Total (95% CI)	**426**	**418**		**100%**	**0.5[0.31,0.81]**
Total events: 159 (CS), 209 (Placebo)					
Heterogeneity: Tau^2=0.32; Chi^2=21.27, df=11(P=0.03); I^2=48.29%					
Test for overall effect: Z=2.86(P=0)					



CS therapy Placebo

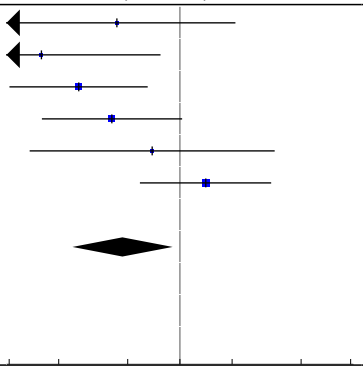
Analysis 1.2. Comparison 1 Any steroid (po, IM, IV, inhaled) vs placebo, Outcome 2 Admitted to hospital (1-2 hours).

Study or subgroup	CS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Lin 1997	7/23	4/22		75.23%	1.97[0.49,7.99]
Scarfone 1993	1/41	2/40		24.77%	0.48[0.04,5.46]
Total (95% CI)	**64**	**62**		**100%**	**1.38[0.41,4.67]**
Total events: 8 (CS), 6 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.98, df=1(P=0.32); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					

CS therapy Placebo

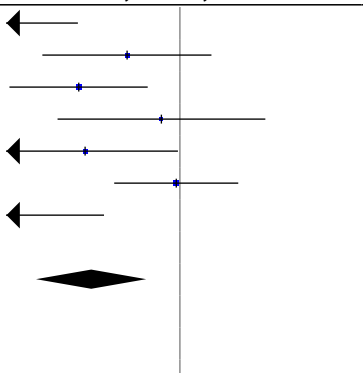
Analysis 1.3. Comparison 1 Any steroid (po, IM, IV, inhaled) vs placebo, Outcome 3 Admitted to hospital (3-4 hours).

Study or subgroup	CS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Connett 1994a	13/19	15/18		11.96%	0.43[0.09,2.09]
Connett 1994b	7/18	12/15		11.88%	0.16[0.03,0.77]
Littenberg 1986	9/48	23/49		21.36%	0.26[0.1,0.65]
Scarfone 1993	11/41	19/40		21.14%	0.41[0.16,1.03]
Tal 1990	4/17	4/13		11.44%	0.69[0.14,3.52]
Wolfson 1994	17/42	15/46		22.22%	1.41[0.59,3.36]
Total (95% CI)	**185**	**181**		**100%**	**0.47[0.24,0.91]**
Total events: 61 (CS), 88 (Placebo)					
Heterogeneity: Tau^2=0.32; Chi^2=9.73, df=5(P=0.08); I^2=48.63%					
Test for overall effect: Z=2.24(P=0.02)					



Analysis 1.4. Comparison 1 Any steroid (po, IM, IV, inhaled) vs placebo, Outcome 4 Admitted to hospital (5-6 hours).

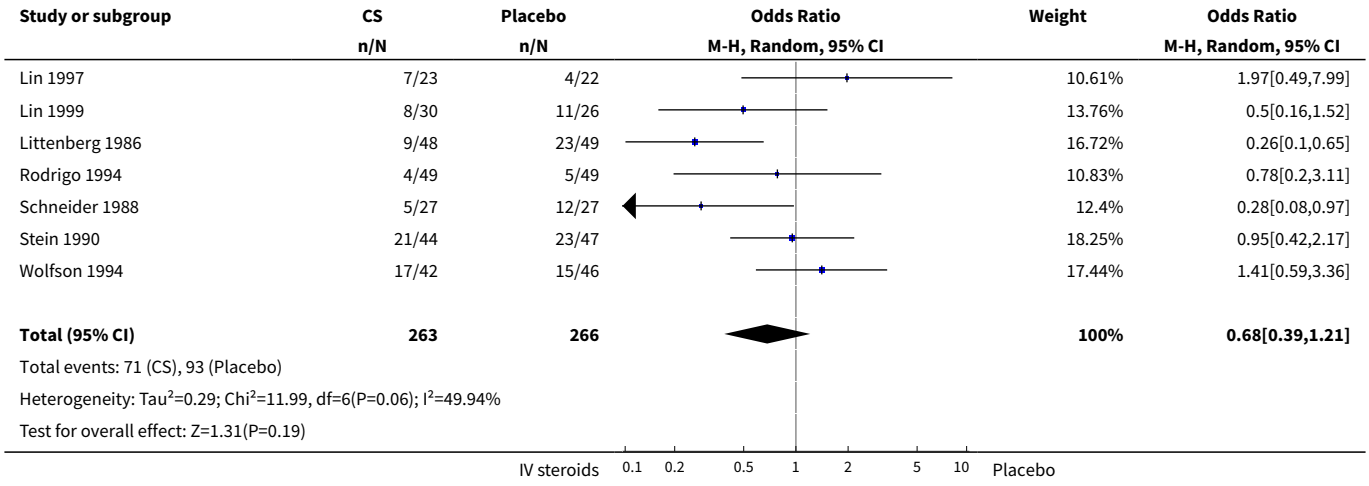
Study or subgroup	CS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Connett 1994a	10/37	27/33		14.35%	0.08[0.03,0.26]
Lin 1999	8/30	11/26		14.54%	0.5[0.16,1.52]
Littenberg 1986	9/48	23/49		16.41%	0.26[0.1,0.65]
Rodrigo 1994	4/49	5/49		12.38%	0.78[0.2,3.11]
Schneider 1988	5/27	12/27		13.58%	0.28[0.08,0.97]
Stein 1990	21/44	23/47		17.28%	0.95[0.42,2.17]
Storr 1987	53/73	65/67		11.47%	0.08[0.02,0.36]
Total (95% CI)	**308**	**298**		**100%**	**0.31[0.15,0.64]**
Total events: 110 (CS), 166 (Placebo)					
Heterogeneity: Tau^2=0.63; Chi^2=17.77, df=6(P=0.01); I^2=66.24%					
Test for overall effect: Z=3.16(P=0)					



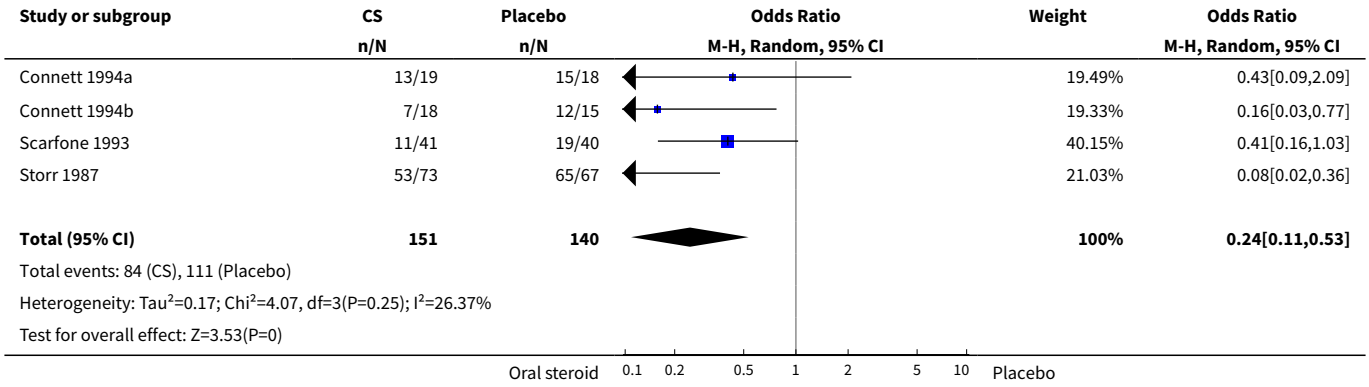
Comparison 2. Route of administration (Admission)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IV vs placebo	7	529	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.39, 1.21]
2 Oral vs Placebo	4	291	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.11, 0.53]

Analysis 2.1. Comparison 2 Route of administration (Admission), Outcome 1 IV vs placebo.



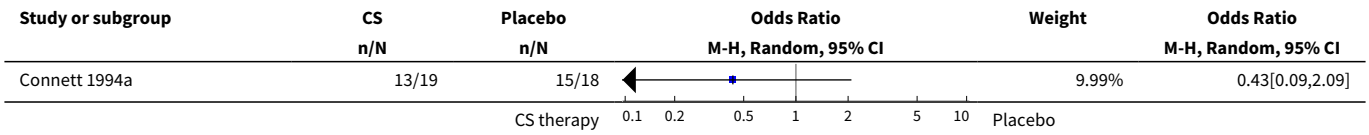
Analysis 2.2. Comparison 2 Route of administration (Admission), Outcome 2 Oral vs Placebo.

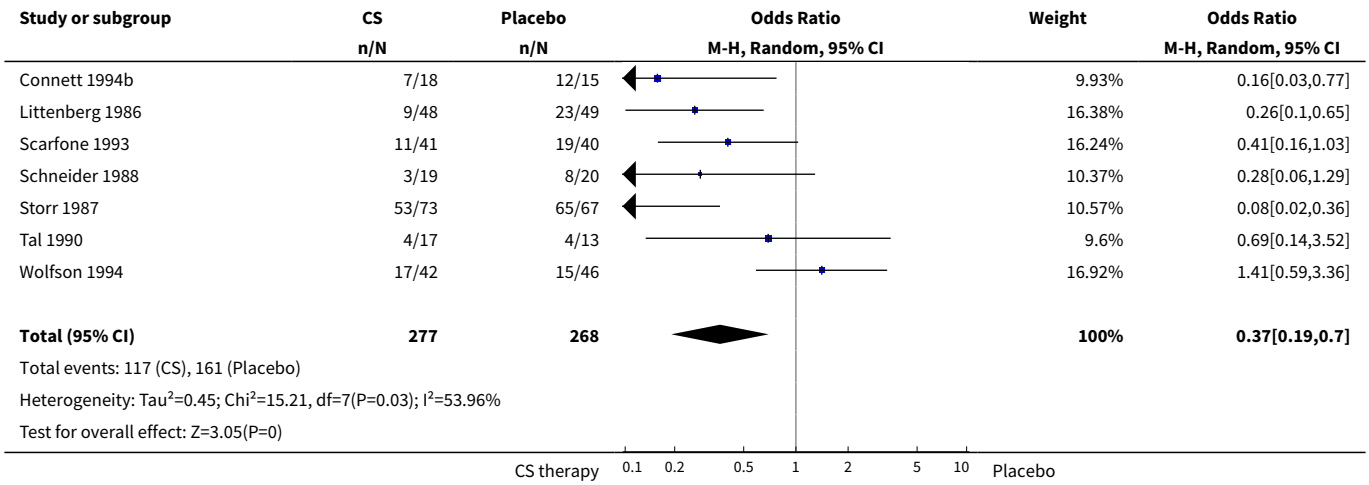


Comparison 3. Chronic corticosteroid use prior to ED

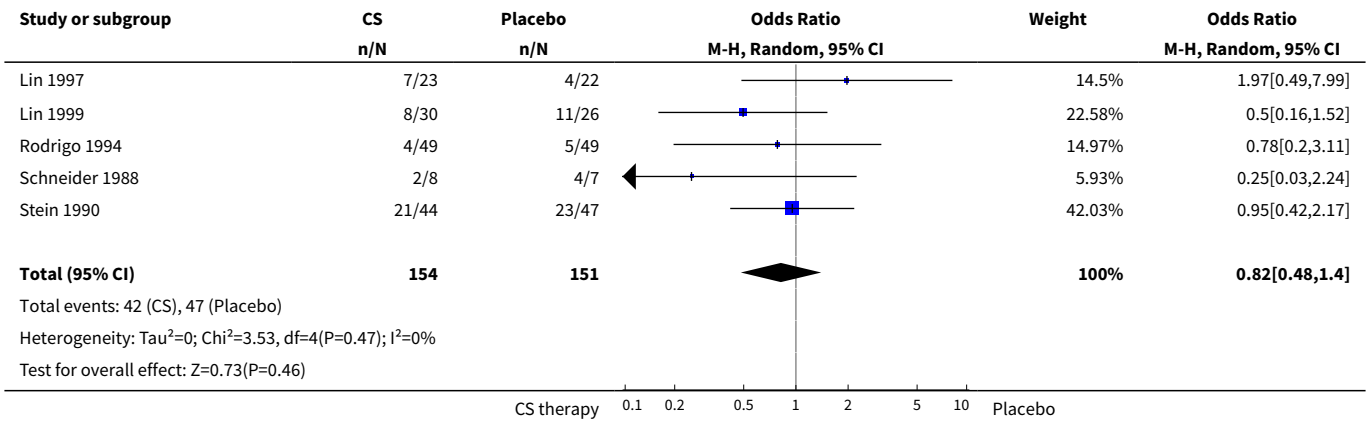
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Excluded	8	545	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.19, 0.70]
2 Mixed population	5	305	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.48, 1.40]

Analysis 3.1. Comparison 3 Chronic corticosteroid use prior to ED, Outcome 1 Excluded.





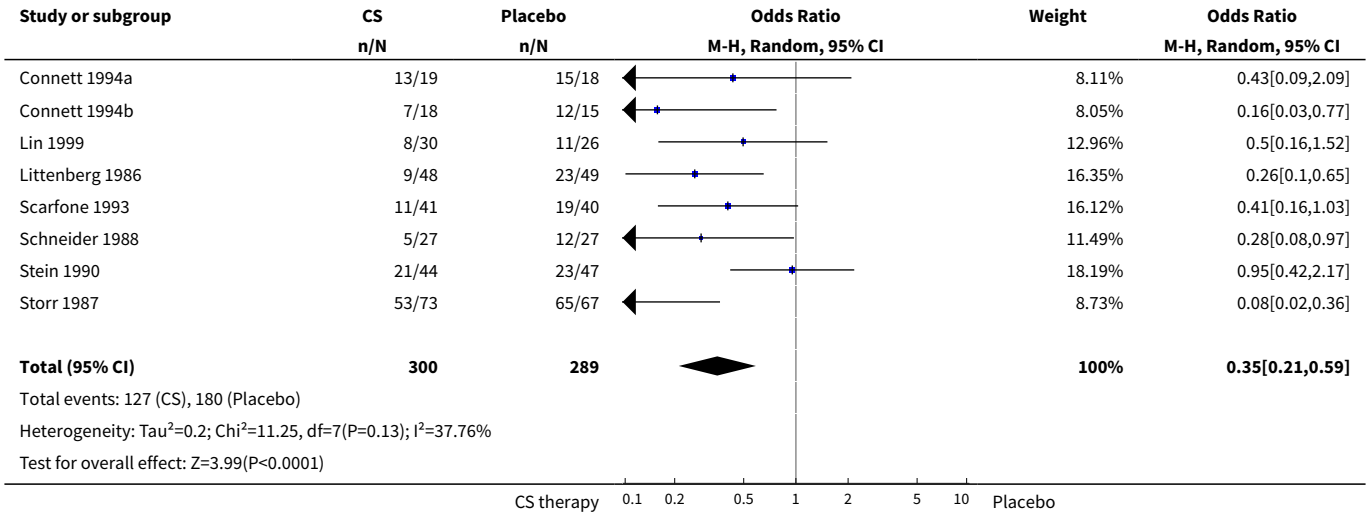
Analysis 3.2. Comparison 3 Chronic corticosteroid use prior to ED, Outcome 2 Mixed population.



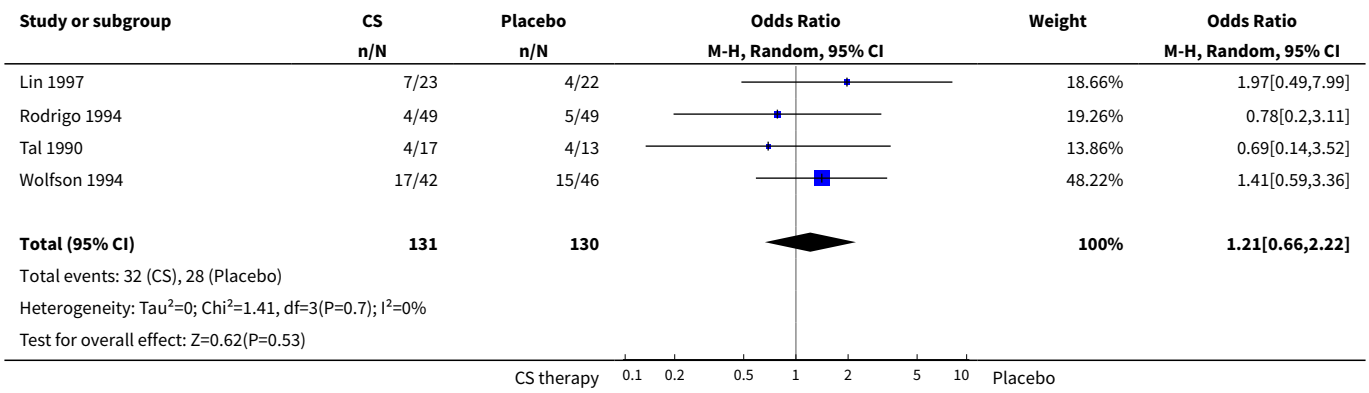
Comparison 4. Severity at Admission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 High Admit Rate (Placebo Admission Rate > 40%)	8	589	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.21, 0.59]
2 Low Admit Rate (Placebo Admission Rate < 40%)	4	261	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.66, 2.22]

Analysis 4.1. Comparison 4 Severity at Admission, Outcome 1 High Admit Rate (Placebo Admission Rate > 40%).



Analysis 4.2. Comparison 4 Severity at Admission, Outcome 2 Low Admit Rate (Placebo Admission Rate < 40%).

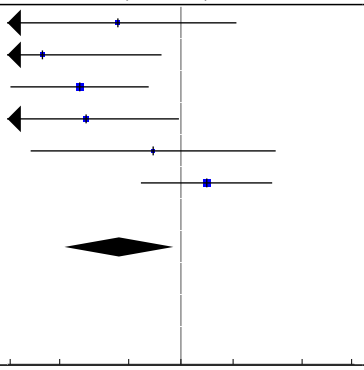


Comparison 5. Quality Assessment (Admission)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 High quality (Cochrane)	6	339	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.21, 0.90]
2 Low quality (Cochrane)	6	505	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.28, 1.18]

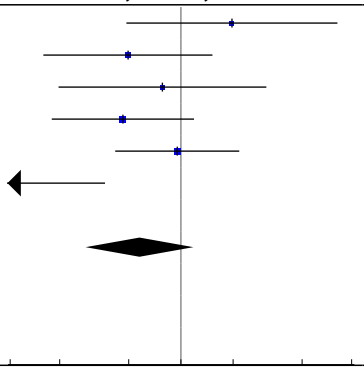
Analysis 5.1. Comparison 5 Quality Assessment (Admission), Outcome 1 High quality (Cochrane).

Study or subgroup	CS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Connett 1994a	13/19	15/18		13.02%	0.43[0.09,2.09]
Connett 1994b	7/18	12/15		12.93%	0.16[0.03,0.77]
Littenberg 1986	9/48	23/49		21.88%	0.26[0.1,0.65]
Schneider 1988	5/27	12/27		17.05%	0.28[0.08,0.97]
Tal 1990	4/17	4/13		12.49%	0.69[0.14,3.52]
Wolfson 1994	17/42	15/46		22.64%	1.41[0.59,3.36]
Total (95% CI)	**171**	**168**		**100%**	**0.44[0.21,0.9]**
Total events: 55 (CS), 81 (Placebo)					
Heterogeneity: Tau²=0.41; Chi²=10.32, df=5(P=0.07); I²=51.54%					
Test for overall effect: Z=2.23(P=0.03)					



Analysis 5.2. Comparison 5 Quality Assessment (Admission), Outcome 2 Low quality (Cochrane).

Study or subgroup	CS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Lin 1997	7/23	4/22		14.02%	1.97[0.49,7.99]
Lin 1999	8/30	11/26		17.34%	0.5[0.16,1.52]
Rodrigo 1994	4/49	5/49		14.26%	0.78[0.2,3.11]
Scarfone 1993	11/36	19/39		19.77%	0.46[0.18,1.19]
Stein 1990	21/44	23/47		21.6%	0.95[0.42,2.17]
Storr 1987	53/73	65/67		13.02%	0.08[0.02,0.36]
Total (95% CI)	**255**	**250**		**100%**	**0.58[0.28,1.18]**
Total events: 104 (CS), 127 (Placebo)					
Heterogeneity: Tau²=0.44; Chi²=11.61, df=5(P=0.04); I²=56.92%					
Test for overall effect: Z=1.51(P=0.13)					

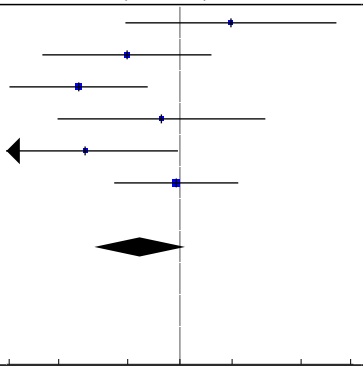


Comparison 6. Population

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Asthmatic Adults Only	6	441	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.32, 1.07]
2 Asthmatic Children Only	6	409	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.17, 0.94]

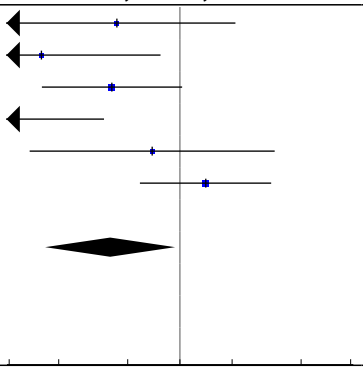
Analysis 6.1. Comparison 6 Population, Outcome 1 Asthmatic Adults Only.

Study or subgroup	CS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Lin 1997	7/23	4/22		12.54%	1.97[0.49,7.99]
Lin 1999	8/30	11/26		16.59%	0.5[0.16,1.52]
Littenberg 1986	9/48	23/49		20.57%	0.26[0.1,0.65]
Rodrigo 1994	4/49	5/49		12.81%	0.78[0.2,3.11]
Schneider 1988	5/27	12/27		14.82%	0.28[0.08,0.97]
Stein 1990	21/44	23/47		22.68%	0.95[0.42,2.17]
Total (95% CI)	**221**	**220**		**100%**	**0.58[0.32,1.07]**
Total events: 54 (CS), 78 (Placebo)					
Heterogeneity: Tau²=0.24; Chi²=8.78, df=5(P=0.12); I²=43.08%					
Test for overall effect: Z=1.75(P=0.08)					



Analysis 6.2. Comparison 6 Population, Outcome 2 Asthmatic Children Only.

Study or subgroup	CS n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Connett 1994a	13/19	15/18		14.38%	0.43[0.09,2.09]
Connett 1994b	7/18	12/15		14.31%	0.16[0.03,0.77]
Scarfone 1993	11/41	19/40		20.86%	0.41[0.16,1.03]
Storr 1987	53/73	65/67		15.04%	0.08[0.02,0.36]
Tal 1990	4/17	4/13		13.92%	0.69[0.14,3.52]
Wolfson 1994	17/42	15/46		21.48%	1.41[0.59,3.36]
Total (95% CI)	**210**	**199**		**100%**	**0.4[0.17,0.94]**
Total events: 105 (CS), 130 (Placebo)					
Heterogeneity: Tau²=0.71; Chi²=13.65, df=5(P=0.02); I²=63.37%					
Test for overall effect: Z=2.1(P=0.04)					

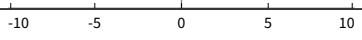


Comparison 7. PEFR

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 PEFR @ 60 minutes	4	132	Std. Mean Difference (IV, Random, 95% CI)	0.22 [-0.41, 0.86]
4 PEFR @ 120 minutes	1	56	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.89, 0.16]
5 Final PEFR	8	479	Mean Difference (IV, Random, 95% CI)	-7.91 [-15.98, 0.17]

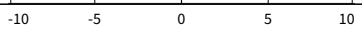
Analysis 7.2. Comparison 7 PEFR, Outcome 2 PEFR @ 60 minutes.

Study or subgroup	Systemic CS N	Systemic CS Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Connett 1994a	7	-41 (4.8)	8	-42.7 (3.7)		19.51%	0.38[-0.65,1.4]
Connett 1994b	9	-44.2 (4.4)	7	-44.3 (3.5)		20.28%	0.02[-0.96,1.01]
Lin 1997	23	-48 (9.6)	22	-56 (8.6)		29.02%	0.86[0.25,1.47]
Lin 1999	30	-234 (100)	26	-200 (100)		31.19%	-0.34[-0.86,0.19]
Total ***	**69**		**63**			**100%**	**0.22[-0.41,0.86]**
Heterogeneity: Tau²=0.26; Chi²=8.62, df=3(P=0.03); I²=65.19%							
Test for overall effect: Z=0.69(P=0.49)							



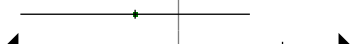
Analysis 7.4. Comparison 7 PEFR, Outcome 4 PEFR @ 120 minutes.

Study or subgroup	Systemic CS N	Systemic CS Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Lin 1999	30	-251 (100)	26	-214 (100)		100%	-0.36[-0.89,0.16]
Total ***	**30**		**26**			**100%**	**-0.36[-0.89,0.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.35(P=0.18)							



Analysis 7.5. Comparison 7 PEFR, Outcome 5 Final PEFR.

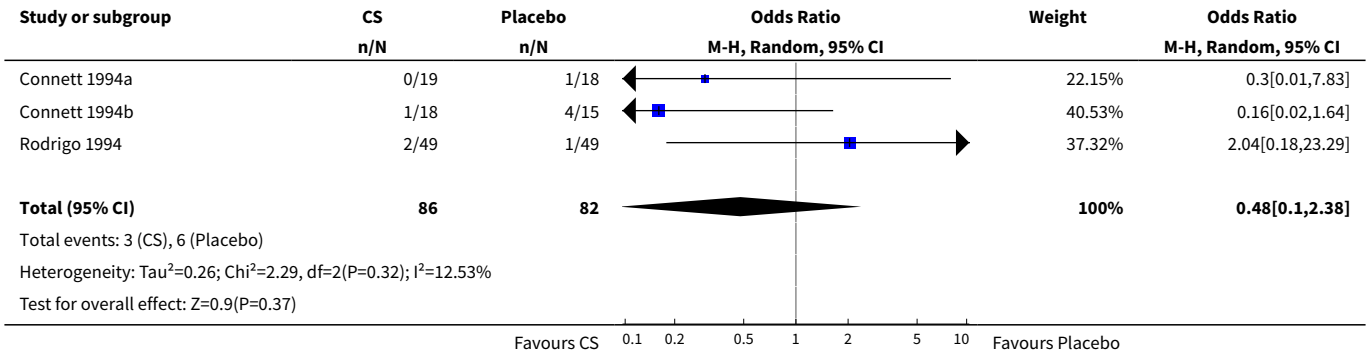
Study or subgroup	Systemic CS N	Systemic CS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Connett 1994a	7	-52.8 (4.6)	8	-44.7 (4.8)		16.22%	-8.1[-12.86,-3.34]
Connett 1994b	9	-74.3 (4)	7	-48.6 (6.3)		15.99%	-25.7[-31.05,-20.35]
Lin 1997	23	-48 (9.6)	22	-56 (8.6)		16%	8[2.68,13.32]
Lin 1999	30	-251 (100)	26	-214 (100)		2.08%	-37[-89.52,15.52]
Littenberg 1986	48	-65 (7.5)	49	-57.8 (7.5)		16.8%	-7.2[-10.19,-4.21]
Rodrigo 1994	49	-57.7 (17.3)	49	-55.2 (16.1)		15.41%	-2.5[-9.12,4.12]
Stein 1990	44	-364 (101)	47	-370 (101)		3.1%	6[-35.53,47.53]
Storr 1987	32	-61 (17)	29	-50 (17)		14.42%	-11[-19.54,-2.46]
Total ***	**242**		**237**			**100%**	**-7.91[-15.98,0.17]**
Heterogeneity: Tau²=98.62; Chi²=81.63, df=7(P<0.0001); I²=91.42%							
Test for overall effect: Z=1.92(P=0.05)							



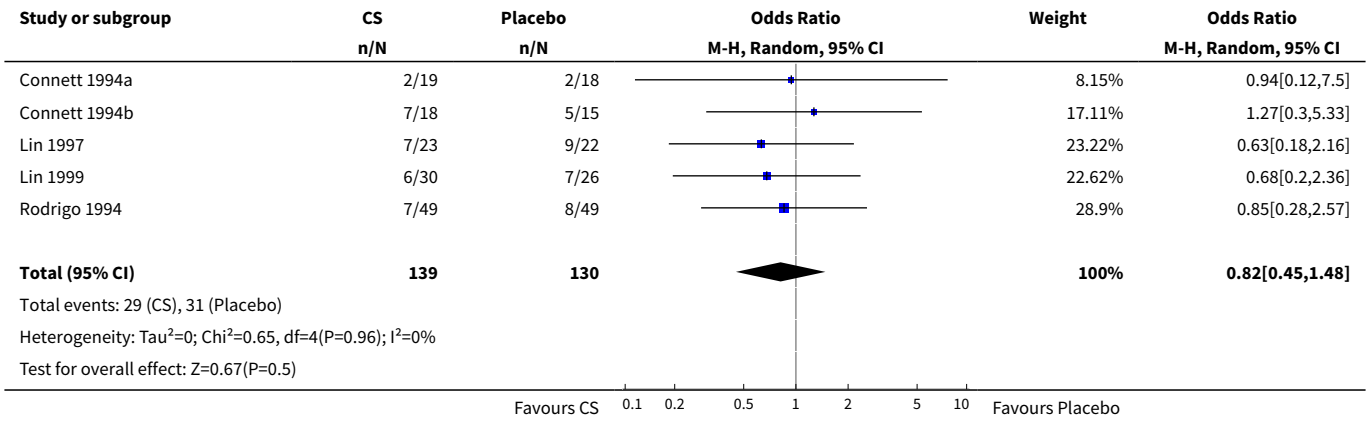
Comparison 8. Adverse effects

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Nausea	3	168	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.10, 2.38]
2 Tremor	5	269	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.45, 1.48]
3 Headache	2	134	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.26, 4.23]

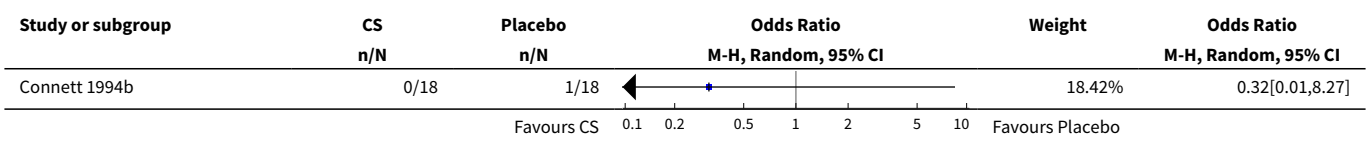
Analysis 8.1. Comparison 8 Adverse effects, Outcome 1 Nausea.

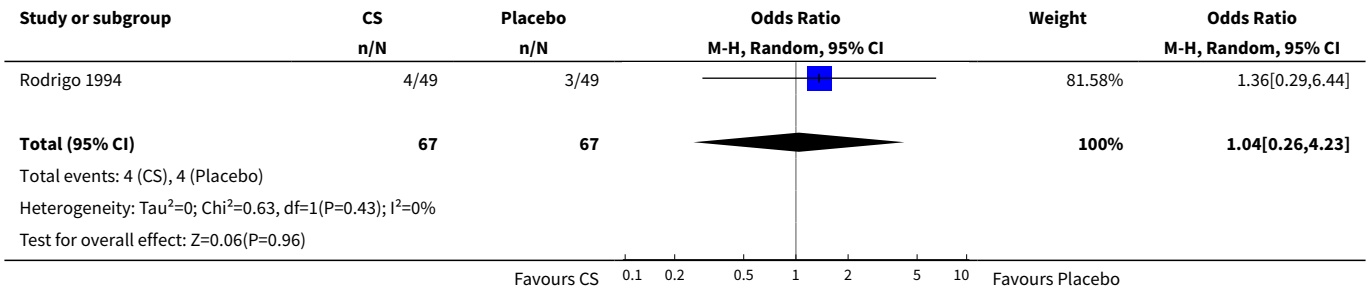


Analysis 8.2. Comparison 8 Adverse effects, Outcome 2 Tremor.



Analysis 8.3. Comparison 8 Adverse effects, Outcome 3 Headache.

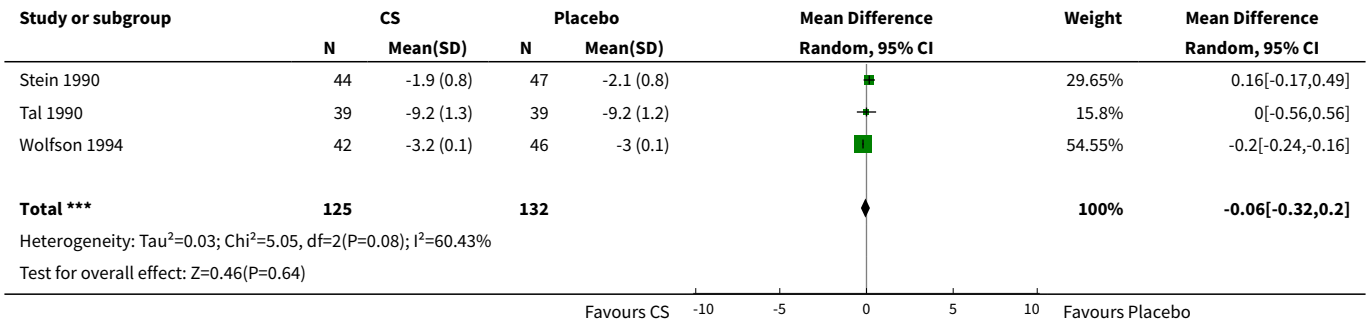




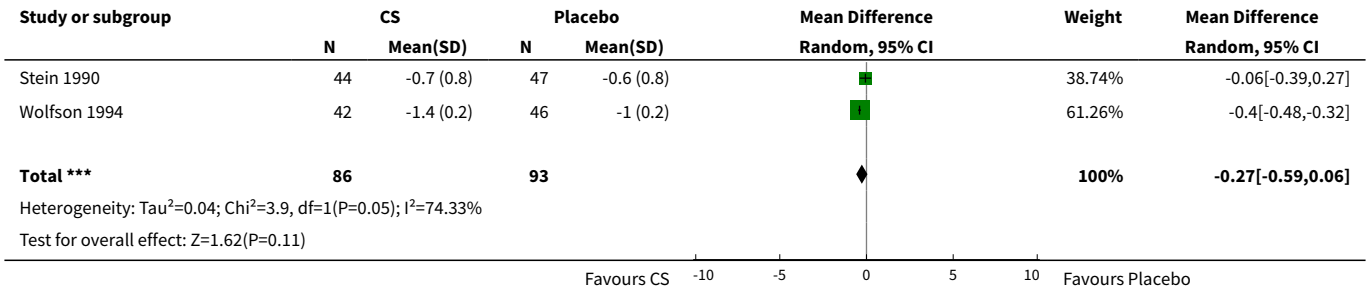
Comparison 9. Symptoms scores

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Initial Score	3	257	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.32, 0.20]
2 Final Score	2	179	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.59, 0.06]

Analysis 9.1. Comparison 9 Symptoms scores, Outcome 1 Initial Score.



Analysis 9.2. Comparison 9 Symptoms scores, Outcome 2 Final Score.



WHAT'S NEW

Date	Event	Description
23 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1998
Review first published: Issue 2, 2000

Date	Event	Description
2 November 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Rowe BH: initiated review, wrote protocol and funding application, completed searches and selection, completed data entry and analysis, principal author and assigned ARG editor.
Spooner C: contributed to protocol, study selection, completed quality assessment, performed editing and manuscript review, and converted final review to RevMan4.
Ducharme FM: contributed to protocol, contributed to study selection and quality assessment, and completed manuscript review.
Bretzlaff JA : contributed to protocol, completed searches and study selection, completed data extraction and entry, and manuscript review.
Bota GW: contributed to protocol, study selection and manuscript review.

DECLARATIONS OF INTEREST

The 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. Dr. Rowe has received unrestricted educational grants for research from Astra, Janssen-Ortho, Boehringer-Ingelheim, Forest, Glaxo, Merck, and Sepracor. Dr. Ducharme has received support from Boehringer-Ingelheim. However, none of the authors are considered paid consultants by any pharmaceutical company that produces CS agents.

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- NHS Research and Development, UK.

External sources

- Ministry of Health (Ontario); Emergency Health Services RAC #11469N, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

*Emergency Service, Hospital; Acute Disease; Administration, Oral; Asthma [*drug therapy]; Glucocorticoids [*therapeutic use]; Injections, Intramuscular; Injections, Intravenous; Placebo Effect; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans