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Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease

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ABSTRACT

Background

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a major cause of hospital admission and mortality. They contribute to long-term decline in lung function, physical capacity and quality of life. The most common causes are infective, and treatment includes antibiotics, bronchodilators and systemic corticosteroids as anti-inflammatory agents.

Objectives

To assess the effects of corticosteroids administered orally or parenterally for treatment of acute exacerbations of COPD, and to compare the efficacy of parenteral versus oral administration.

Search methods

We carried out searches using the Cochrane Airways Group Specialised Register of Trials, MEDLINE and CENTRAL (Cochrane Central Register of Controlled Trials), and checked references of included studies and trials registries. We conducted the last search in May 2014.

Selection criteria

Randomised controlled trials comparing corticosteroids administered orally or parenterally with an appropriate placebo, or comparing oral corticosteroids with parenteral corticosteroids in the treatment of people with acute exacerbations of COPD. Other interventions (e.g. bronchodilators and antibiotics) were standardised for both groups. We excluded clinical studies of acute asthma.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration.

Main results

Sixteen studies (n = 1787) met inclusion criteria for the comparison systemic corticosteroid versus placebo and 13 studies contributed data (n = 1620). Four studies (n = 298) met inclusion criteria for the comparison oral corticosteroid versus parenteral corticosteroid and three studies contributed data (n = 239). The mean age of participants with COPD was 68 years, median proportion of males 82% and mean forced expiratory volume in one second (FEV_1) per cent predicted at study admission was 40% (6 studies; n = 633). We judged risk of selection, detection, attrition and reporting bias as low or unclear in all studies. We judged risk of performance bias high in one study comparing systemic corticosteroid with control and in two studies comparing intravenous corticosteroid versus oral corticosteroid.

Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n = 917) with median treatment duration 14 days, odds ratio (OR) 0.48 (95% confidence interval (CI) 0.35 to 0.67). The evidence was graded as high quality and it would have been necessary to treat nine people (95% CI 7 to 14) with systemic corticosteroids to avoid one treatment failure. There was moderate-quality evidence for a lower rate of relapse by one month for treatment with systemic corticosteroid in two studies (n = 415) (hazard ratio (HR) 0.78; 95% CI 0.63 to 0.97). Mortality up to 30 days was not reduced by treatment with systemic corticosteroid compared with control in 12 studies (n = 1319; OR 1.00; 95% CI 0.60 to 1.66).

FEV_1, measured up to 72 hours, showed significant treatment benefits (7 studies; n = 649; mean difference (MD) 140 mL; 95% CI 90 to 200); however, this benefit was not observed at later time points. The likelihood of adverse events increased with corticosteroid treatment (OR 2.33; 95% CI 1.59 to 3.43). Overall, one extra adverse effect occurred for every six people treated (95% CI 4 to 10). The risk of hyperglycaemia was significantly increased (OR 2.79; 95% CI 1.86 to 4.19). For general inpatient treatment, duration of hospitalisation was significantly shorter with corticosteroid treatment (MD -1.22 days; 95% CI -2.26 to -0.18), with no difference in length of stay the intensive care unit (ICU) setting.

Comparison of parenteral versus oral treatment showed no significant difference in the primary outcomes of treatment failure, relapse or mortality or for any secondary outcomes. There was a significantly increased rate of hyperglycaemia in one study (OR 4.89; 95% CI 1.20 to 19.94).

Authors' conclusions

There is high-quality evidence to support treatment of exacerbations of COPD with systemic corticosteroid by the oral or parenteral route in reducing the likelihood of treatment failure and relapse by one month, shortening length of stay in hospital inpatients not requiring assisted ventilation in ICU and giving earlier improvement in lung function and symptoms. There is no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid on treatment failure, relapse or mortality. There is an increase in adverse drug effects with corticosteroid treatment, which is greater with parenteral administration compared with oral treatment.

PLAIN LANGUAGE SUMMARY

Do systemic corticosteroids improve treatment outcomes in flare-ups of chronic obstructive pulmonary disease?

Why is this question important?

Chronic obstructive pulmonary disease (COPD), also referred to as emphysema or chronic bronchitis, is a long-term lung condition commonly associated with smoking. People with COPD usually have persistent symptoms of breathlessness and may experience flare-ups (exacerbations) on occasion, often precipitated by infection, in which symptoms become markedly worse and further medical intervention is required beyond regular treatment by inhalers.

Systemic (i.e. not inhaled corticosteroids) such as prednisolone, prednisone and cortisone, are anti-inflammatory drugs commonly used in the treatment of exacerbations. We wanted to assess the effectiveness of systemic corticosteroids and whether different routes of administration have impacts on response to treatment of COPD exacerbations.

How did we answer the question?

We looked for all studies that compared corticosteroid, given either by injections (parenterally) or tablets (orally), with matching dummy injections or tablets and all studies that compared corticosteroid given by injections with corticosteroid given by tablets.

What did we find?

We found 16 studies including over 1700 people with COPD who experienced a flare-up that required additional medical treatment that compared corticosteroid given by injections or tablets with dummy treatment. Four studies with nearly 300 people compared corticosteroid injections with corticosteroid tablets. More men than women took part in the studies and they were usually in their late 60s, with moderately severe symptoms of COPD. Most studies took place in hospitals, two in intensive care units with people who needed breathing support, and three studies involved people who were treated at home. The last search for studies to include in the review was done in May 2014.

There were three studies where people knew which treatment they were getting, but otherwise studies were generally well designed.

People treated with either corticosteroid injections or tablets compared with dummy treatment were less likely to experience treatment failure, 122 fewer people per 1000 treated, with a lower rate of relapse by one month. They had shorter stays in hospital if they did not require assisted ventilation in an intensive care unit, and their lung function and breathlessness improved more quickly during treatment. However, they had more adverse events while taking treatment, especially a temporary increase in glucose levels in blood. Corticosteroid treatment did not reduce the number of people who died within one month of their flare-up.

In studies comparing two ways of giving corticosteroid, either by injections or tablets, there were no differences in treatment failure, the time in hospital or number of deaths after discharge; however, a temporary increase in glucose levels in blood was more likely with injections than tablets.

Conclusion

There is high-quality evidence that is unlikely to be changed by future research that people who experience flare-ups of COPD benefit from treatment with corticosteroid given by injections or tablets with the increased risk of some temporary side effects.

Summary of findings for the main comparison. Systemic corticosteroid compared with placebo for acute exacerbations of COPD

Systemic corticosteroid compared with placebo for acute exacerbations of COPD

Patient or population: acute exacerbations COPD
Settings: outpatient, inpatient and people in ICU

Intervention: systemic corticosteroid
Comparison: 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				
		Systemic corticosteroid				
Treatment failure Need to intensify therapy/ED or hospital admission Follow-up: 3-30 days	**276 per 1000**	**154 per 1000** (118 to 203)	**OR 0.48** (0.35 to 0.67)	917 (9 studies)	⊕⊕⊕⊕ **high**	-
Relapse Treatment for AE of COPD or hospital re-admission Follow-up: 1-4 months	**215 per 1000**	**174 per 1000** (122 to 242)	**OR 0.77** (0.51 to 1.17)	596 (5 studies)	⊕⊕⊕⊖ **moderate** [1]	In 2 studies (n = 415) relapse to 1 month was lower with systemic corticosteroid compared with placebo (HR 0.78; 95% CI 0.63 to 0.97
Improvement in lung function - early effect FEV_1 (L) as absolute or change Follow-up: 3 days	The mean FEV_1 in control groups ranged from 0.77 to 0.91 L	The mean early improvement in lung function in the intervention group was **0.14 L higher** (0.09 to 0.20 higher)	-	649 (7 studies)	⊕⊕⊕⊕ **high**	-
Decreased breathlessness - early effect Borg scale or VAS Follow-up: 3 days	The mean change in breathlessness in control group was 1.8 units using the Borg scale and 1.5 units on the VAS scale	The mean early decrease in breathlessness in the intervention group was **0.35 standard deviations higher** (0.05 to 0.64 higher)	-	178 (3 studies)	⊕⊕⊕⊖ **moderate** [2]	Effect size on Borg scale 0.93 units; 95% CI 0.18 to 1.7 (MCID = 2); effect size on VAS scale 5.24; 95% CI 0.75 to 9.59 (MCID = 10).

Adverse drug effect Follow-up: 2-26 weeks	**285 per 1000**	**481 per 1000** (388 to 577)	**OR 2.33** (1.59 to 3.43)	736 (8 studies)	⊕⊕⊕⊕ **high**	-
Hyperglycaemia	**124 per 1000**	**282 per 1000** (208 to 371)	**OR 2.79** (1.86 to 4.19)	804 (6 studies)	⊕⊕⊕⊕ **high**	-

*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).
AE: acute exacerbation; **CI:** confidence interval; **COPD:** chronic obstructive pulmonary disease; **ED:** emergency department; **FEV_1:** forced expiratory volume in 1 second; **HR:** hazard ratio; **MCID:** minimum clinically important difference; **OR:** odds ratio; **VAS:** visual analogue scale.

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] Wide CIs include significant benefit and harm (-1 for imprecision).
[2] Upper or lower CI of effect size crosses 0.5 (-1 for imprecision).

Summary of findings 2. Treatment route: intravenous corticosteroid compared with oral corticosteroid for acute exacerbations of COPD

Intravenous corticosteroid compared with oral corticosteroid for acute exacerbations of COPD

Patient or population: acute exacerbations of COPD
Settings: inpatient
Intervention: intravenous corticosteroid
Comparison: oral corticosteroid

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Oral corticosteroid	**Intravenous corticosteroid**				
Treatment failure Need to intensify therapy Follow-up: 7-14 days	**162 per 1000**	**115 per 1000** (62 to 201)	**OR 0.67** (0.34 to 1.3)	298 (3 studies)	⊕⊕⊕⊖ **moderate** [1]	-
Relapse Hospital readmission for COPD	**155 per 1000**	**149 per 1000** (84 to 249)	**OR 0.95** (0.5 to 1.8)	298 (3 studies)	⊕⊕⊕⊖ **moderate** [1]	-

Follow-up: 4-12 weeks						
Breathlessness - early effect VAS 0-10. Scale from: 0 to 10. Follow-up: 3 days	The early breathlessness VAS in control groups ranged from mean 4.4 to 7.5 units	The early mean breathlessness in the intravenous corticosteroid group was **0.62 higher** (0.55 lower to 1.78 higher)	-	75 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	-
Mortality after discharge (1-3 months) Follow-up: 1-3 months	**27 per 1000**	**37 per 1000** (12 to 111)	**OR 1.4** (0.44 to 4.51)	298 (3 studies)	⊕⊕⊕⊖ **moderate** [1,3]	-
Duration of hospitalisation Days Follow-up: mean 14 days	Mean duration in the control group ranged from 10.6 to 11.2 days	The mean duration of hospitalisation in the intravenous corticosteroid group was **1.54 longer** (0.09 lower to 3.17 higher)	-	298 (3 studies)	⊕⊕⊖⊖ **low** [1,2]	-
Adverse drug effect - hyperglycaemia Follow-up: mean 12 days	**200 per 1000**	**550 per 1000** (231 to 833)	**OR 4.89** (1.2 to 19.94)	40 (1 study)	⊕⊕⊕⊖ **moderate** [4]	-
PaO_2 mmHg Follow-up: 7 days	The mean PaO_2 in the control group was 66.5 mmHg	The mean PaO_2 in the intravenous corticosteroid group was **1.2 mmHg lower** (8.61 lower to 6.21 higher)	-	38 (1 study)	⊕⊕⊖⊖ **low** [1,4,5]	-

*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; **COPD:** chronic obstructive pulmonary disease; **OR:** odds ratio; **PaO_2:** partial pressure of oxygen dissolved in arterial blood; **VAS:** visual analogue scale.

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] Wide CIs include significant benefit and harm (-1 for imprecision).
[2] Participants and physicians not blinded to treatment in 2 studies (-1 for risk of bias).
[3] Participants and physicians not blinded to treatment in 2 studies; however, the risk of bias for the event mortality was considered to be low.
[4] Single inpatient study (-1 indirectness).
[5] Participants and physicians not blinded to treatment; however, the risk of bias for the outcome measurement was considered to be low.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases (GOLD 2013). A diagnosis of COPD is considered on a clinical basis in the presence of symptoms such as dyspnoea, chronic cough or sputum production and exposure to known risk factors. Confirmation of COPD diagnosis is based on demonstration of persistent airflow limitation with spirometry, according to the criterion post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio less than 0.7, as specified in guidelines including GOLD: Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD 2013).

COPD is an important and increasing cause of mortality, estimated to be the fifth leading cause of death in 2000, responsible for 2.75 million deaths (Lopez 2006). Worldwide mortality due to COPD is projected to rise to 4.5 million deaths in 2020, and become the third leading cause (Murray 1997). Morbidity is high and worldwide in 2000 COPD resulted in 16.5 million years of life lost, almost 10 million years lived with disability and 26.5 million disability-adjusted life years (Lopez 2006).

COPD prevalence measured in a worldwide study to estimate the Burden of Lung Disease (BOLD) showed the prevalence of stage II or higher severity (FEV_1 less than 80% predicted) is 10.1% (standard error (SE) 4.8%) overall, 11.8% (SE 7.9%) for men and 8.5% (SE 5.8%) for women (Buist 2007). International variation in prevalence and severity stage of COPD is partially explained by variation in smoking prevalence and other risk factors (Buist 2007).

Exacerbations and co-morbidities contribute to the varying natural history of COPD in individual people (GOLD 2013). Exacerbations contribute to long-term decline in lung function (Donaldson 2002), and reduced physical activity (Donaldson 2005), and are associated with increased risk of death (Soler-Cataluna 2005). They also have a profound and long-lasting effect on quality of life (QoL) (Seemungal 1998; Groenewegen 2001; Wilkinson 2004); in 10% of exacerbations, pre-exacerbation QoL was not recovered after three months (Seemungal 2000).

COPD exacerbations may require hospitalisation, although exacerbations with less severe symptoms and signs are often managed as an outpatient (NICE 2010). Hospital-at-home, or early discharge services if available, may be used as an alternative way of caring for people with exacerbations of COPD who would otherwise need to be admitted or stay in hospital (Jeppesen 2012; NICE 2010). The treatment of exacerbations is a large contributor to the economic burden of COPD (Sullivan 2000; Schermer 2002), with a high proportion of costs being due to hospitalisations (Crockett 2001; Oostenbrink 2004).

Studies on the frequency of exacerbations usually use an 'event-based' definition based on healthcare utilisation (Effing 2009), and different events may be a proxy for severity, with unscheduled clinic or emergency department visits rated 'moderate' and those requiring hospitalisation labelled 'severe' (Rodriguez-Roisin 2000). However, the clinical onset of an acute exacerbation is defined according to symptoms, although there is no universally agreed definition (Rodriguez-Roisin 2000). Type 1 exacerbations were defined by Anthonisen on the basis of three major symptoms; increased dyspnoea, sputum volume and sputum purulence; Type 2 exacerbations had only two of the major symptoms and Type 3 exacerbations had one major symptom plus cough, wheeze or symptoms of an upper respiratory tract infection (Anthonisen 1987). A later definition required an increase in two of the 'major symptoms' of dyspnoea, sputum volume or sputum purulence, or one major symptom with an increase in one 'minor symptom' for two days (wheeze, sore throat, cough or common cold symptoms) (Seemungal 2000). More recently, a standardised measure for assessing the frequency, severity and duration of exacerbations of COPD using participant-reported outcomes has been developed for use in clinical studies (Leidy 2010).

COPD exacerbations can be precipitated by several factors, the most common causes being infective, with bacterial pathogens identified in just over 50% and viral causes in around 25% of people (Sherk 2000). Non-infective causes such as air pollution and other environmental conditions that increase airway inflammation may account for 15% to 20% of exacerbations (Sethi 2008). Exacerbations become more frequent and more severe as the severity of COPD increases (Suissa 2012), although the rate at which they occur may reflect an independent susceptibility phenotype, the 'frequent exacerbator' (Hurst 2010).

Description of the intervention

The acute inflammatory response to airway infection is influenced by both pathogenic and host factors, resulting in increased airway and systemic inflammation (Sethi 2008). Airway inflammation is significantly increased during exacerbations of COPD, with evidence of increased neutrophils, lymphocytes and eosinophils seen in airways and in sputum (Papi 2006; Bathoorn 2008; Falk 2008). Systemic inflammation is also present in COPD; many circulating inflammatory mediators are elevated both in stable COPD and during exacerbations. C-reactive protein is a known marker of systemic inflammation whose levels are elevated during exacerbations and it is a likely participant in the inflammatory cascade (Falk 2008).

How the intervention might work

Theoretical mechanisms for clinical improvement in lung function in people treated with corticosteroids during exacerbations may include reduction in airway inflammation or a decrease in airway oedema (Wedzicha 2000).

Corticosteroid use may be associated with a number of adverse effects, including fluid retention, hypertension, diabetes mellitus, adrenal suppression, osteoporosis and increased fracture risk (Vestergaard 2007). Although the risks are greater with longer-term use than short-term use (Henzen 2000), their benefits in the management of acute COPD exacerbations must be balanced against adverse effects (McEvoy 1997).

Why it is important to do this review

Previous versions of this systematic review showed beneficial effects of treatment with systemic corticosteroids in acute exacerbations of COPD on treatment failure (Wood-Baker 2001; Walters 2009), and reduced length of hospital stay, reduced dyspnoea, improved oxygen saturation and improved lung function measures (Walters 2009). The findings of these systematic reviews

(based on searches of the literature to 2008) are reflected in current guidelines for the treatment of acute exacerbations of COPD that recommend the use of systemic corticosteroids (GOLD 2013), both within and outside hospital (NICE 2010).

Long-term follow-up of a population-based inception cohort of people with COPD suggested the need to investigate the effects of systemic corticosteroids in severe exacerbations requiring non-invasive ventilation (Suissa 2012). However, in previous versions of this systematic review, studies in which participants received assisted ventilation for a severe exacerbation were excluded and we wish to update the evidence and extend the review to include the setting of assisted ventilation. With the finding of increased risk of subsequent exacerbations following first hospitalisation (Suissa 2012), and observation of higher individual risk of exacerbations in frequent exacerbators (Hurst 2010), we wished to include subgroup analysis by frequency and severity of exacerbations in this version of the review.

OBJECTIVES

To assess the effects of corticosteroids administered orally or parenterally for treatment of acute exacerbations of COPD, and to compare the efficacy of parenteral versus oral administration.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) in which treatment with oral or parenteral corticosteroids was compared with appropriate placebo, or in which treatment with oral corticosteroids was compared with parenteral corticosteroid for acute exacerbations of COPD.

Types of participants

We included studies that recruited people with a guideline-typical clinical diagnosis of COPD of any severity (GOLD 2013), based on persistent (post-bronchodilator) airflow limitation, confirmed for example by FEV_1/FVC ratio less than 0.7 and history of exposure to risk factors (tobacco smoke, smoke from home cooking and heating fuels, occupational dusts and chemicals).

Participants must have experienced an acute functional deterioration, thus allowing a wide definition of an acute exacerbation, which could include any combination of increased breathlessness or sputum volume, sputum purulence, cough or wheeze and symptoms or overt respiratory tract infection. Participants could be treated in primary care, or hospital secondary care, including when requiring assisted ventilation. We excluded trials of people with acute asthma.

Types of interventions

We included studies comparing:

- corticosteroid, administered either parenterally or orally with placebo-control injections or tablets as appropriate;
- oral corticosteroid with parenteral corticosteroid.

We permitted other non-corticosteroid co-interventions (e.g. bronchodilators and antibiotics) as long as they were not part of the randomised treatments.

Types of outcome measures

We divided outcome data into early (defined as up to and including 72 hours from study entry) and late (occurring after 72 hours and up to the last available measurement during study treatment) time points.

Primary outcomes

1. Treatment failure: defined as necessity to intensify pharmacological treatment, hospital admission during outpatient treatment or return to emergency department during outpatient treatment.
2. Relapse: defined as treatment or hospital admission for a COPD exacerbation after completion of study treatment.
3. Mortality.

Secondary outcomes

1. Adverse drug effects.
2. Arterial blood gas (ABG) measurements (partial pressure of oxygen dissolved in arterial blood (PaO_2) and partial pressure of carbon dioxide dissolved in arterial blood ($PaCO_2$)).
3. Symptom scores: measuring breathlessness, symptoms of cough, wheeze, sputum production ; preferably using validated scales.
4. Lung function, pre- and post-bronchodilator including FEV_1, FVC), peak expiratory flow (PEF).
5. Health status: QoL assessments using validated scales.
6. Physical capacity: timed walking tests, endurance tests,
7. Duration of hospitalisation.
8. Duration of assisted ventilation.

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials, 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 the Airways Group Module for further details). We searched all records in the Specialised Register coded as 'COPD' (Airways Trials Search Co-ordinator) most recently in June 2013 using the following terms:

"adrenal cortex hormone*" or steroid* or glucocorticoid* or corticoid* or corticosteroid* or beclomethasone or betamethasone or fluticasone or cortisone or dexamethasone or hydrocortisone or prednisolone or prednisone or methylprednisolone or methylprednisone or triamcinolone.

We performed the most recent search (DT/CW) of MEDLINE for the period 12 months from June 2012 (Appendix 1) and of EMBASE for the period 2010 to June 2013 (Appendix 2).

We ran previous searches of these databases for the review published in 1999, and updated versions in 2004 and in 2007.

Searching other resources

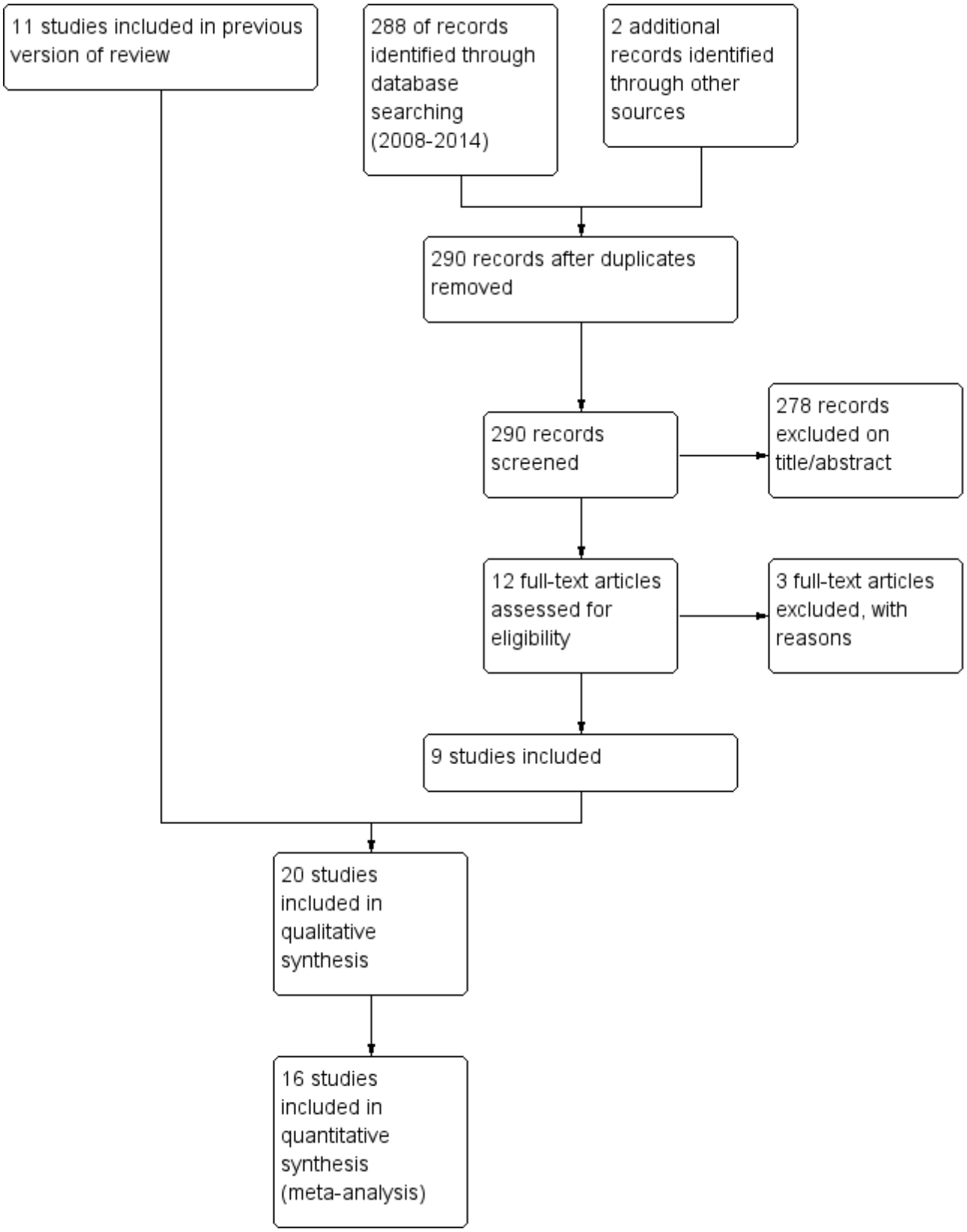
In addition, we searched the bibliographies of each RCT and any review articles identified for additional papers. We searched the registers of ongoing clinical trials ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/).

Data collection and analysis

Selection of studies

At least two review authors (DT, CW) assessed all potentially relevant trials for relevance. We screened the full text to independently select trials for inclusion and identify and record reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third person (JW). We identified and excluded duplicates and collated multiple reports of the same study so that each study (rather than each report) was the unit of interest in the review. We recorded the selection process as a PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram for 2008-2014 literature searches.



Data extraction and management

We used a data collection form for study characteristics and outcome data. Two review authors (DT, CW) independently extracted the following study characteristics from included studies.

1. Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: n, mean age, age range, gender, diagnostic criteria for exacerbation, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: study treatment, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (two of JW, DT, CW) independently extracted outcome data from included studies. We entered data into the Review Manager 5 (JW, DT, CW) and a second review author double-checked entries. We checked that data were entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study (two of JW, CW, DT) using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another review author. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias(es).

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

In addition, we assessed each study for the basis of the diagnosis of COPD using the following criteria.

1. Was the age of participants over 45 years?
2. Was the smoking history greater than 10 pack-years?
3. Were participants with a previous physician diagnosis of asthma excluded?
4. Was there evidence of fixed airflow obstruction?

Measures of treatment effect

For continuous variables, we analysed data as mean difference (MD), with 95% confidence interval (CI). We used standardised mean difference (SMD) with 95% CI if different scales of measurement had been used for an outcome. The SMD is a statistic that expresses the difference in means between treatment groups in units of the pooled standard deviation (SD). We analysed dichotomous outcomes using Mantel-Haenszel odds ratio (OR) with a 95% CI. Where events were rare, we employed the Peto OR. We entered scale data with a consistent direction of effect.

We undertook meta-analyses only where it was meaningful; when treatments, participants and the underlying clinical question were similar.

When skewed data were available (reported as medians and interquartile ranges), we described them narratively.

For 'time-to-event' outcomes such as log hazard ratios (HR), we used the fixed-effect generic inverse variance outcome to combine results. This method gives a weighted mean of the effect estimates of separate studies (Higgins 2011). We calculated number needed to treat for an additional beneficial outcome (NNTB) from the pooled OR and its CI using the baseline risk in the control group.

Unit of analysis issues

We analysed dichotomous data using participants as the unit of analysis. For continuous data, the MD based on change from baseline was preferred over MD based on absolute when both were available.

Dealing with missing data

We contacted investigators to obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results using a sensitivity analysis**.**

Assessment of heterogeneity

We carried out an assessment of possible heterogeneity, where the null hypothesis is that all studies are evaluating the same effect, for pooled effects using a Breslow-Day test of heterogeneity; a P value > 0.05 was considered to indicate a significant difference between studies. In addition, we used the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins 2003). Interpretation of statistical heterogeneity was as follows: 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity (Higgins 2011).

We assessed clinical and methodological heterogeneity by recording differences in study design and participant characteristics between individual studies. When we found substantial heterogeneity, we reported it and explored possible causes by pre-specified subgroup analysis.

Assessment of reporting biases

We tried to minimise reporting bias from non-publication of studies or selective outcome reporting by using a broad search strategy,

checking references of included studies and relevant systematic reviews, and contacting authors for additional outcome data. We visually inspected funnel plots when 10 or more studies contributed to analysis for an outcome.

Data synthesis

We used a fixed-effect model, and, in addition, we performed a sensitivity analysis with a random-effects model if there was unexplained heterogeneity. We presented the findings of our primary outcomes in a 'Summary of findings' table according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (generated with the use of GRADEPRO software).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed by:

- duration of corticosteroid treatment (number of days' treatment is reported in the user-defined order in analysis tables);
- setting (i.e. primary care, hospital secondary care or requiring assisted ventilation).

Analysis by frequency and severity of exacerbations was not possible owing to lack of data in studies.

Sensitivity analysis

In the assessment of heterogeneity, we considered possible causes arising from details of study design. We performed sensitivity analyses using random-effects models versus fixed-effect models, by risk of bias and by other potential confounders.

RESULTS

Description of studies

Results of the search

We carried out an initial search in 1996, using the Cochrane Airways Group COPD RCT register and MEDLINE; the search retrieved 108 references and we subsequently identified 85 papers as suitable for consideration in the review, with eight RCTs included in the original review. We located two additional studies in searches up to August 2004 and included them in the 2005 update of the review (Maltais 2002; Aaron 2003). In the 2009 review update, from searches to August 2008, we identified 10 studies for potential inclusion of which Chen 2005 was included.

For this review update in 2014, we undertook searches on 28 June 2013 and 23 May 2014 (see Figure 1). The 2003 search yielded 140 and the 2014 search yielded 148 references after duplicates were removed and we identified two studies for the new comparison of route of treatment from those previously excluded. We excluded 278 references on title or abstract. We excluded three references as they did not randomise participants to corticosteroid treatment or did not use placebo control (Roede 2008; Wang 2011; Bafadhel 2012). We included five additional studies comparing systemic corticosteroids with placebo (Cordero 1996; Gunen 2007; Alia 2011: Zheng 2011; Abroug 2014). We included two studies comparing oral and parenteral corticosteroids (Ridha 2006; Ceviker 2014), with two studies for this treatment comparison that had previously been excluded now included (Willaert 2002; de Jong 2007).

Included studies

See Characteristics of included studies table for details.

For the comparison systemic corticosteroid versus placebo, we included 16 studies in the review. Four were published in abstract form only (Rostom 1994; Cordero 1996; Wood-Baker 1998; Zheng 2011). Three studies contained no data that could be included and no responses to requests for data have been received (Rostom 1994; Cordero 1996; Zheng 2011). Unpublished data were available for Wood-Baker 1998 and data were sought and supplied by the authors for Chen 2005. Authors of eight published studies supplied additional data (Emerman 1989; Bullard 1996; Thompson 1996; Davies 1999; Niewoehner 1999; Maltais 2002; Aaron 2003; Alia 2011). Thus, 13 studies contribute some outcome data for this comparison.

For the comparison parenteral corticosteroid versus oral corticosteroid, we included three published studies in the review that contributed outcome data (de Jong 2007; Willaert 2002; Ceviker 2014), while one study was only published as an abstract and no response has been received to a request for data for inclusion in the review (Ridha 2006). We requested additional data for Ceviker 2014, but we received no response.

Table 1 summarises across the 20 studies: setting; exclusion of people with asthma, prior inhaled corticosteroid use, exacerbation definition, duration of study treatment, participants per cent male, mean age, FEV_1, pack-years' smoking history, number of withdrawals.

The setting for participant recruitment and intervention delivery was hospital inpatients in 12 studies (Albert 1980; Rostom 1994; Wood-Baker 1998; Davies 1999; Niewoehner 1999; Maltais 2002; Willaert 2002 Chen 2005; de Jong 2007; Gunen 2007; Zheng 2011; Ceviker 2014), hospital intensive care units (ICU) in two studies (Alia 2011; Abroug 2014), and, in two studies, the intervention was initiated in the emergency department with subsequent admission only if required clinically (Emerman 1989; Bullard 1996). In Bullard 1996, participants were kept in the emergency department for six hours, and 26 of 113 participants were discharged within 24 hours. In Emerman 1989, a single intravenous infusion of methylprednisolone was given in the emergency department and participants were observed over a minimum of four hours. Subsequently 30 of 96 participants required admission and for some participants allocation to treatment group was not maintained after re-admission. Three studies recruited outpatients (Cordero 1996; Thompson 1996; Aaron 2003), and the setting was not specified for Ridha 2006.

We attempted to verify the diagnosis of COPD using the criteria age of people over 40 years, smoking history greater than 10 pack-years, exclusion of people with a previous physician diagnosis of asthma and evidence of fixed airflow obstruction for all studies (see notes in Characteristics of included studies). The important criterion of irreversible airflow obstruction determined by spirometry was specified in 12 studies (Bullard 1996; Cordero 1996; Thompson 1996; Wood-Baker 1998; Davies 1999; Niewoehner 1999; Maltais 2002; Aaron 2003; de Jong 2007; Gunen 2007; Alia 2011; Abroug 2014). Where specified, the mean length of smoking history ranged from 32 to 80 pack-years. The demographics of participants in these studies, particularly age, smoking history and severity of airflow obstruction suggests low likelihood of contamination with

people with asthma, although this cannot be verified in Rostom 1994; Bullard 1996; Chen 2005; Ridha 2006; Gunen 2007; Zheng 2011; and Ceviker 2014, as they made no reference to the exclusion of people with asthma or the smoking history of participants. Of 2078 participants randomised to treatment in the 20 included studies, the mean age was 68 years and median proportion of males included was 82% (range 52% to 100%). For six studies reporting lung function, the mean FEV_1 per cent predicted at study admission was 40% (range 27% to 64%).

Definition of an exacerbation of chronic obstructive pulmonary disease

In 11 studies, some combination of worsening symptoms was specified, including dyspnoea or cough, or increase in sputum volume or purulence. Niewoehner 1999 and Aaron 2003 used a clinical diagnosis of an exacerbation of COPD without specifying the criteria. Albert 1980; Emerman 1989; Bullard 1996; and Ceviker 2014 specified acute respiratory insufficiency as an inclusion criterion.

Interventions

For studies included in the comparison systemic corticosteroid versus placebo, systemic corticosteroid treatment varied. Two studies used only short intravenous courses (less than four days' length) (Albert 1980; Emerman 1989), four studies used intravenous administration followed by oral treatment (Rostom 1994; Bullard 1996; Niewoehner 1999; Gunen 2007), and two studies used intravenous administration (Alia 2011; Zheng 2011). Among the seven studies using oral corticosteroids throughout treatment, the initial dose of prednisolone used varied from 30 mg to 60 mg fixed dose daily or 1 mg/kg in Abroug 2014, with higher initial doses being tapered in Niewoehner 1999 and Thompson 1996. The length of treatment with oral corticosteroids varied from five to 15 days although Niewoehner 1999 included an arm in which treatment was continued for eight weeks.

Primary outcomes

The primary outcome, treatment failure occurring during the treatment period, met the review definition in a variety of ways during periods varying in length from two to 30 days (Table 2). Five studies used attendance or return to the emergency department or doctor's clinic (Emerman 1989; Bullard 1996; Thompson 1996; Niewoehner 1999; Aaron 2003). Eight studies used deterioration leading to intensification of pharmacological treatment (Thompson 1996; Wood-Baker 1998; Davies 1999; Niewoehner 1999; Maltais 2002; Willaert 2002; de Jong 2007; and Ceviker 2014). Six studies used the requirement for assisted ventilation or ICU admission (Niewoehner 1999; Maltais 2002; Willaert 2002; de Jong 2007; Gunen 2007; and Ceviker 2014).

Relapse occurred at a later time point to treatment failure, after completion of treatment during varied periods of follow-up from one to four months, and was based on treatment for an acute exacerbation in two studies (Davies 1999; Aaron 2003), or hospital re-admission for COPD in four studies (Davies 1999; Niewoehner 1999; de Jong 2007; Ceviker 2014), and hospital admission for which the cause was not specified in three studies (Willaert 2002; Chen 2005; Gunen 2007).

Excluded studies

We excluded 18 studies from this review; reasons for exclusion are shown in the Characteristics of excluded studies table.

Risk of bias in included studies

Full details of our judgements for the included studies, with supporting information for each judgement, can be found in Characteristics of included studies table. A summary of risk of bias across all studies is shown in Figure 2. We rated all studies either low or unclear risk of selection bias. We rated risk of performance bias as either low or unclear in all studies comparing systemic corticosteroid versus placebo, with the exception of Abroug 2014, which was an open-label study without placebo control that we judged at high risk. We judged two of three studies comparing intravenous corticosteroid versus oral corticosteroid at high risk of performance bias. Detection bias was either low or unclear in 19 studies. Attrition bias risk was low in 60% of studies and high in 15% of studies. We rated all studies as either low or unclear risk of reporting bias.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

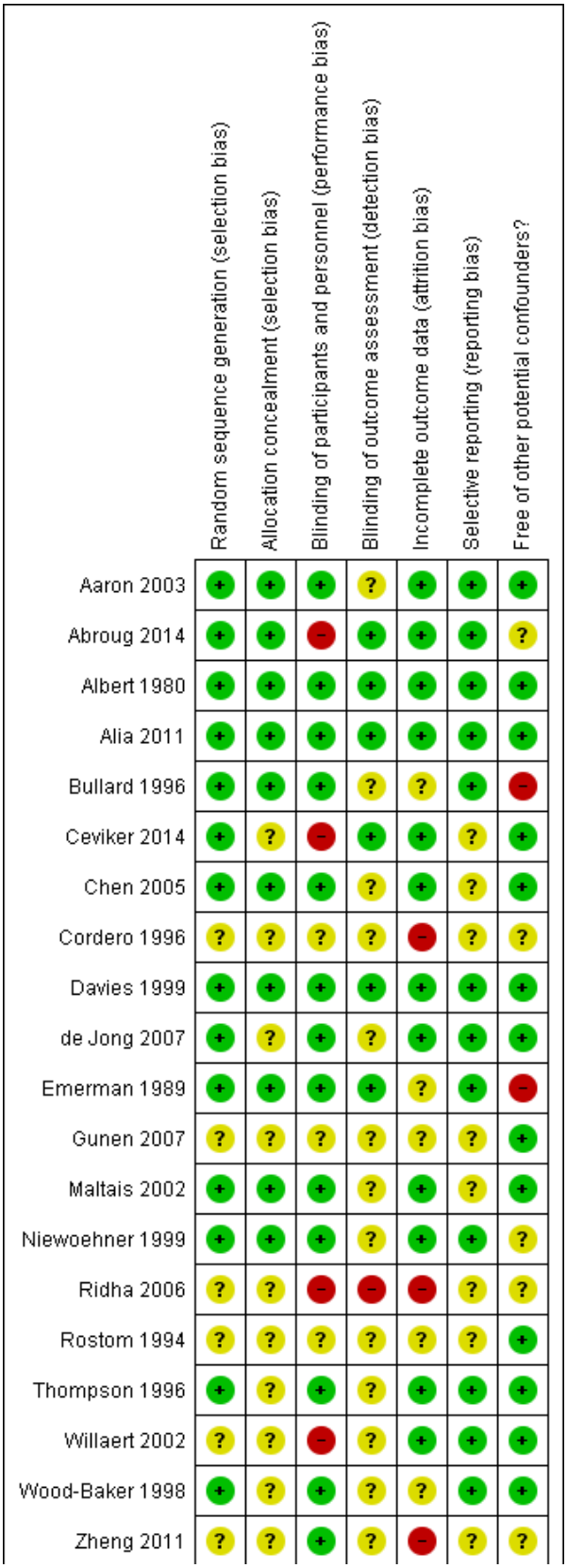


Figure 2. (Continued)

Allocation

All 20 studies were described as randomised; in 14 studies assessment of random sequence generation indicated low risk of bias and in the remaining six studies information was lacking and risk of bias was unclear. In 10 studies, concealment of allocation was assessed at low risk of bias, with lack of information in 10 studies considered at unclear risk.

Blinding

Blinding of participants and treating personnel was adequate with low risk of bias in 13 of 19 studies; in three studies, risk of bias was unclear and we judged four studies at high risk of bias due to lack of blinding (Willaert 2002; Ridha 2006; Ceviker 2014; Abroug 2014). Blinding for outcome assessment indicated low risk of bias in six studies, unclear risk in 13 studies and high risk of bias one study (Ridha 2006).

Incomplete outcome data

We rated 12 studies as low risk of bias due to incomplete outcome data because the number of drop-outs per group was low and even. In five studies, bias risk was unclear and three studies only published as abstracts were rated at high risk (Cordero 1996; Ridha 2006; Zheng 2011).

Selective reporting

We rated 12 studies as low risk of bias due to selective reporting as all likely outcomes were reported. The risk of bias was unclear in eight studies when there was insufficient information.

Effects of interventions

See: **Summary of findings for the main comparison** Systemic corticosteroid compared with placebo for acute exacerbations of COPD; **Summary of findings 2** Treatment route: intravenous corticosteroid compared with oral corticosteroid for acute exacerbations of COPD

Comparison 1: systemic corticosteroid versus placebo

Twelve studies with 1620 participants contribute outcome data for systemic corticosteroids versus placebo (Summary of findings for the main comparison).

Primary outcomes

Treatment failure (Analysis 1.1)

Definition of treatment failure and the time period during which an event occurred varied across studies (Table 2). Systemic corticosteroids reduced the risk of treatment failure by over half when compared with placebo in nine studies (n = 917), of which seven studies contributed data, with median treatment duration of 14 days (OR 0.48; 95% CI 0.35 to 0.67; Analysis 1.1; Figure 3). There was only minor heterogeneity between studies ($Chi^2 = 11.75$; degrees of freedom (df) = 8; P value = 0.16); $I^2 = 32\%$). It would have been necessary to treat nine people (95% CI 7 to 14) with systemic corticosteroids to avoid one treatment failure during the treatment period. The funnel plot did not indicate a strong likelihood of publication bias (Figure 4). We rated the quality of evidence for this outcome as high.

Figure 3.

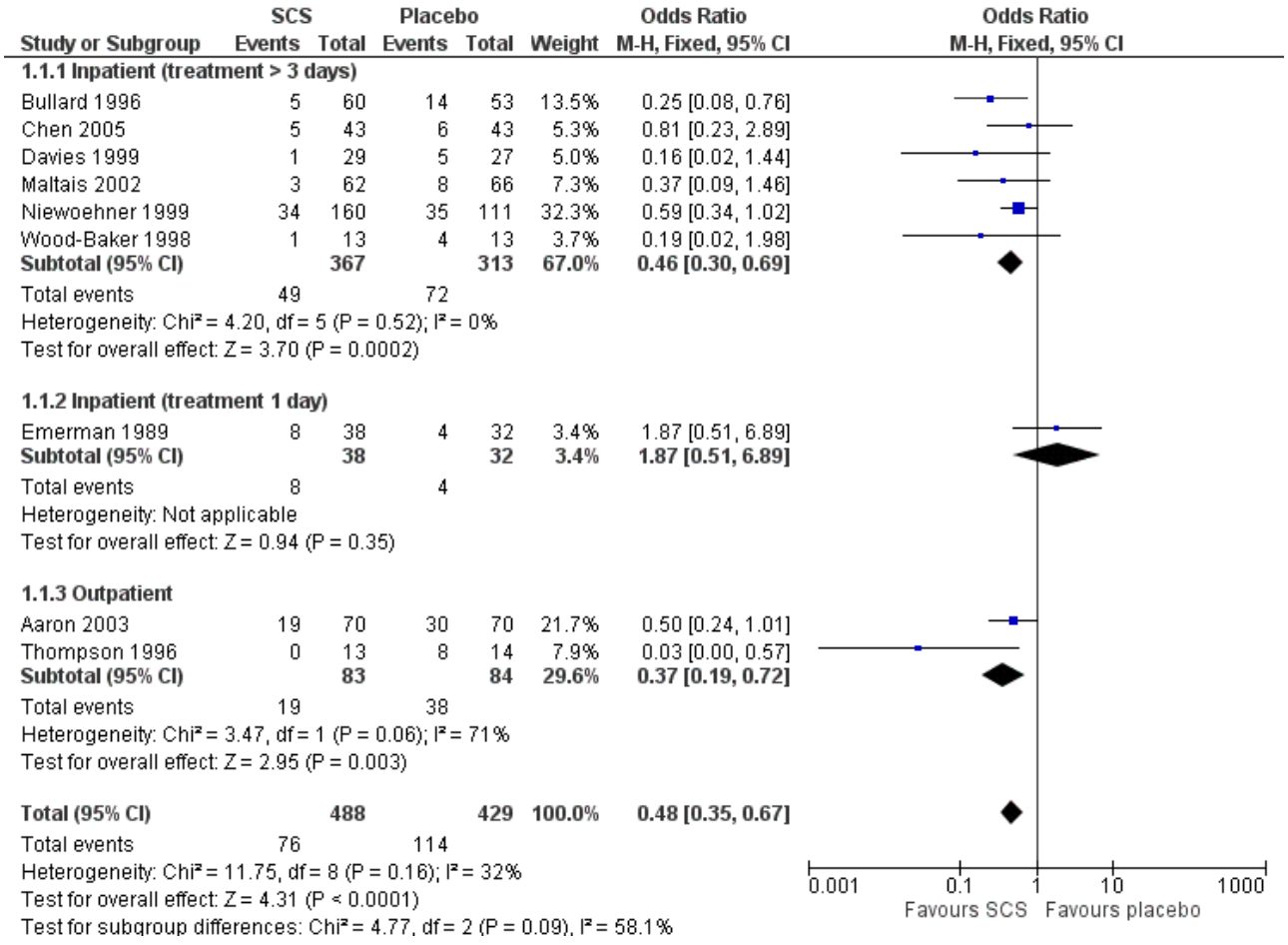
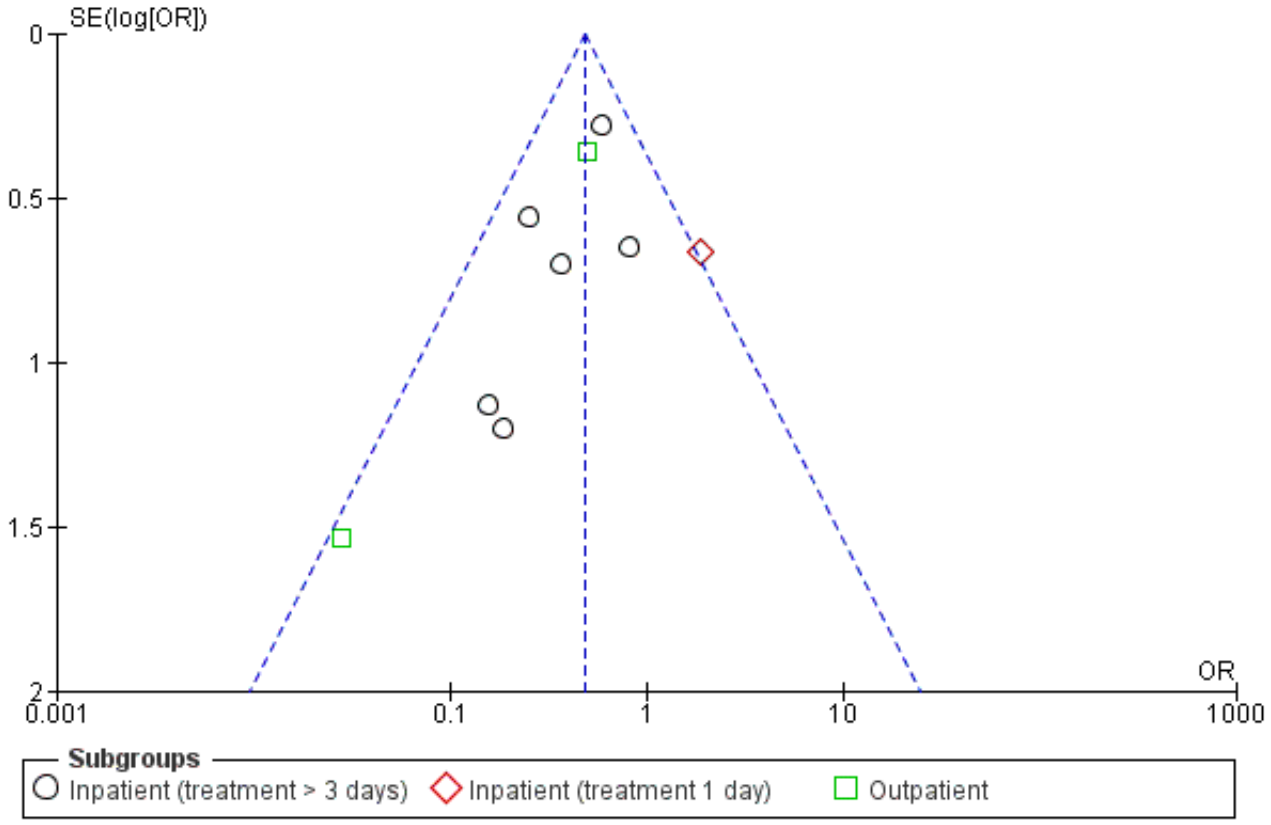


Figure 4.



In subgroup analyses, the reduction in likelihood of treatment failure between seven and 30 days for six inpatient studies (n = 680) with treatment duration greater than three days, was similar to the pooled overall result (OR 0.46; 95% CI 0.30 to 0.69), with no heterogeneity. For two outpatient studies (n = 167), the likelihood of treatment failure between 14 and 30 days with systemic corticosteroid compared with placebo was also lower (OR 0.37; 95% CI 0.19 to 0.72) (Aaron 2003; Thompson 1996. There was substantial heterogeneity in the fixed-effect analysis (Chi^2 = 3.47; df = 1; P value = 0.06; I^2 = 71%). Oral corticosteroid treatment differed in these studies, with the dose used being higher in Thompson 1996.

In the Emerman 1989 study (n = 70), which used a single intravenous dose of systemic corticosteroid and assessed treatment failure over two days, the likelihood of treatment failure was not lower with systemic corticosteroid treatment (OR 1.87; 95% CI 0.51 to 6.89).

When Emerman 1989 was excluded from the meta-analysis, the test for subgroup differences showed no difference between inpatient and outpatient studies (Chi^2 = 0.28, df = 1; P value = 0.59; I^2 = 0%). However, the result with Emerman 1989 included indicated some difference although it was not statistically significant (Chi^2 = 4.77, df = 2; P value = 0.09); I^2 = 58.1%).

Relapse (Analyses 1.2 and 1.3)

The HR for relapse up to 30 days in two large studies (n = 415) showed a significant reduction for treatment with systemic corticosteroid with no heterogeneity (HR 0.78; 95% CI 0.63 to 0.97; Analysis 1.2) (Aaron 2003; Niewoehner 1999). However, the reduced likelihood of relapse on treatment with systemic corticosteroid in five studies (n = 596) over periods of one to four months was not statistically significant with no heterogeneity between studies (OR 0.67; 95% CI 0.42 to 1.07; Analysis 1.3). We rated the quality of evidence for this outcome as moderate, which was downgraded once as wide CI values include significant benefit and harm.

Mortality (Analysis 1.4)

Mortality up to 30 days was not reduced by treatment with systemic corticosteroid compared with placebo in 11 studies (n = 1319; OR 1.00; 95% CI 0.60 to 1.66; Analysis 1.4; Figure 5). There were four subgroups, inpatient studies greater or less than three days' treatment, ICU treatment and outpatient treatment. No heterogeneity was found overall or in any subgroup analysed. The funnel plot did not indicate a strong likelihood of publication bias (Figure 6). We rated the quality of evidence for this outcome as moderate, which was downgraded once as wide CI values include significant benefit and harm.

Figure 5.

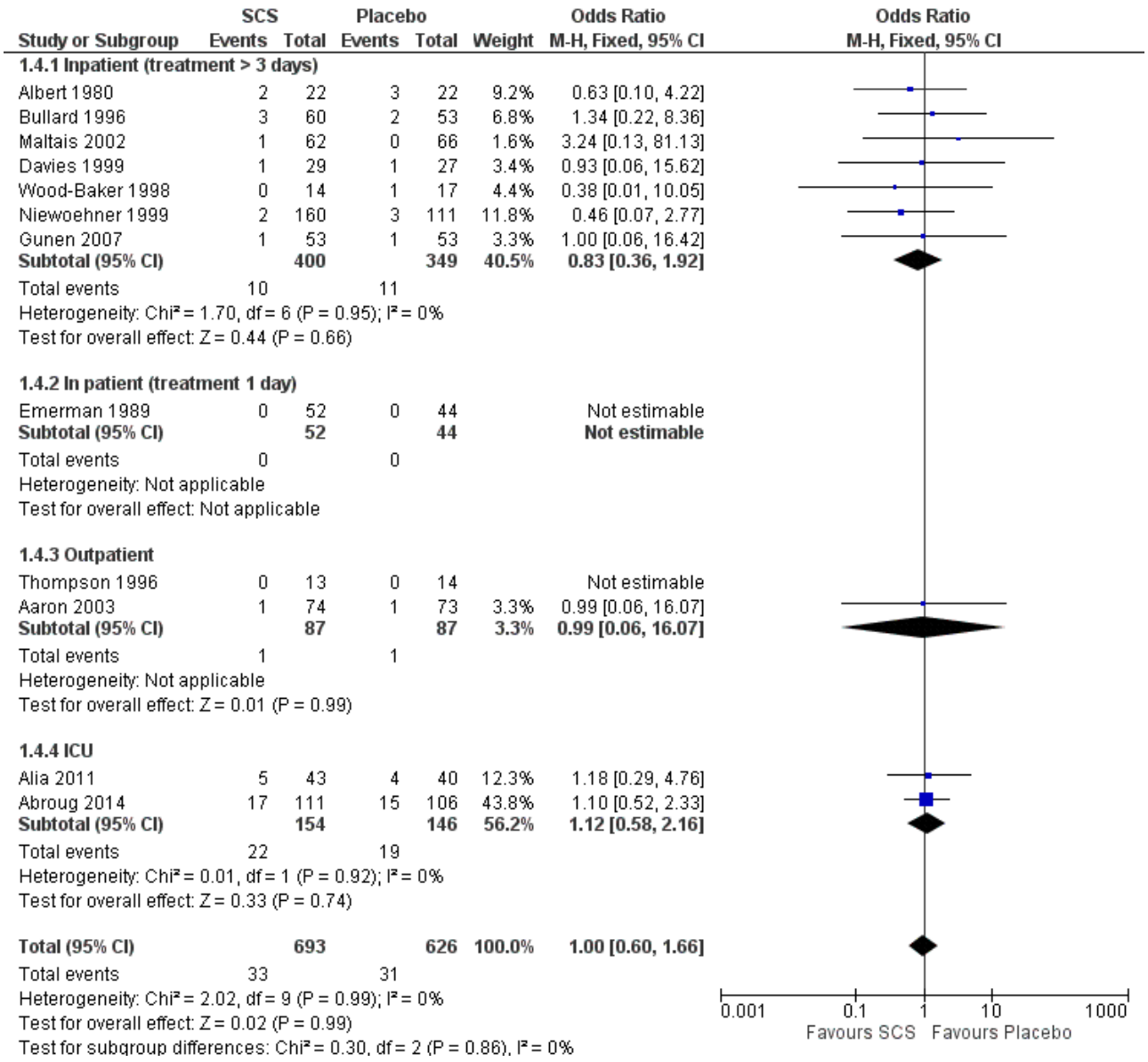
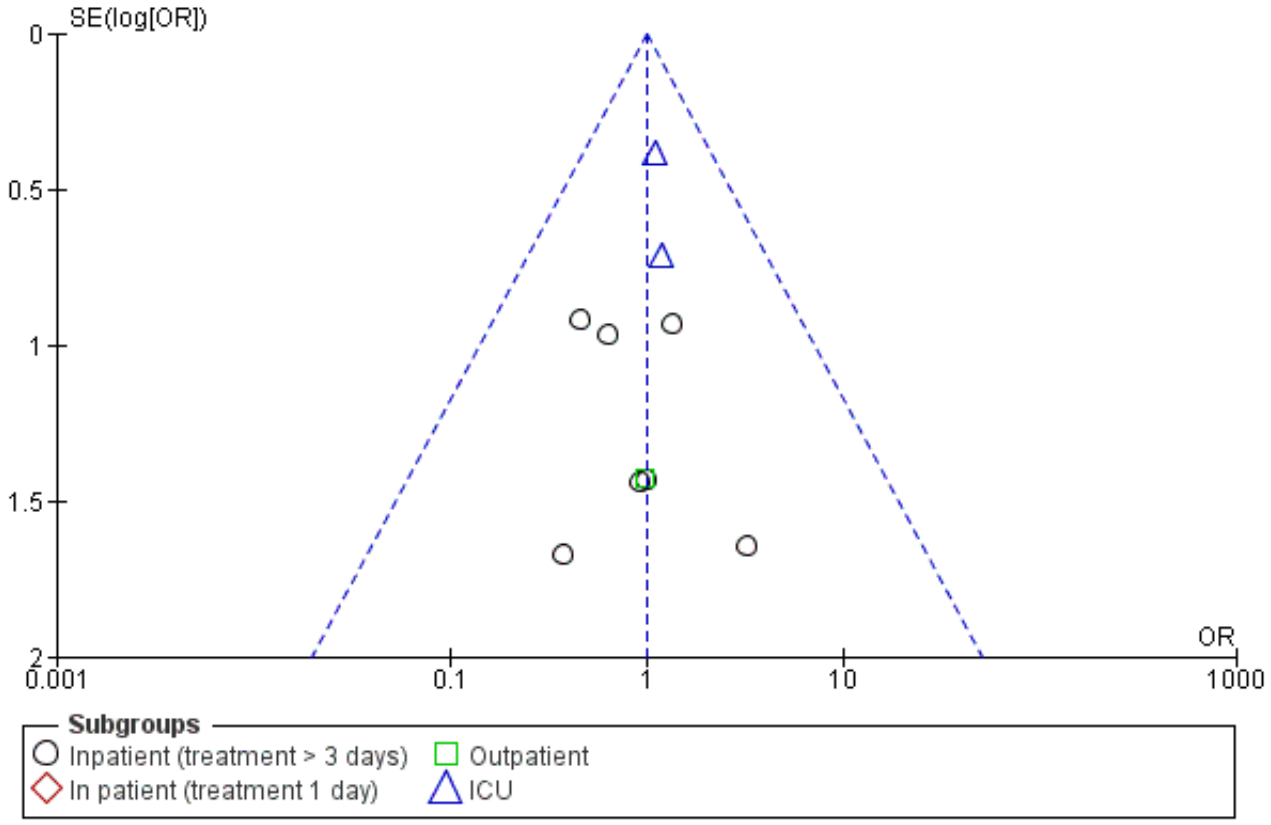


Figure 6.



Early outcomes: 72 hours or less

Lung function (Analyses 1.5 to 1.10)

FEV_1 was significantly increased with corticosteroid treatment in seven studies (n = 649), with no heterogeneity between studies (MD 140 mL; 95% CI 90 to 200; Analysis 1.5). This effect size is thought to be clinically meaningful (Donohue 2005). The FEV_1 per cent predicted was also greater at this time point in three studies, with no significant heterogeneity (n = 231; MD 3.85%; 95% CI 0.18 to 7.52; Chi^2 = 2.62; df = 2; P value = 0.27; I^2 = 24%; Analysis 1.6). There was no increase in FVC with corticosteroid treatment in three studies (n = 123; MD 200 mL; 95% CI -50 to 450). PEF was significantly increased with corticosteroid treatment in two studies with significant heterogeneity (n = 137; MD 22.52 L/minute; 95% CI 5.02 to 40.03; Chi^2 = 4.48, df = 1; P value = 0.03; I^2 = 78%; Analysis 1.10).

Symptom scores (Analysis 1.11)

Breathlessness was assessed using the Borg dyspnoea scale (Maltais 2002), and visual analogue scales (VAS) for overall dyspnoea (Thompson 1996; Wood-Baker 1998), and dyspnoea related to specific activities (talking, dressing, washing, walking) (Wood-Baker 1998). Corticosteroid treatment significantly decreased dyspnoea when results were pooled using the SMD in three studies, with some heterogeneity that might not be important (n = 178; SMD 0.35; 95% CI 0.05 to 0.64; Chi^2 = 2.89; df = 2; P value = 0.24; I^2 = 31%; Analysis 1.11). This equates to an effect size on the Borg scale of 0.93 units (95% CI 0.18 to 1.7) or on the VAS scale of 5.24 (95% CI 0.75 to 9.59). The effect sizes are less than the suggested minimal clinically important differences of 2 units for the Borg scale and 10 units for the VAS (Ries 2005). We rated the quality of evidence for this outcome as moderate, being downgraded once as the upper CI crossed an effect size of 0.5.

Arterial blood gas measurements (Analyses 1.12 and 1.13)

Conditions for measurement of ABGs varied across studies. In Thompson 1996 and Gunen 2007, ABGs were measured while breathing room air at rest and, in Maltais 2002, conditions were variable, with some participants using supplementary oxygen and some breathing room air. Corticosteroid treatment compared with placebo significantly increased arterial oxygenation in three studies, with no heterogeneity (n = 233; PaO_2 MD 3.71 mmHg; 95% CI 0.55 to 6.88; Analysis 1.12). In these three studies of inpatients and one study in ICU (Alia 2011), $PaCO_2$ was decreased with corticosteroid treatment compared with placebo, with moderate heterogeneity between studies in different settings (n = 316; MD -2.21 mmHg; 95% CI -3.84 to -0.58; Chi^2 = 7.23, df = 3; P value = 0.06; I^2 = 58%; Analysis 1.13).

Late outcomes: end of treatment

Lung function (Analyses 1.14 to 1.18)

FEV_1 was not significantly increased with corticosteroid treatment compared with placebo in seven studies (n = 669; MD 90 mL; 95% CI -10 to 190; Analysis 1.14). There was little heterogeneity between inpatient studies (Chi^2 = 6.21, df = 4; P value = 0.18; I^2 = 36%) and

moderate heterogeneity in pooled inpatient and outpatient studies (Chi^2 = 11.28; df = 6; P value = 0.08; I^2 = 47%). There was an increase in FEV_1 per cent predicted in two studies with corticosteroid treatment, with no significant heterogeneity (n = 129; MD 6.14; 95% CI 1.32 to 10.96; Analysis 1.15). PEF improved with corticosteroid treatment in two studies, with moderate heterogeneity (n = 112; MD 119.06 L/minute; 95% CI 64.39 to 173.73; Chi^2 = 2.27; df = 1; P value = 0.13; I^2 = 56%; Analysis 1.19). There was no increase in FVC, FVC per cent predicted or the ratio of FEV_1/FVC with corticosteroid treatment compared with placebo at the end of treatment.

Symptom scores (Analyses 1.20 to 1.22)

Dyspnoea was measured using the transitional dyspnoea index (Aaron 2003), with a positive score indicating improvement and a change of one unit considered clinically significant (Mahler 1984). There was a significant benefit with corticosteroid treatment in Aaron 2003 (effect size MD 1.88 units; 95% CI 0.23 to 3.53; Analysis 1.20). VAS symptom scores were reported by Wood-Baker 1998; Davies 1999; and Chen 2005. The improvement in dyspnoea with corticosteroid treatment in four studies was not significant, with no heterogeneity (n = 301; SMD 0.18; 95% CI -0.05 to 0.41; Analysis 1.22).

Arterial blood gas measurements (Analyses 1.23 and 1.24)

Corticosteroid treatment significantly improved PaO_2 compared with placebo in four inpatient studies, with no heterogeneity between studies (n = 200; PaO_2 MD 6.86 mmHg; 95% CI 2.75 to 10.96; Analysis 1.23). There was no significant decrease in $PaCO_2$ with corticosteroid treatment in three studies, with moderate heterogeneity: (n = 188; MD -1.81 mmHg; 95% CI -5.06 to 1.44; Chi^2 = 4.89; df = 2; P value = 0.09; I^2 = 59%; Analysis 1.24).

Health-related quality of life (Analysis 1.25)

Only Aaron 2003 (n = 147) reported data on quality of life with the total Chronic Respiratory Disease index and did not find a significant improvement with corticosteroid treatment after 10 days.

Functional capacity (Analysis 1.26)

Wood-Baker 1998 reported data on six-minute walk tests in 18 participants at 14 days and found no improvement with corticosteroid treatment (Wise 2005).

Length of stay and duration of ventilation (Analyses 1.27 and 1.28)

There was substantial heterogeneity in the outcome 'length of stay' between studies in a general inpatient setting versus an ICU setting for people who required assisted ventilation. The test for subgroup differences was significant (P value = 0.04; I^2 = 75.4%) and we decided not to pool the subgroups. In the general inpatient setting, there was a shorter duration of hospital stay for corticosteroid treatment compared with placebo in two studies, with no heterogeneity (n = 296; MD -1.22 days; 95% CI -2.26 to -0.18). Davies 1999 also reported a lower median stay of seven days for corticosteroid treatment and nine days for placebo, while in Maltais 2002, the corticosteroid treatment group median length of stay was six days and eight days for placebo. We rated the quality of evidence for this outcome as high. However, in the ICU setting for people requiring assisted ventilation, there was no difference in length of ICU stay for corticosteroid treatment compared with control, with moderate heterogeneity (n=300; MD 0.65 days; 95% CI -0.84 to 2.15; P value = 0.17; I^2 = 46%; Analysis 1.27).

The duration of assisted ventilation in two studies in an ICU setting was not significantly reduced with corticosteroid treatment compared with control (n = 300; MD -1.03 days; 95% CI -3.44 to 1.38).

Adverse effects (Analyses 1.29 to 1.41)

An adverse drug reaction was more than twice as likely with corticosteroid treatment compared with placebo in eight studies (n = 736; OR 2.33; 95% CI 1.59 to 3.43; Analysis 1.29). Overall, one extra adverse effect occurred for every six people treated (95% CI 4 to 10). Six studies reported data specifically on hyperglycaemia (Davies 1999; Niewoehner 1999; Maltais 2002; Aaron 2003; Alia 2011; Abroug 2014). There was an increased likelihood of hyperglycaemia with corticosteroid compared with placebo treatment, with no significant heterogeneity (n = 804; OR 2.79; 95% CI 1.86 to 4.19; P value = 0.25; I^2 = 24%; Analysis 1.30). Overall, one extra participant developed hyperglycaemia for every seven treated with systemic corticosteroids (95% CI 5 to 12). We rated the quality of evidence for this outcome as high.

The risk of hypertension did not differ with corticosteroid treatment compared with placebo in two studies in inpatients and ICU, although there was moderate heterogeneity (n = 274; OR 1.20; 95% CI 0.44 to 3.25; Chi^2 = 2.06; df = 1; P value = 0.15; I^2 = 51%; Analysis 1.31). The risk of gastrointestinal bleeding did not differ with corticosteroid treatment compared with placebo in two studies in ICU (n = 300; OR 0.93; 95% CI 0.12 to 6.91; Analysis 1.32).

In the ICU-based studies of Alia 2011 and Abroug 2014, there was no increased likelihood of ventilator-associated pneumonia with corticosteroid treatment (n = 300; OR 1.23; 95% CI 0.44 to 3.40).

There was a non-significant two-fold increase in likelihood of an adverse psychiatric event with corticosteroid treatment compared with placebo in two studies (n = 331; OR 2.15; 95% CI 0.95 to 4.88; Analysis 1.37).

The outpatient study of Aaron 2003 and the inpatient study of Niewoehner 1999 reported incidences of other specific adverse effects. In single studies, there were significantly increased risks of weight gain and insomnia with corticosteroid treatment compared with placebo. In these studies, there were no significantly increased risks with corticosteroid treatment compare with placebo for anxiety, depression, dyspepsia, delirium or secondary infection.

Comparison 2: intravenous corticosteroid versus oral corticosteroid

Three studies with 298 participants contributed outcome data for intravenous corticosteroids versus oral corticosteroids (see Summary of findings 2).

Primary outcomes

Treatment failure (Analysis 2.1)

There was no significant reduction in risk of treatment failure with intravenous corticosteroid treatment and oral corticosteroid treatment in three studies in inpatients, with no heterogeneity (n = 298; OR 0.67; 95% CI 0.34 to 1.30; Analysis 2.1). We rated the quality of evidence for this outcome as moderate, being downgraded once as wide CI values included significant benefit and harm.

Relapse (Analysis 2.2)

The odds of relapse after completion of treatment was not significantly reduced by treatment with intravenous corticosteroid compared with oral corticosteroid in three studies, with no heterogeneity between studies (n = 298; OR 0.95; 95% CI 0.50 to 1.80; Analysis 2.2). We rated the quality of evidence for this outcome as moderate, being downgraded once as wide CI values included significant benefit and harm.

Mortality (Analysis 2.3)

Mortality after discharge between one and three months was not reduced by treatment with intravenous corticosteroid compared with oral corticosteroid in three studies, with no significant heterogeneity (n = 298; OR 1.40; 95% CI 0.44 to 4.51; Chi^2 = 2.41; df = 2; P value = 0.30; I^2 = 17%; Analysis 2.3). We rated the quality of evidence for this outcome as moderate, being downgraded once as wide CI values included significant benefit and harm.

Early outcomes: 72 hours or less

Lung function (Analyses 2.4 and 2.5)

Only one study reported lung function measures at the early time point, and neither FEV_1 nor FVC was significantly increased with intravenous corticosteroid treatment compared with oral corticosteroid.

Symptom scores (Analyses 2.5 to 2.8)

Dyspnoea was not significantly decreased with intravenous corticosteroid treatment compared with oral corticosteroid in two inpatient studies using a VAS measure, with no heterogeneity (n = 75; MD 0.62; 95% CI -0.55 to 1.78; Analysis 2.6). We rated the quality of evidence for this outcome as low, being downgraded twice as wide CI values included significant benefit and harm and participants and physicians were not blinded to treatment in the two studies. In one single study (n = 38), there were no differences in VAS scores for cough or sputum volume.

Late outcomes: end of treatment

Lung function (Analyses 2.9 to 2.11)

FEV_1 did not differ significantly at the end of treatment with intravenous corticosteroid compared with oral corticosteroid treatment in three studies, with no heterogeneity present (n = 285; MD -20 mL; 95% CI -80 to 30; Analysis 2.9). There was no difference in FVC in two studies with intravenous corticosteroid compared with oral corticosteroid treatment, with no heterogeneity present (n = 75; MD -50 mL; 95% CI -33 to 22; Analysis 2.10).

Symptom scores (Analyses 2.12 to 2.14)

Dyspnoea was not significantly improved with intravenous corticosteroid treatment compared with oral corticosteroid in two inpatient studies using a VAS measure, with no heterogeneity (n = 75; MD 1.28; 95% CI -0.24 to 2.80; Analysis 2.12), and in one single study (n = 38) there were no differences in VAS scores for cough or sputum volume.

Arterial blood gas measurements (Analyses 2.15 and 2.16)

There were no significant differences in between intravenous corticosteroid compared with oral corticosteroid treatment in a single study in PaO_2 (n = 38; MD -1.20 mmHg; 95% CI -8.61 to 6.21; Analysis 2.15) or $PaCO_2$ (MD 5.50 mmHg; 95% CI -0.79 to 11.79; Analysis 2.16).

Health status and quality of life (Analyses 2.17 to 2.22)

The Clinical COPD Questionnaire (CCQ) measuring health status (symptoms, functional state and mental state) and the St George's Hospital Respiratory Questionnaire (SGRQ) measuring respiratory-related QoL were reported in one study (n = 210), with no differences between intravenous corticosteroid and oral corticosteroid treatment found for either measure after one week (n = 210; CCQ: MD 0.10; 95% CI -0.17 to 0.37; Analysis 2.17; SGRQ: MD -0.70; 95% CI -4.33 to 2.93; Analysis 2.18). There were no differences in the Dyspnoea, Fatigue, Mastery or Emotion domains of the Chronic Respiratory Questionnaire (CRQ) between intravenous corticosteroid and oral corticosteroid treatment in one study (n = 21) after four weeks.

Length of stay (Analysis 2.23)

There was a non-significant increase in duration of hospital stay for intravenous corticosteroid compared with oral corticosteroid treatment in three studies, with no significant heterogeneity (n = 298; MD 1.54 days; 95% CI -0.09 to 3.17; Chi^2 = 2.93; df = 2; P value = 0.23; I^2 = 32%; Analysis 2.23). We rated the quality of evidence for this outcome as low, being downgraded twice as wide CI values included significant benefit and harm and participants and physicians were not blinded to treatment in the two studies.

Adverse events (Analyses 2.24 and 2.25)

In one single inpatient study, there was an increased likelihood of hyperglycaemia with intravenous corticosteroid compared with oral corticosteroid treatment (n = 40; OR 4.89; 95% CI 1.20 to 19.94; Analysis 2.24) (Ceviker 2014). We rated the quality of evidence for this outcome as moderate, being downgraded once for indirectness based on a single study. The risk of hypertension was not significantly increased in this study (OR 8.20; 95% CI 0.40 to 169.90; Analysis 2.25).

DISCUSSION

Summary of main results

This updated review addressed the use of systemic corticosteroid (oral or parenteral) in the treatment of acute exacerbations of COPD. The review included 16 studies with 1787 participants, mostly conducted with inpatients, that compared systemic corticosteroid with placebo and four studies with 298 inpatients comparing parenteral corticosteroid versus oral corticosteroid.

Systemic corticosteroid treatment compared with placebo significantly decreased treatment failure up to one month and relapse after treatment for inpatients and outpatients, and improved lung function (FEV_1, per cent predicted FEV_1, PEF), symptoms of breathlessness and blood gases (PaO_2, $PaCO_2$) within three days. At the end of treatment, systemic corticosteroid treatment compared with placebo significantly improved some lung function measures (per cent predicted FEV_1, PEF) and blood gases (PaO_2) and reduced the length of hospital stay by around one to two days in people who did not require treatment with assisted ventilation in an ICU. In terms of adverse events, no significant difference was observed in rates of mortality up to one month

but there was at least a two-fold increase in adverse drug effects, especially for hyperglycaemia, which showed a four-fold increase.

Parenteral corticosteroid treatment compared with oral corticosteroid treatment did not significantly decrease treatment failure, or improve lung function, QoL, respiratory symptoms or blood gases. There was no significant difference in the rate of mortality between one and three months of follow-up but parenteral corticosteroid treatment was associated with a significantly increased rate of the adverse drug effect hyperglycaemia compared with oral treatment.

Overall completeness and applicability of evidence

The criteria for an acute exacerbation were explicit in most studies, either an increase in respiratory symptoms or respiratory insufficiency. Most studies used accepted criteria for COPD diagnosis. There was imbalance in the gender ratio of participants in the included studies, ranging from 52% to 100% males. This reflects the historically higher incidence of COPD in men; however, the increasing smoking rates among women means that the incidence of COPD is increasing in women (Chapman 2001). There seems to be no good reason to expect a different response to treatment in women based on studies in asthma and corticosteroid use, so the findings are applicable to all people with COPD.

Most studies explicitly excluded participants with asthma, as is generally the case in efficacy studies in COPD. However, excluding participants with a history of asthma excludes a population with increased risk of developing COPD. There is an association between fixed airflow obstruction in adults aged 40 to 44 years and early-onset current clinical asthma, equivalent to a 33 pack-year history of smoking (OR 3.7; 95% CI 1.5 to 9.3) (Perret 2013). This may limit the generalisability of the findings.

The current review expanded and updated a previous version of the review that excluded people requiring assisted ventilation treated in ICU and additionally compared the route of delivery of systemic corticosteroid, parenteral or oral. The decision to treat an acute exacerbation of COPD at home or admit for inpatient treatment is related to clinical assessment of severity of the person's condition. The findings of this review may be generalisable to both outpatient and inpatient settings and thus to exacerbations of a range of severity. Two studies of inpatients requiring assisted ventilation in ICU contributed data. We did not pool data on length of stay in participants who required assisted ventilation in ICU with data from studies in the general hospital setting.

Randomised trials in this review do not provide data on the use of repeated treatment with systemic corticosteroid in people with COPD and we were unable to perform subgroup analysis by frequency and severity of exacerbations.

The sensitivity analysis removing studies in which a significant proportion of participants were crossed over to active treatment (i.e. Emerman 1989; Bullard 1996), gave results that were very similar to those of the original pooled analysis for treatment failure, mortality and lung function.

Quality of the evidence

The methodological quality of the included trials that contributed data was good, and the three conference abstracts of unknown quality did not contribute any data to the analysis. In the comparison of systemic corticosteroid and placebo treatment, only one study was not double blind. This study contributed to analysis of objectively measured outcomes and results were unlikely to be compromised by detection or performance biases. Two studies comparing routes of administration of systemic corticosteroid were not double blind, and results for objective outcomes such as mortality were unlikely to be compromised by detection or performance biases. The evidence for symptoms and duration of hospitalisation was downgraded for possible detection or performance bias. The studies judged at high risk of attrition bias did not contribute data to any analyses.

Potential biases in the review process

Review authors made every effort to identify all relevant published and unpublished studies by using additional methods to identify studies that might not have been found in the main electronic search (e.g. searching drug company databases and clinical trial registration sites, checking reference lists). We did not routinely contact individual trial authors for additional data unless outcomes were clearly selectively reported. All authors adhered to the most recent best practice guidelines in terms of study selection, resolution of disagreements, data extraction and analysis to reduce bias and errors.

Agreements and disagreements with other studies or reviews

The results of one cohort study, conducted at 414 US hospitals in 2006 to 2007 in a non-intensive care setting, showed oral corticosteroid treatment for acute exacerbations of COPD was not associated with worse outcomes than when high-dose intravenous corticosteroid treatment was given during the first two hospital days (Lindenauer 2010). Another Cochrane review comparing systemic corticosteroid treatment for seven days or less with longer treatment in acute exacerbations of COPD concluded there were insufficient data to base firm conclusions on the optimal duration of corticosteroid therapy (Walters 2011).

AUTHORS' CONCLUSIONS

Implications for practice

This updated review and meta-analysis provide high-quality evidence to support the use of systemic corticosteroid by the oral or parenteral route for exacerbations of chronic obstructive pulmonary disease (COPD). Treatment reduces the likelihood of treatment failure, shortens hospital stay when assisted ventilation is not required, and improves lung function and symptoms. There is no evidence that corticosteroid administration by a parenteral route is more effective than oral treatment. There is an increase in adverse drug effects with corticosteroid treatment, which is greater with parenteral administration compared with oral treatment. The specific adverse drug effects are known pharmacological effects of corticosteroids and are unlikely to persist after treatment ceases.

Implications for research

Future studies of systemic corticosteroid use for exacerbation of COPD should report results for participants by previous exacerbation frequency to enable assessment of repeated systemic corticosteroid treatment. There is a need for more studies in severe exacerbations of COPD in people who require assisted ventilation. Data for cost-effectiveness comparisons should be collected.

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Wood-Baker R, Walters E, Gibson P. Oral corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2001, Issue 1. [DOI: 10.1002/14651858.CD001288]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aaron 2003

Methods	Design: parallel group Duration: treatment for 10 days Setting: ED of 10 participating hospitals in Canada
Participants	Number screened: 1087 of which 202 eligible

Aaron 2003 *(Continued)*

	Number randomised: 147 (74 prednisone/2 withdrew, 2 hospitalised; 73 placebo/1 withdrew, 1 hospitalised, 1 lost to follow-up) Number completed: 140 evaluated at 30 days Baseline details: Mean age (years): prednisone group: 68.9 ± 11.2; placebo group: 69.9 ± 10.4 Gender: M = 84, F = 63 Diagnosis COPD: evidence of irreversible airflow obstruction in the ED, with $FEV_1/FVC < 0.70$, an $FEV_1 <$ 70% predicted value, post-bronchodilator improvement in FEV_1 of < 20% AE criteria: clinical diagnosis of recent exacerbation of COPD Inclusion criteria: age > 35 years; 15 pack-years' smoking history; evidence of irreversible airflow obstruction in the ED, with $FEV_1/FVC < 0.70$, an $FEV_1 <$ 70% predicted value, post-bronchodilator improvement in FEV_1 of < 20% Exclusion criteria: subsequent admission to hospital from ED; diagnosis of asthma or atopy; use of oral or IV corticosteroids within the preceding 30 days; received oral or IV corticosteroids in the ED; findings on chest radiography consistent with the presence of pneumonia or congestive heart failure; adverse reactions to oral corticosteroids; severe uncontrolled diabetes mellitus or renal, hepatic or cardiac failure
Interventions	Experimental: prednisone 40 mg capsule (oral admin), once daily for 10 days (10D SS course) Control: matched placebo, identical in taste and appearance once daily for 10 days Co-interventions: trimethoprim 160 mg with sulphamethoxazole 800 mg twice daily or if allergic doxycycline 100 mg twice daily. Inhaled albuterol and inhaled ipratropium bromide Confounders: inhaled corticosteroids and all other medications used by the participants at the time of enrolment were continued throughout the study in both groups
Outcomes	Primary outcome: treatment failure defined as an unscheduled visit to a doctor's clinic or a return to the ED because of worsening dyspnoea within 30 days after randomisation Secondary outcomes: change from day 1 to day 10 in FEV_1, severity of dyspnoea and disease-specific QoL Measurement: treatment failure participants assessed 3, 10 and 30 days after randomisation. Secondary outcomes assessed on days 1 and 10. Analysed: relapse rates, FEV_1 (post-bronchodilator measurements), severity of dyspnoea (transitional dyspnoea index), disease-specific QoL (Chronic Respiratory Disease Index Questionnaire); adverse effects of prednisone Reported: hyperglycaemia as an adverse effect Mortality: 2 in prednisone group, 1 in placebo group Adverse effects: increased appetite, weight gain, insomnia, hyperglycaemia (subjectively reported but not objectively measured as not part of protocol)
Notes	Likelihood of COPD: age > 35 years, > 15 pack-years' smoking history, diagnosis of asthma exclusion, evidence of fixed airflow obstruction at presentation Funding: grants from the Canadian Institutes of Health Research (MCT-41545), the Ontario Ministry of Health Emergency Health Services Research Advisory Committee (13098), the Ontario Thoracic Society and the Canadian Institute of Health Research 21st Century Chairs Program (to Dr. Rowe). Authors declared previous support from pharmaceutical companies; no notable conflict

Risk of bias

Bias	Authors' judgement	Support for judgement

Aaron 2003 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random listing of the 2 treatment assignments blocked in groups of 4 and stratified according to the ED
Allocation concealment (selection bias)	Low risk	Central allocation of a randomisation schedule prepared through a computer-generated random listing of the 2 treatment assignments blocked in groups of 4 and stratified according to the ED. Randomisation occurred at the time of discharge from the ED. Neither research staff nor participants were aware of the treatment assignment before randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither research staff nor participants were aware of the treatment assignment before or after randomisation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals accounted for with reasons, 4 in each group
Selective reporting (reporting bias)	Low risk	Outcomes in methods all reported
Free of other potential confounders?	Low risk	Inhaled corticosteroids and all other medications used by the participants at the time of enrolment were continued throughout the study in both groups. Characteristics of both groups were similar at baseline

Abroug 2014

Methods	Design: parallel group open-label randomised study Duration: conducted 2008-2011 Setting: ICU in 2 tertiary teaching hospitals: CHU Fattouma Bourguiba, Monastir and CHU Tahar Sfar, Mahdia, affiliated with the University of Monastir, Tunisia
Participants	Number screened: 518 Number randomised: 217, 111 prednisone, 106 control Number completed: 217 Baseline details: Age median (IQR) (years): prednisone 70 (63-75), control 68 (63-75) Gender: prednisone M = 99, F = 12; control M = 92, F = 14 Baseline FEV_1 median (IQR) (L): prednisone 0.82 (0.59-1.12), control 0.75 (0.57-0.95) GOLD stage COPD: prednisone stage III = 30% stage IV = 70%; control stage III = 27%, stage IV = 73% LTOT: prednisone 72%, control 67% Diagnosis COPD: airflow obstruction post-bronchodilator ratio $FEV_1/FVC < 0.7$, previously documented or present on discharge from ICU

Abroug 2014 *(Continued)*

	AE criteria: change in participant's baseline dyspnoea, cough or sputum (or both) requiring a change in regular medication with acute respiratory failure defined by severe hypoxaemia PaO_2 < 60 mmHg or arterial oxygen saturation < 90% on room air associated with hypercapnia (or both), $PaCO_2$ ≥ 45 mmHg associated with pH ≤ 7.35 and clinical signs of excessive respiratory muscle activity (contraction of accessory respiratory muscles and respiration rate ≥ 25 breaths/minute) Inclusion criteria: all participants aged > 40 years, ≥ 10 pack-years' smoking history, with known or strongly suspected COPD admitted to participating ICU for AE COPD with hypercapnic acute respiratory failure requiring ventilatory support Exclusion criteria: evidence of pneumonia, treated for COPD, people with asthma defined by a reversible obstructive disease following nebulised bronchodilators, uncontrolled left heart failure, systemic corticosteroids for exacerbation within 30 days prior to screening, absolute contraindication to corticosteroids (active gastroduodenal ulcer, severe uncontrolled sepsis, hepatitis or other active viral disease or neuromuscular disease (or both))
Interventions	Experimental: oral prednisone 1 mg/kg daily either until discharge or for a maximum of 10 days, median duration 8 days (IQR 5-10) Control: usual care (undefined) Co-interventions: all included participants received ventilatory support (NIV or conventional) prednisone NIV 76%, conventional 24%: control NIV 76%, conventional 24% Nebulised beta2-agonists (terbutaline, 5 mg every 6 hours) and ipratropium bromide (0.5 mg every 8 hours) Antibiotics prescribed at discretion of physician in charge: prednisone 82%, control 79%. Treatment period: up to 10 days Follow-up period: maximum 30 days
Outcomes	Primary outcome: ICU mortality Secondary outcomes: duration of ventilator support (sum of conventional and NIV if ventilated with both); length of ICU stay; rate of NIV failure (intubation rate in participants managed initially with NIV); corticosteroidal complications: occurrence of secondary infections, hyperglycaemic episodes necessitating initiation of insulin therapy (corresponding to a blood glucose level ≥180 mg/dL in participants without pre-existing diabetes) or increase in initial insulin therapy, ICU-acquired muscular weakness, or significant gastrointestinal bleeding inducing a fall in the haemoglobin level ≥ 2 g/dL
Notes	Trial registration: Clinicaltrials.gov/NCT01353235. Date of registration 17 May 2011 Protocol: not available. Trial approved by the ethics committee of both centres. Sample size target 300, but study was ended before completion of the planned sample size because of the slow inclusion rate Length of stay and duration of mechanical ventilation published as median and IQR. Mean and SD assumptions based on *Cochrane Handbook for Systematic Reviews of Interventions* Section 7.7.3.5. The width of the IQR is approximately 1.35 SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed at each centre by a random number table, and was stratified according to the type of mechanical ventilation (either conventional or NIV)

Abroug 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	Participants were randomised (by means of sealed envelopes that were opened sequentially)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study, control group received usual care, no placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label study, control group received usual care. Outcomes of mortality and duration of ICU stay were objective endpoints
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomised were included in outcome measures
Selective reporting (reporting bias)	Low risk	All outcomes listed in methods and trial registration were reported
Free of other potential confounders?	Unclear risk	Study halted early because of the slow inclusion rate

Albert 1980

Methods	Design: parallel group Setting: people with chronic airflow limitation hospitalised due to acute respiratory insufficiency from acute and chronic bronchitis, Veterans Hospital, Washington, USA Duration: treatment for 72 hours
Participants	Number screened: 45 Number randomised: 44 Number completed: 40 Baseline details: Mean age (years): 61.5 Gender: M = 44, F = 0 Diagnosis COPD: chronic bronchitis defined as cough and sputum production most days for at least 3 months of the 2 previous years, chronic airflow obstruction -FEV_1 < 60% predicted or FEV_1/FVC < 60% AE criteria: hospitalised with acute respiratory insufficiency, acute bronchitis defined as an increase in cough and sputum production within 5 days Inclusion criteria: acute respiratory insufficiency, PaO_2 < 65 mmHg on room air (after correcting for hyperventilation) or $PaCO_2$ > 50 mmHg with pH < 7.35 or alveolar-arterial oxygen difference > 10 mmHg above that within the previous 2 years; chronic bronchitis defined as cough and sputum production most days for at least 3 months of the 2 previous years; FEV_1 < 60% predicted or FEV_1/FVC < 60% Exclusion criteria: personal or family history of asthma, increase in FEV_1 of > 30% after inhaled bronchodilator when clinically stable; history of eczema or allergic rhinitis, consolidation on admission chest X-ray, corticosteroid therapy within the last 30 days

Albert 1980 *(Continued)*

Interventions	Experimental: methylprednisolone (Upjohn) 0.5 mg/kg, IV, 6 hourly, for 72 hours (3D Systemic Steroid course) Control: matched placebo, IV, 6 hourly, for 72 hours Co-interventions: IV aminophylline, inhaled isoproterenol, IV ampicillin or oral tetracycline, supplemental oxygen to maintain SaO_2 above 85%
Outcomes	Analysed: pre- and post-bronchodilator bedside spirometry. Reported: ABG, serum theophylline concentration, blood glucose concentration Mortality: 2 participants in the corticosteroid group (at 30 hours and 9 days) Morbidity: experimental group; psychosis (n = 1), gastrointestinal bleed (n = 1). Control group; dermatitis (n = 1), pneumonia (n = 1), gastrointestinal bleed (n = 1) In comparison of treatments, the post-bronchodilator spirometric measurements at 72 hours were used for analysis. The spirometric measurements were estimated from the baseline values and graphical changes at 72 hours. The baseline SD was used for all time points
Notes	Likelihood of COPD: no age limitations, no smoking history required, history of asthma exclusion, airflow obstruction previously or 1 month after acute presentation Funding: no external sources declared. In-house study assistance from the Veterans Administration Hospital, Washington

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by table of random numbers using 20 subject blocks. Participants allocated to consecutive numbers
Allocation concealment (selection bias)	Low risk	Randomisation by table of random numbers using 20 subject blocks
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants, investigators, respiratory therapists and other hospital personnel were unaware of allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, respiratory therapists and other hospital personnel were unaware of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant was not randomised. Data from 2 participants in the placebo group were not analysed
Selective reporting (reporting bias)	Low risk	Outcomes listed in methods are reported
Free of other potential confounders?	Low risk	None identified

Alia 2011

Methods	Design: parallel group Duration: recruitment began in June 2005 and concluded in July 2009. Participants were enrolled during a mean time of 19.6 months (range 5-49 months). Setting: 8 hospitals in 4 countries (Hospital Universitario de Getafe, Hospital Fundación Alcorcón, Hospital Clinic de Barcelona, Consorci Hospitalari Parc Taulí, and Hospital Principe de Asturias in Spain; Hospital ABC in Mexico; Clinica Universitaria Bolivariana in Colombia and University of Texas Health Science Center in the USA (University Hospital and Audie L. Murphy Veterans Affairs Hospital))
Participants	Number screened: 354 Number randomised: 83 Number completed: 83 Baseline details: Age (years): methylprednisolone 69.1 (SD 9.7), control 67.6 (SD 10.7) Gender: M = methylprednisolone 32 (74%), control 34 (85%) Diagnosis COPD: known COPD and hospitalised with exacerbation that required ventilator support either conventional with intubation or NIV AE criteria: defined as the presence of ≥ 2 of: worsening dyspnoea, increase in sputum purulence or increase in sputum volume Inclusion criteria: acute hypercapnic respiratory failure (pH < 7.35, with a $PaCO_2$ > 45 mmHg) requiring invasive or non-invasive mechanical ventilation Exclusion criteria: asthma or atopy; use of systemic corticosteroids within the preceding month; use of systemic corticosteroids for the treatment of COPD exacerbation for > 24 hours at the time of randomisation; clinical or radiological evidence of pneumonia; uncontrolled LVF requiring the use of inotropes or vasoactive drugs; uncontrolled arterial hypertension; uncontrolled diabetes mellitus; neuromuscular disease; allergy or adverse reaction (or both) to corticosteroid therapy
Interventions	Experimental: methylprednisolone 0.5 mg/kg every 6 hours for 72 hours, 0.5 mg/kg every 12 hours on days 4-6, and 0.5 mg/kg/day on days 7-10 Control: placebo normal saline 50 mL IV Co-interventions: inhaled beta2- agonist (salbutamol 2.5 mg every 6 hours or 2 puffs from an MDI at least 4 times daily) and inhaled ipratropium bromide (0.5 mg every 6 hours or 2 puffs from an MDI at least 4 times daily). Any participant who was receiving inhaled corticosteroid therapy before randomisation was continued on this therapy. Systemic antibiotics were used at the judgement of the treating physicians Treatment period: 10 days Follow-up period: not reported
Outcomes	Primary outcomes: duration of mechanical ventilation, length of ICU stay, need for intubation in people treated with NIV Secondary outcomes: length of hospital stay,

Alia 2011 *(Continued)*

	ICU mortality Adverse events: secondary infection, gastrointestinal bleeding, arterial hypertension, hyperglycaemia, hospital acquired pneumonia
Notes	Likelihood of COPD: no age restrictions, no criterion for required pack history, diagnosis of asthma exclusion, required ventilator support although no specified threshold for fixed airflow obstruction at presentation Trial registration: ClinicalTrials.gov/NCT01281748 Financial disclosure: none reported. Funding/Support: study funded in part by grant PI041233 from Fondo de Investigación Sanitaria Study lasted 5 years because of a lower enrolment rate, mainly due to a reduction in ICU admissions of people with COPD exacerbations and a high rate of exclusion Protocol: days 1-5: ABG analysis, plasma C-reactive protein level, white blood cell count, maximal blood glucose level, daily dose insulin, intrinsic positive end expiratory pressure (intubated participants) Emailed data request to authors - 7 September 2013 (Esteban). Data provided for outcomes - length of hospital stay, ICU stay and mechanical ventilation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by hospital pharmacy at each centre by a random number table with permuted blocks of 4, with stratification according to the type of mechanical ventilation (conventional or NIV)
Allocation concealment (selection bias)	Low risk	Allocation schedule was concealed with sealed envelopes that were opened sequentially
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pharmacists dispensed the IV medications in a blinded manner. Nurses who were administering the medications, the physicians who were caring for the participants, were unaware of the treatment assignments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The local investigators and research personnel who collected the data were unaware of the treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants' data reported
Selective reporting (reporting bias)	Low risk	All outcomes reported. ClinicalTrials.gov/NCT01281748
Free of other potential confounders?	Low risk	Study lasted 5 years because of a lower enrolment rate, mainly due to a reduction in ICU admissions of people with COPD exacerbations and a high rate of

Alia 2011 *(Continued)*

	exclusion. Authors do not believe that this limitation affected the study findings, main change in practice over time was higher use of NIV

Bullard 1996

Methods	Design: parallel group Duration: recruited March-August 1993, and November 1993-February 1994. Treatment for up to 8 days then follow-up for 2 weeks Setting: single-centre tertiary hospital, Chang Gung Memorial Hospital, Linkou, Taiwan, ED with subsequent admission if required
Participants	Number screened: not reported Number randomised: 138 (18 excluded on chest X-ray - 6 cardiac asthma, 2 pneumothoraces, 5 pneumonia, 3 severe bronchiectasis, 2 bronchogenic cancer. 1 participant in placebo group died, 2 incorrect diagnosis, 2 withdrew consent). Number completed: 113 26 participants were discharged from the ED within 24 hours (16 in the corticosteroid group and 10 in the placebo group) Baseline details: Mean age (years): 66 Gender: M = 97, F = 16 Diagnosis COPD: no details of previous clinical COPD diagnosis AE criteria: moderate-to-severe dyspnoea presenting to ED, FEV_1 < 60% predicted or FEV_1/FVC < 60% Inclusion criteria: > 40 years of age; suspected chronic airflow limitation, presenting with dyspnoea and a FEV_1 < 60% predicted or FEV_1/FVC < 60% Exclusion criteria: pneumothorax, pneumonia, intubation within 2 hours, hospitalisation for a co-existent disease, known corticosteroid use
Interventions	Experimental: hydrocortisone 100 mg, IV, within 15 minutes of arrival. Hydrocortisone 100 mg IV 4 hourly for 4 days for those participants hospitalised. Participant received prednisolone 40 mg, orally, daily for 4 days either on discharge from the ED or if admitted having completed the IV therapy (5D-8D systemic steroid treatment) Control: IV placebo administered within 15 minutes of arrival. Subsequent treatment not clearly reported Co-interventions: inhaled fenoterol, inhaled ipratropium bromide, IV aminophylline Confounders: IV hydrocortisone could be administered at the discretion of chest medicine physicians. 12 participants received cross-over treatment or had their treatment stopped after 24 hours
Outcomes	Analysed: FEV_1 (at 6 hours) published results for lower limit of 95% CI control group missing a minus sign as 95% CI in the paper does not include the point estimate as reported; PEF (at 6 hours) published results for lower limit of 95% CI control group missing a minus sign as 95% CI in the paper does not include the point estimate as reported Reported: admissions, discharges from the ED within 24 hours, serum aminophylline concentration, re-attendance to the ED, subjective assessment of dyspnoea.

Bullard 1996 *(Continued)*

	Others: none reported Mortality: 3 deaths in corticosteroid group, 2 in the placebo. Morbidity: not reported
Notes	Likelihood of COPD: people > 40 years of age, no requirement for past smoking, asthma not an exclusion, chronic airflow limitation suspected Funding: no sources of funding declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random numbers table was used to generate randomisation codes
Allocation concealment (selection bias)	Low risk	Allocation was performed using consecutive allocation of participants to prepackaged treatments based on random code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were blinded to treatment allocation. Investigators did not break the code during the course of the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16/60 corticosteroid group and 10/53 of placebo group were discharged from ED within 24 hours. 12 participants had a physician-directed change to their study intervention following admission to hospital (either given corticosteroids or corticosteroids stopped). Treatment failure defined as a return to the ED within 14 days. The author of this study noted that results of treatment administered in the ED and measured in the first 24 hours were reliable, later measurement of outcomes was affected by breaks in protocol after admission
Selective reporting (reporting bias)	Low risk	All outcomes supplied by author
Free of other potential confounders?	High risk	IV hydrocortisone could be administered at the discretion of chest medicine physicians. 12 participants received cross-over treatment or had their treatment stopped after 24 hours

Ceviker 2014

Methods	Design: parallel group Duration: 3 months (following discharge) Setting: State Hospital, Gumushane, Turkey
Participants	Number screened: not available Number randomised: 40 Number completed: 38 Number withdrawals: 2 (developed severe respiratory failure)

Ceviker 2014 *(Continued)*

	Baseline details: Mean age (years): oral group: 69.0 (± 10.5), IV group: 67.1 (±8.4) Smoking history: oral group: 56.3 (±38.8), IV group: 69.0 (±38.5) Diagnosis COPD: previous documented diagnosis of COPD AE criteria: presence of an exacerbation, which, in the opinion of the attending physician, necessitated admission to hospital Inclusion criteria: aged > 40 years, previous documented diagnosis of COPD, ≥ 10 pack-years' smoking history, exacerbation requiring hospitalisation based on opinion of attending doctor Exclusion criteria: the presence of pneumonia, uncontrolled hypertension or diabetes mellitus, previously diagnosed bronchiectasis, need for mechanical ventilation, use of systemic corticosteroids during the preceding month and a history of gastrointestinal bleeding during the preceding 3 months
Interventions	Group 1: oral methylprednisolone 32 mg/day Group 2: IV methylprednisolone 1 mg/kg/day for 4 days, then 0.5 mg/kg/day for 3 days Co-interventions: salbutamol 2.5 mg and Ipratropium 0.5 mg - every 6 hours, antibiotics (if meet Anthonisen criteria), nasal oxygen (according to attending physician's decision) Treatment period: 7 days Follow-up period: 3 months
Outcomes	Reported: During treatment period: Pre- and post-bronchodilator spirometry: days 7, 90 ABGs: days 2, 4, 7, 90 Symptom scores: days 2, 4, 7. Adverse events: daily questioning of the participants and daily measurements of blood pressure and blood glucose levels during the treatment period During 3 months' follow-up: visits to the ED or unplanned visits to family physicians and admission to hospital Treatment failure defined as severe respiratory failure requiring mechanical ventilation or need for systemic corticosteroids beyond 7 days intervention period Relapse defined as re-admission for COPD during 12-week follow-up No legend was provided for certain outcomes (ABG, symptom scores, lung function tests, length of hospital stay). Data for symptom score were obtained from a graph - confirmation is required
Notes	Likelihood of COPD: aged > 40 years for inclusion, > 10 pack-years' smoking history, asthma not an exclusion, previously documented COPD diagnosis, no criteria specified for airflow obstruction Funding: no sources of funding declared Trial registration: not located, pre-study protocol not available Emailed data request to authors - 7 September 2013, 30 September 2013 (Ceviker). No response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were randomised to 1 of 2 treatment regimens according to a previously prepared randomisation list
Allocation concealment (selection bias)	Unclear risk	This list was kept by 1 of the investigators (AS), who was also in contact with the nurses responsible for the treatment of the participants

Ceviker 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No use of placebo, participants and hospital staff not blind to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participant interviews and measurements were performed by another investigator (YC), who remained blinded to the treatment regimens
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals (2 participants) accounted for (reasons supplied), otherwise, all data reported
Selective reporting (reporting bias)	Unclear risk	All outcomes listed in methods are reported but protocol not available
Free of other potential confounders?	Low risk	Characteristics of both groups were similar at baseline

Chen 2005

Methods	Design: parallel group Duration: 14 days Setting: inpatients, unknown number of centres, China
Participants	Number screened: not reported Number randomised: 130 Number completed: 121 Baseline details: Mean age (years): 7-day corticosteroids 70.3, 14-day corticosteroids 71.7, placebo 73.0 (not significantly different) Age range: not reported Gender: M = 98, F = 32 Diagnosis COPD: criteria for COPD not reported AE criteria: not reported Diagnosis and severity: FEV_1 (L) baseline 7-day corticosteroids 0.79 (SD 0.25), 14-day corticosteroids 0.74 (SD 0.21), placebo 0.74 (SD 0.32), baseline PaO_2 (mmHg) 7-day corticosteroids 69.06 (SD 11.54), 14-day corticosteroids 68.07 (SD 13.53), placebo 67.48 (SD 11.61) Current smokers: 7-day corticosteroids 18/44 (41%), 14-day corticosteroids 20/43 (47%), placebo 18/43 (42%) (not significantly different) Inclusion criteria: not reported Exclusion criteria: not reported, people with asthma excluded: not reported, bronchodilator reversibility tested: not reported
Interventions	Group 1 prednisolone 30 mg/day 7 days + placebo 7 days Group 2 prednisolone 30 mg/day 10 days + 15 mg/day 5 days Group 3 placebo 14 days Delivery: oral Co-interventions permitted/dose: not reported Co-interventions not permitted: not reported

Chen 2005 *(Continued)*

Outcomes	Outcomes measured: lung function, ABG measurement, days hospitalisation, symptoms scores, rate of treatment failure, side effects corticosteroids, rate of relapse Outcomes reported: FEV_1, FEV_1/FVC ratio, PEF, PaO_2, number relapsed, number failed treatment, number side effect Follow-up assessment points: not reported Prednisolone 14-day treatment group data used in this review
Notes	Full paper published in Chinese 2008. Abstract publication 2005. Study and outcome data also provided by authors Likelihood of COPD: unknown if age threshold, unknown pack-years' smoking threshold, asthma an exclusion, fixed airflow obstruction, FEV_1/FVC < 70%, FEV_1 < 80% predicted Funding: no sources disclosed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stochastic function used to create 150 numbers 0-1. Randomisation code prepared by an assistant not involved in other parts of study. Sealed envelopes prepared before study initiation by assistant
Allocation concealment (selection bias)	Low risk	Sealed envelopes used and allocated by third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of identical boxes and medications. Allocated by third party. Researchers blinded to medications
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Description of withdrawals/drop-outs given. Intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Not fully published, no protocol
Free of other potential confounders?	Low risk	Information not reported

Cordero 1996

Methods	Design: parallel group randomised controlled study Duration: conducted April-September 1995 Setting: outpatients, University Hospital La Fe, Valencia, Spain
Participants	Number screened: not reported Number randomised: 30 Number completed: Baseline details: M = 30, F = 0 Median age (range) (years): not reported Diagnosis COPD: airflow obstruction FEV_1 > 70% predicted or FEV_1/FVC < 60% predicted AE criteria: not described Inclusion criteria: male, > 50 years, airflow obstruction Exclusion criteria: asthma or atopy
Interventions	Experimental: oral prednisone 40 mg daily 10 days Control: placebo 10 days Co-interventions: standardised treatment, inhaled beta-agonists, anticholinergics, inhaled corticosteroids, antibiotics, physiotherapy Treatment period: 10 days Follow-up period: 14 days
Outcomes	Reported: spirometry, PEF, ABG, PaO_2, Borg dyspnoea scale Measurements: days 1, 7, 14
Notes	Likelihood of COPD: > 50 years for inclusion, unknown pack-years' smoking history, unknown if asthma an exclusion, fixed airflow obstruction, FEV_1/FVC < 60%, FEV_1 < 70% predicted Funding: no sources disclosed Protocol: not available, no registration located Published as conference abstract only. Emailed data request to authors 20 September 2012, 9 August 2013 (Cordero), 16 August 2013 (Sole). No response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised controlled study, method not reported
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details

Cordero 1996 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	High risk	Results data incomplete in abstract
Selective reporting (reporting bias)	Unclear risk	No details, protocol not available
Free of other potential confounders?	Unclear risk	No information on group characteristics at baseline

Davies 1999

Methods	Design: parallel group Duration: follow-up for 6 weeks Setting: single centre, people presenting to an ED of a university hospital, Liverpool UK
Participants	Number screened: 246 Number randomised: 60; prednisolone 29, placebo 29 Number completed: 27; prednisolone (1 withdrew, 1 died), 22 placebo (5 withdrew, 1 died, 1 lost to follow-up) Baseline details: Mean age (years): 67 Gender: M = 34, F = 16 Diagnosis COPD: not specified AE criteria: increased breathlessness and 2 of following criteria: increased sputum - volume or purulence, cough frequency or severity, increased wheeze Inclusion criteria: diagnosis of COPD, aged 40-80 years. FEV_1 < 70% and FEV_1/FVC < 75% Exclusion criteria: personal/family history of asthma, uncontrolled LVF, pneumonia, oral corticosteroids within last month, pH < 7.26
Interventions	Experimental: prednisolone 30 mg orally for 14 days Control: matched placebo Treatment for 14 days Co-interventions: nebulised salbutamol and ipratropium bromide, oxygen and antibiotics at physician's judgement
Outcomes	FEV_1; FVC; visual analogue scale of symptoms; length of hospitalisation data removed due to skewed data, was previously mentioned in text, but not data analysis; ABG, sputum culture Treatment failure: defined arterial PH falling < 7.26, physician or participant decision lack of progress requiring further treatment, QoL (SGRQ) Measurements: daily symptoms, lung function 5 days, 6 weeks SGRQ, AE

Davies 1999 *(Continued)*

	Mortality: 2 deaths, 1 in each treatment group Adverse drug effects: heartburn and glycosuria
Notes	Likelihood of COPD: aged > 40 years, > 20 pack-years' smoking history, history of asthma exclusion, evidence of fixed airflow obstruction Funding: Glaxo Wellcome supplied oral corticosteroids and placebo. Fazakerley Foundation for funding research of L. Davies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by hospital pharmacy according to random number table
Allocation concealment (selection bias)	Low risk	Randomisation by random number table by hospital pharmacy and allocation to consecutive participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants, investigators, respiratory physicians, technicians and other hospital staff were masked to treatment status until the end of the study. Use of identical placebo tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants, investigators, respiratory physicians, technicians and other hospital staff were masked to treatment status until the end of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All withdrawals accounted for, intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	All outcomes in methods were reported
Free of other potential confounders?	Low risk	Characteristics of both groups were similar at baseline

de Jong 2007

Methods	Design: parallel group prospective, randomised, double-blind, double-dummy, placebo-controlled, parallel-group clinical study with treatment failure as the primary outcome Duration: June 2001 to June 2003 Setting: inpatients, single centre, Isala Klinieken, Zwolle, the Netherlands
Participants	Number screened: 435 Number randomised: 210; 107 IV group, 103 oral group Number completed: 193 Number withdrawals: 17 (6 withdrew consent before day 4 of the study, 2 in IV group and 4 in oral group 11 excluded from the per-protocol analysis because they did not fulfil inclusion or exclusion criteria, 6 IV group, 5 oral group) Baseline details: Smoking history (mean) (pack-years): IV group: 37.2 (SD 20.2) oral group: 40.5 (SD 23.1)

de Jong 2007 *(Continued)*

	Baseline lung function (mean) (L): IV group: 1.0 (SD 0.43), 36% predicted (SD 14%); oral group: 1.0 (SD 0.40), 39% predicted (SD 17%) Mean age (years): IV group: 69.8 (SD 8.6), oral group 71.6 (SD 8.1) Gender: IV group: M = 76.6%, oral group: M = 72.8% Diagnosis COPD: airflow limitation was defined as an FEV_1/FVC ratio of < 70% and FEV_1 of < 80% predicted (at least GOLD severity stage II) AE criteria: defined as a history of increased breathlessness and the presence of at least 2 of the following symptoms for at least 24 6 hours: increased cough frequency or severity, increased sputum volume or purulence and increased wheeze Inclusion criteria: aged > 40 years, > 10 pack-years' smoking history, evidence of airflow limitation Exclusion criteria: people who had signs of a very severe exacerbation on hospital admission (arterial pH < 7.26 or PaCO2 > 9.3 kPa), significant or unstable co-morbidity, history of asthma, participated in another study within the 4 weeks before hospital admission, previously randomised into this study, had clinically significant findings on chest radiography other than COPD, known hypersensitivity to prednisolone, known to be totally non-compliant
Interventions	IV group: IV prednisolone 60 mg + placebo medication 5-day course, up to 7 days tapering course oral prednisolone 30 mg Oral group: oral prednisolone 60 mg + placebo medication 5-day course, up to 7 days tapering course oral prednisolone 30 mg Co-interventions: nebulised ipratropium bromide and albuterol 4 times daily together with oral amoxicillin/clavulanate. In case of allergy to this regimen, doxycycline was prescribed Treatment period: 12 days Follow-up period: 90 days
Outcomes	Reported: by early < 2 weeks, late 2-12 weeks; death from any cause, admission to the ICU, re-admission to the hospital because of COPD, necessity to intensify pharmacological treatment Spirometry days 1 and 7 Health status SGRQ days 1 and 7. Minimal clinically important difference #0.4, range 0-100 Health-related QoL 24-hour version CCQ daily on days 1-7. Minimal clinically important difference #0.4, range 0-6 Treatment failure defined as intensification of pharmacological treatment with open-label corticosteroids Relapse defined as re-admission to the hospital for COPD between 2 and 12 weeks Analysis: per-protocol IV group 99 (of 107 participants), oral group 94 (of 103 participants)
Notes	Likelihood of COPD: aged > 40 years, > 10 year-packs' smoking history, history of asthma exclusion, evidence of fixed airflow obstruction Funding: sources not disclosed; authors reported on 23 January 2007 to the ACCP that no significant conflicts of interest existed with any companies/organisations whose products or services may be discussed in the article

de Jong 2007 *(Continued)*

Trial registration: ClinicalTrials.gov/NCT00311961

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a computer minimisation programme for the following 10 parameters: use of oral prednisolone, use of inhaled corticosteroids, theophylline use 30 days before hospital admission, admission to the hospital because of an exacerbation of COPD in the last year, age, gender, smoking history, use of supplemental oxygen at home, pCO2 and time since the diagnosis of COPD (i.e. < 5, 5-10, 10-15 or > 15 years, or unknown)
Allocation concealment (selection bias)	Unclear risk	Allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding: double blind. Active and placebo medication had a similar appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All withdrawals accounted for, per-protocol analysis
Selective reporting (reporting bias)	Low risk	Registration protocol available, all outcomes reported
Free of other potential confounders?	Low risk	Characteristics of both groups were similar at baseline

Emerman 1989

Methods	Design: parallel group Duration: Setting: single centre, ED of a urban county general hospital, Cleveland USA
Participants	Number screened: not reported Number randomised: 100 Number completed: 96 (4 lost to follow-up) Baseline details: Mean age (years): 64 (SD6.7) Gender: M = 50, F = 46 Diagnosis COPD: clinical history of emphysema or chronic bronchitis AE criteria: presenting to ED with respiratory distress, initial spirometry FEV_1 < 70% predicted or FEV_1/FVC < 60%

Emerman 1989 *(Continued)*

	Inclusion criteria: aged > 50 years Exclusion criteria: history of asthma, episodes of respiratory distress before 35 years of age, oral or IV corticosteroids within 1 month, pneumonia, acute congestive heart failure, other conditions requiring hospitalisation
Interventions	Experimental: methylprednisolone 100 mg IV (1D systemic corticosteroid treatment) Control: matched placebo solution IV Co-interventions: inhaled isoetharine, nasal oxygen and IV aminophylline Exclusions: no antibiotics given
Outcomes	Analysed: spirometry, outcomes reported as percentage of predicted lung function measurements, hospitalisation rate Reported: return to the ED. Active intervention was a single IV infusion of methylprednisolone given in the ED with participants observed over a minimum of 4 hours. Subsequently 30 of 96 participants required admission and for some participants allocation to treatment group was not maintained after re-admission Follow-up measurements: 48 hours Others: none reported Mortality: none reported Adverse drug effects: none reported
Notes	Likelihood of COPD: aged > 50 years; past smoking not required, but mean smoking history > 50 pack-years so most participants will have a significant smoking history; asthma excluded; chronic airflow obstruction not known Funding: no sources disclosed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned to treatment arms, randomisation was by allocation of participants to receive corticosteroid or placebo that were prepared by the hospital pharmacy in a pre-determined random order, identical in appearance and labelling
Allocation concealment (selection bias)	Low risk	Order of treatment prepared by the hospital pharmacy in a pre-determined random order
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical in appearance and labelling. Participants, treating physicians and investigators blinded to allocation until termination of study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators blinded to allocation until termination of study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	30 of 96 participants required admission and for some participants allocation to treatment group was not maintained after re-admission

Emerman 1989 *(Continued)*

Selective reporting (reporting bias)	Low risk	Results reported for outcomes in methods
Free of other potential confounders?	High risk	Allocation to treatment group was not maintained for an unknown number of participants after re-admission

Gunen 2007

Methods	Design: parallel group Duration: treatment 15 days, follow-up 1 month Setting: inpatients, single centre, Turgut Ozal Research Centre of Inonu University, Malatya, Turkey
Participants	Number screened: not reported Number randomised: 159 (group 1 = 53, group 2 = 53, group 3 = 53) Number completed: 121 (group 1 = 39, group 2 = 40, group 3 = 42) Number withdrawals: 11 participants lost to follow-up post discharge group 1 = 4, group 2 = 3, group 3 = 4. Deaths group 1 = 1, group 2 = 1 Baseline details: Age (years): 64.1 (SD 8.9) Gender: group 1: M = 35, F = 4; group 2: M = 33, F = 7; group 3: M = 35, F = 7 FEV_1 at admission: 37.2% predicted (SD 12.2) Diagnosis COPD: people with COPD hospitalised for an exacerbation prospectively enrolled, COPD according to the criteria set by the ATS AE criteria: presence of worsening in at least 2 of the following symptoms: cough, purulent sputum and dyspnoea. Inclusion criteria: level II exacerbation Exclusion criteria: hospitalised for pneumonia, pulmonary emboli, congestive heart failure and pneumothorax. Risk of imminent respiratory failure requiring mechanical ventilation or direct admission to the ICU (level III exacerbation). Utilised systemic corticosteroids or had an exacerbation in the preceding month
Interventions	Group 1: salbutamol nebulised 2.5 mg 4 times daily and ipratropium bromide nebulised 0.5 mg 4 times daily Group 2 prednisolone IV 40 mg plus nebulised salbutamol 2.5 mg 4 times daily and nebulised ipratropium bromide 0.5 mg 4 times daily Group 3 budesonide nebulised 1500 mg 4 times daily; combined nebulised solution of salbutamol and ipratropium bromide 4 times daily ipratropium bromide 0.5 mg and salbutamol 2.5 mg/2.5 mL Co-interventions: nebulised salbutamol as rescue medication. All participants were given supplemental oxygen and systemic methylxanthines, antibiotics were used where signs of bacterial infection existed: group 1 = 59, group 2 = 63, group 3 = 57% Treatment period: 15 days; at least 10 days in hospital remainder continued after discharge: group 2 systemic corticosteroids methylprednisolone 32 mg tablets in the morning or group 3 or nebulised inhaled budesonide 1500 mg 4 times daily

Gunen 2007 *(Continued)*

	Follow-up period: 1-month. Combivent aerosol, ipratropium bromide 20 µg plus salbutamol 100 µg x 2 puffs 4 times daily; and methylxanthines
Outcomes	Reported: complete blood counts, detailed biochemical analysis, spirometric measurements and ABG analysis at admission, 24 hours, 72 hours, 7 days and 10 days Status after discharge was assessed by telephone calls and home visits every week during a 1-month period after discharge Adverse effects: COPD deterioration, admission to the ICU, respiratory failure, participant withdrawal for any reason, delayed discharge (beyond 15 days), inhospital deaths, deaths after discharge within 1 month, exacerbation, rehospitalisation rates within 1 month after discharge. Paper reports total number of exacerbations in 30 days and no response received to request for author clarification on whether data refer to number of participants or number of events. Data not used
Notes	Likelihood of COPD: age inclusion not known; smoking history threshold not known, but mean smoking history > 40 pack-years so most participants will have a significant smoking history; asthma not an exclusion; required COPD diagnosis according to 1087 ATS standards Funding: no sources of funding disclosed Trial registration: ClinicalTrials.gov/NCT00274222 Protocol: not available Data on treatment failure and adverse effects were sought from author. Emailed data request to authors 30 September 2013 (Gunen). No response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly sorted into 1 of 3 groups - method not specified
Allocation concealment (selection bias)	Unclear risk	Participants were randomly sorted into 1 of 3 groups. No details on allocation method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants received apparently identical treatment, given same number of scheduled nebulised solutions every day (8 times a day) and were infused with a single physiological saline solution (50 mL) IV in the morning
Blinding of outcome assessment (detection bias)	Unclear risk	No details on investigator or assessor blinding

Gunen 2007 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data from 38 enrolled participants were not evaluated due to exclusion during hospitalisation period of the study; group 1 = 39, group 2 = 40, group 3 = 42. The main reasons for exclusion were: the inability to perform 2 consecutive spirometric examinations (n = 10), non-compliance with the treatment (n = 8), adverse effects (n = 6), treatment failure or admission to the ICU (n = 5), withdrawal of consent (n = 5) and request for early discharge (n = 4). Not clear which group these drop-outs occurred in. Rates of drop-outs similar: group 1 = 26%, group 2 = 24%, group 3 = 21%
Selective reporting (reporting bias)	Unclear risk	Protocol: not available
Free of other potential confounders?	Low risk	Characteristics of both groups were similar at baseline

Maltais 2002

Methods	Design: parallel group Duration: recruited over 20 months, treatment for 10 days Setting: 34 centres (Belgium n = 3, Canada n = 11; France n = 20) participated; people in clinic or ED with deterioration in their respiratory status subsequently admitted to hospital
Participants	Number screened: 687 in 11 months, 75 enrolled Number randomised: 199 (prednisone n = 62, placebo n = 66) Number completed: 147 assessed at day 10 (prednisone n = 55, placebo n=55) Baseline details: Mean age (years): 70 Gender: M= 162; F = 37 Diagnosis COPD: based on clinical evaluation compatible with chronic bronchitis or emphysema as defined by the ATS and when available, baseline spirometry had to confirm the presence of irreversible airflow obstruction (post-bronchodilator FEV_1 70% normal predicted value and $FEV_1/FVC < 70\%$ AE criteria: recent (i.e. within 14 days) history of acute COPD exacerbation defined as increased breathlessness Inclusion criteria: requiring admission to hospital; recent acute COPD exacerbation (within 14 days), defined as increased breathlessness; aged > 50 years; > 20 pack-years' smoking history Exclusion criteria: history of asthma, allergic rhinitis or atopy; exposure to systemic corticosteroids within 1 month; if used, inhaled beclomethasone equivalent > 1500 g/day; at risk of imminent acute respiratory failure requiring mechanical ventilation or admission to ICU; diagnosis of a specific underlying cause for the exacerbation (e.g. pneumonia, pneumothorax, heart failure)
Interventions	Experimental: prednisone 30 mg orally every 12 hours and placebo Pulmicort Respules/Nebuamp for 72 hours followed by prednisone 40 mg/day orally and placebo turbuhaler for 7 days (10-day systemic corticosteroid course) Control: placebo nebulisation and tablets for 72 hours and placebo turbuhaler for 7 days Co-interventions: nebulised - agonists, ipratropium bromide, oral antibiotics (used in 83% budesonide, 84% prednisone, 80% placebo), and supplemental oxygen. Methylxanthines allowed, if prescribed before the study as a regular medication

Maltais 2002 *(Continued)*

Outcomes	Analysed: post-bronchodilator FEV_1; pre-bronchodilator FEV_1; ABGs (0-72 hours); dyspnoea score; duration of hospitalisation; length of hospitalisation data removed due to skewed data, was previously given in text, but not in data analysis; occurrence of adverse events Reported: primary variable to assess treatment efficacy was the change in post-bronchodilator FEV_1 from 0 to 72 hours Secondary endpoints included: changes in pre-bronchodilator FEV_1; dyspnoea score; ABGs from 0 to 72 hours; duration of hospitalisation; occurrence of adverse events, defined as any medical event reported by the participants from study entry to day 10 Measurements: participants were assessed every 12 hours during the acute phase (from 0 to 72 hours), at hospital discharge, and at day 10 Mortality: 1 death in prednisone group Adverse drug effects: hyperglycaemia
Notes	Likelihood of COPD: aged > 50 years, > 20 pack-years' smoking history, diagnosis of asthma exclusion, evidence of fixed airflow obstruction at presentation if spirometry available Funding: financial support from AstraZeneca Canada Dr. Robert Jenkins and Ms. Joanna Lee, AstraZeneca Canada assisted in reviewing and preparing the manuscript, and AstraZeneca R&D Lund, Kurt Nikander advised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised; computerised single list using blocks of consecutive participant number, proportion 1 : 1 : 1
Allocation concealment (selection bias)	Low risk	Allocated on site next available sequential participant number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as placebo-controlled, double-blind, double dummy; identical nebuliser ampoules and placebo tablets used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details on assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	28 participants were withdrawn from the study during the acute phase for the following reasons: adverse events (n = 12), treatment failure according to the evaluation of the attending physician (n = 9), inclusion or exclusion criteria not fulfilled (n = 4), need for a prohibited medication (n = 2) and withdrawal of participant's consent (n = 1). The proportion of drop-outs during the acute phase was similar in the 3 groups: 10 (14%) participants in the budesonide group, 7 (11%) in the prednisone group, and 11 (17%) in the placebo group

Maltais 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All outcomes reported
Free of other potential confounders?	Low risk	Characteristics of both groups were similar at baseline

Niewoehner 1999

Methods	Design: parallel group Duration: November 1994 to October 1996. Treatment for 57 days, follow-up for 6 months Setting: hospitalised people with exacerbations of COPD, 20 centres, Veterans Affairs USA
Participants	Number screened: 1840 Number recruited: 271 Number withdrawals: oral prednisolone 2 weeks, n = 10, oral prednisolone 8 weeks n = 8, placebo n = 10. Follow-up data complete for 19 withdrawals Mean age (years): oral prednisolone 2 weeks: 67.1 (SD10.6); oral prednisolone 8 weeks: 68.1 (SD 6.8); placebo group: 67.8 (SD 10.0) Gender: M = 268, F = 3 Diagnosis COPD: clinical diagnosis. Likelihood of COPD: aged > 50 years, > 30 pack-years' smoking history, diagnosis of asthma exclusion, evidence of airflow obstruction AE criteria: clinical diagnosis of exacerbations of COPD Inclusion criteria: aged > 50 years, > 30 pack-years' smoking history, FEV_1 < 1.5 L or inability to perform spirometry due to dyspnoea Exclusion criteria: diagnosis of asthma, use of systemic corticosteroids within the preceding 30 days, co-morbidities making survival for 1 year unlikely, inability to give informed consent Smoked in past 3 months: oral prednisolone 2 weeks 52%, oral prednisolone 8 weeks 50%, placebo 50% FEV_1 (L): oral prednisolone 2 weeks 0.77 (SD 0.29); oral prednisolone 8 weeks 0.79 (SD 0.29); placebo 0.75 (SD 0.27)
Interventions	Group 1: IV methyl prednisolone 125 mg 6 hourly for 72 hours followed by oral prednisolone 60 mg day 4- day 7, 40 mg day 8 to day 11, 20 mg day 12 to day 43, 10 mg day 44 to day50, 5 mg day 51 to day 56 (60-day SS course). Treatment 8 weeks Group 2: IV methyl prednisolone 125 mg 6 hourly for 72 hours followed by oral prednisolone 60 mg day 4 to day 7, 40 mg day 8 to day 11, 20 mg day 12 to day 15 followed by oral placebo day 16 to day 57 (15-day systemic corticosteroid course). Placebo for weeks 3-8 Group 3: IV placebo (5% dextrose) 6 hourly for 72 hours followed by oral placebo day 3 to day 57. Treatment 8 weeks Co-interventions: antibiotics for 7 days. Beta-agonists, ipratropium bromide and triamcinolone administered to all during the 6 months of the study Exclusions: theophyllines, high dose inhaled corticosteroid > 1600 µg/day equivalent beclomethasone
Outcomes	Analysed: time to treatment failure (death, need for intubation and mechanical ventilation, re-admission for COPD, intensification of pharmacological therapy), length of hospital stay, FEV_1, death, complications Reported: theophylline use, prior hospitalisation Outcomes measured: 2, 8, 26 weeks Mortality: 13 in experimental arm, 11 in placebo arm

Niewoehner 1999 *(Continued)*

	Adverse events: 51 in placebo arm and 113 in experimental arm Data from intervention groups 1 and 2 combined in analyses
Notes	Likelihood of COPD: aged > 50 years, > 30 pack-years' smoking history, diagnosis of asthma exclusion, FEV_1 < 1.50 L or an inability to undergo spirometry because of dyspnoea Funding: conducted under the aegis of the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development and supported by a grant from Boehringer Ingelheim Protocol: published (Erbland 1998)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation, stratified randomisation with a permuted-block scheme, stratified according to hospital
Allocation concealment (selection bias)	Low risk	Blinded pharmacists responsible for drug administration
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medication dispensed in blinded fashion, identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: 10 oral prednisolone 2 week, 5 oral prednisolone 8 week, 10 placebo. Follow-up data complete for 19 withdrawals
Selective reporting (reporting bias)	Low risk	Protocol published
Free of other potential confounders?	Unclear risk	There were differences between groups at baseline in pack-years' smoking, previous use of systemic corticosteroids and proportion with diabetes

Ridha 2006

Methods	Design: parallel group, 3 groups Duration: 10 days' treatment, 90 days' follow-up Setting: inpatients, Mami Hospital, Ariana-Tunisia
Participants	Number screened: not reported Number randomised: 52; group 1 n = 18, group 2 n = 17, group 3 n = 17 Number completed: not reported Baseline details: not reported Age: not reported Gender: not reported

Ridha 2006 *(Continued)*

	Diagnosis COPD: not reported AE criteria: not reported Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Group 1 (n = 18): hydrocortisone 400 mg daily IV for 10 days Group 2 (n = 17): prednisone 40 mg once daily for 10 days Group 3 (n = 17): no corticosteroids (control group) no placebo use reported Co-interventions: not known Treatment period: 10 days Follow-up period: 90 days
Outcomes	Primary outcomes: PEF, spirometric measures (FEV_1 level) Secondary outcomes: symptom scores (dyspnoea, cough, sputum), treatment failure Adverse events: hyperglycaemia, epigastric pain Assessment: days 3, 10, 30 and 90 Reported: no results in abstract
Notes	Likelihood of COPD: age limit for inclusion unknown, unknown pack-years' smoking, unknown if asthma an exclusion, fixed airflow obstruction criteria unknown Funding: no sources disclosed Protocol: not available. Abstract only Emailed data request to authors - 4 September 2012, 9 August 2013, 30 September 2013 (Ridha). No response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective controlled study randomised in 3 groups. Method not reported
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control group "no corticosteroids" and placebo use not specified in abstract
Blinding of outcome assessment (detection bias) All outcomes	High risk	No details on assessor blinding and as placebo use was not specified in abstract assessors were unlikely to be blinded
Incomplete outcome data (attrition bias)	High risk	No results or details in abstract

Ridha 2006 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	No results or details in abstract. No protocol or registration found
Free of other potential confounders?	Unclear risk	No results or details in abstract

Rostom 1994

Methods	Design: parallel group Duration: treatment for 19 days, follow-up over 1 month Setting: hospitalised people, Canada Publication: abstract only
Participants	Number recruited: 30 (6 withdrawn, data incomplete in a further 5) Mean age: not reported Gender: not reported Diagnosis COPD: not reported AE criteria: not reported Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Experimental: methylprednisolone 40 mg IV, 6 hourly for 3 days followed by methylprednisolone 32 mg orally daily reducing by 4 mg every second day Control: saline IV followed by oral placebo Duration treatment: 19 days Co-interventions: oxygen, inhaled (nebulised) beta-agonists, theophylline (route not detailed) and oral antibiotics (amoxicillin, trimethoprim/sulphamethoxazole or doxycycline)
Outcomes	Analysed: spirometry Reported: spirometry Others: none reported Mortality: not reported Adverse events: hypertension (n = 1), hyperglycaemia (n = 1) and congestive heart failure (n = 1), but allocation not detailed
Notes	Likelihood of COPD: age limit for inclusion unknown, unknown pack-years' smoking, unknown if asthma an exclusion, fixed airflow obstruction criteria for COPD unknown Funding: no sources disclosed Published as abstract. No objective measurements included in the report. No response to letter of request

Rostom 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other details of randomisation procedure available
Allocation concealment (selection bias)	Unclear risk	Information not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind; no other details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported on assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 withdrawals, no details given
Selective reporting (reporting bias)	Unclear risk	Not full publication
Free of other potential confounders?	Low risk	Characteristics of both groups were similar at baseline

Thompson 1996

Methods	Design: parallel group Duration: May 1991 to April 1993 Setting: single centre, outpatients clinic and ED at a Veterans Affairs Medical Center, USA
Participants	Number screened: 140 clinic, 199 ED Number randomised 11 clinic, 16 ED Baseline details: Mean age (years): prednisolone 65 (SD 9), control 70 (SD 7) Gender: M = 26, F = 1 Diagnosis COPD: clinical diagnosis of chronic bronchitis or emphysema according to ATS criteria. Airflow obstruction, FEV_1 < 60% predicted or FEV_1/FVC ratio < 65% after bronchodilator AE criteria: subjective worsening of dyspnoea or cough for > 24 hours requiring a hospital visit, > 25% increase in inhaled short-acting beta2 agonist use over 24 hours, or an increase in sputum production or purulence (or both). Inclusion criteria: > 20 pack-years' smoking history. Exclusion criteria: family history of asthma; history of asthma, atopy, allergic rhinitis or nasal polyps; history of lung disease other than COPD; use of systemic corticosteroids within 1 month; uncompensat-

Thompson 1996 *(Continued)*

	ed congestive heart failure; pneumonia; fever > 38.5 °C; arterial pH < 7.35; hospitalisation for other reasons.
Interventions	Experimental: prednisolone 60 mg orally daily for 3 days, then 40 mg for 3 days, then 20 mg for 3 days. (9-day systemic corticosteroid treatment) Control: vitamin B6 orally daily Treatment period: 9 days Co-interventions: inhaled beta-agonist (MDI or nebulised 4 hourly) in all. Ipratropium bromide, inhaled corticosteroids and theophylline continued unchanged. Oral antibiotics if evidence of infection on gram stain of sputum.
Outcomes	Analysed: spirometry FEV_1, dyspnoea using visual analogue scale (200 mm scale with improvement in dyspnoea represented by a higher score), failure of study treatment (hospitalisation or requirement for oral prednisolone), ABG. Reported: complete blood count Others: none reported Mortality: none reported Adverse events: none reported Author supplied lung function, ABGs and mortality and adverse events data Results: used result supplied by the trialist for day 3 and 10 $PaCO_2$ and PaO_2
Notes	Likelihood of COPD: age limits not known, > 20 pack-years' smoking pack history, diagnosis of asthma exclusion, FEV_1 post- bronchodilator < 60% predicted or ratio FEV1/ FVC < 65% Funding: supported by the US Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment assigned by computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	information not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, use of similar appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details on assessor/investigator blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participant withdrew from follow-up

Thompson 1996 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol not available. All outcomes in methods reported
Free of other potential confounders?	Low risk	Characteristics of both groups were similar at baseline

Willaert 2002

Methods	Design: parallel group Duration: July 1999 to March 2000. Decision to discharge from hospital based on physician judgement (after a minimum of a 10-day inpatient therapeutic regimen) Follow- up period: 4 weeks Setting: single centre, casualty department of the University Hospital Gasthuisberg, Leuven, Belgium
Participants	Number screened: not reported Number randomised: 48 Number completed: 37 Baseline details: Age (years) IV group = 72 (SD 6), oral group 71 (SD 8) Gender: IV group M = 91.3%, oral group 84.0% Smoking history (pack-years): IV group: mean 27 (SD 16); oral group: mean 36 (SD 18) Baseline lung function (mean): FEV_1: IV group 1.14 L (SD 0.43), oral group 1.10 (SD 0.51) FVC: IV group 2.48 L (SD 0.64), oral group 2.55 L (SD 0.63) FEV_1/FVC: IV group 47% (SD 16%), oral group 42% (SD 12%) Diagnosis COPD: clinical history of COPD AE criteria: increased dyspnoea, increased cough frequency or severity, increased production or purulence of sputum, increased wheeze, lasting for at least 3 days Inclusion criteria: ATS indications for hospitalisation of people with COPD exacerbations. People who had used inhaled or systemic corticosteroids prior to admission to casualty were not excluded. The cumulative dose over a period of 2 weeks prior to admission was recorded and used as a variable in the evaluation of the participants' characteristics Exclusion criteria: personal or family history of asthma (defined as episodic wheezing or dyspnoea that rapidly improved with treatment) or atopy, invasive or non-invasive assisted ventilation, unable to use a MDI successfully as a device for administering bronchodilators
Interventions	IV group: methylprednisolone 40 mg/day IV with a decrease to 20 mg after 10 days and subsequent oral treatment with a further decrease of 4 mg. 4 days. Co-intervention: aerosol therapy salbutamol 10 mg/day and ipratropium bromide 1 mg/day, aerosols Oral group: oral methylprednisolone 32 mg for 1 week followed by 24 mg/day for a period of 4 days and a subsequent decrease of 4 mg/week. Co-intervention: Duovent1 4 x 4 puffs/day (cumulative dose of fenoterol 1.6 mg/day and ipratropium bromide 640 mg/day), MDI with spacer Treatment period: IV group: 14 days, oral group: 14 days plus tapering

Willaert 2002 *(Continued)*

Outcomes	Treatment failure: required invasive or non-invasive assisted ventilation, clinical improvement was not satisfactory and a change of treatment was deemed necessary by the treating physician, participant was not satisfied with his or her own clinical progress and demanded another treatment regimen (non-compliance) Time point: while in hospital, minimum 10 days Relapse defined as re-admission to hospital within 4 weeks Analysed: late re-admission to hospital, followed up over 20 weeks; spirometry, FEV_1, FVC daily for 10 days; Dyspnoea recorded on 10-cm visual analogue scale daily for 10 days; daily use and additional need of bronchodilators; cumulative corticosteroid dose; length of stay; QoL (Chronic Respiratory Disease Index Questionnaire daily for 10 days) Follow-up after discharge: 28 days' follow-up, re-admissions followed up over 20 weeks
Notes	Likelihood of COPD: age limits not known, mean 72 years; threshold pack- years' smoking history not known, mean 30 pack-years' smoking history; diagnosis of asthma exclusion; airflow obstruction criteria not known Funding: the study was supported by the Research Foundation Katholieke Universiteit Leuven grant #OT98/27 and the "Fonds voor Wetenschappelijk Onderzoek Vlaanderen" grants #G.0/ 75.99 and #G.0237.01 Protocol: not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to 1 of the 2 therapy groups, method not described
Allocation concealment (selection bias)	Unclear risk	Allocation method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded, no placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Physicians in charge received no information on the objectives or specific target variables of the trial, thereby minimising bias, although they could not be completely blinded. No information on outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for. IV group: 4 withdrew; 3 ICU, 1 femur fracture. In oral group:,7 withdrew, ICU, 2 progress unsatisfactory, 3 non-compliance 1 lung tumour
Selective reporting (reporting bias)	Low risk	Outcomes in methods fully reported, protocol not available. Inclusion criteria for the study were established before the trial and strictly applied
Free of other potential confounders?	Low risk	Bronchodilators administered via different devices in IV group (aerosol) and oral group (MDI + spacer). Total dose recorded, data available, doses equivalent. Extra bronchodilator did not differ between groups.

Wood-Baker 1998

Methods	Design: parallel 3-group design

Wood-Baker 1998 *(Continued)*

	Duration: 2 weeks Setting: hospitalised people, 2 centres, Australia/New Zealand
Participants	Number recruited: 47 Number commenced treatment: 38 Number analysed: 35 Number completed: study 28. 3 withdrawals, 5 treatment failure, 2 adverse events, 10 protocol violation, 1 death Mean age (years): high-dose arm: 69.3 (SD 5.5), moderate-dose arm: 71.1 (SD 9.7), placebo 71.3 (SD 7.8). Range 61-86 years. Gender: M = 24, F = 14 Diagnosis COPD: clinical diagnosis smoking-related COPD AE criteria: increased breathlessness necessitating hospital admission Inclusion criteria: aged > 40 years, > 10 pack- years' smoking history, FEV_1 FEV1 < 50% predicted. Exclusion criteria: long-term corticosteroid therapy equivalent to > 5 mg prednisolone 5 mg/day or taking oral prednisolone for the current exacerbation; other co-existent lung disease, pneumonia; inability to co-operate with investigations; previous adverse drug reaction to corticosteroids, endoscopically or radiographically confirmed peptic ulcer disease within the past 2 years; history of cardiac failure, current hepatic or renal failure; inadequately treated hypertension
Interventions	High-dose arm: prednisolone 2.5 mg/kg orally daily for 3 days followed by 11 days placebo (3D systemic steroid treatment) Moderate- dose arm: prednisolone 0.6 mg/kg orally daily for 7 days followed by prednisolone 0.3 mg/kg orally daily for 7 days (14D systemic steroid treatment) Control: matched placebo for 14 days Co-interventions: inhaled bronchodilators, oral antibiotics, oral/IV xanthines and oxygen
Outcomes	Measured: spirometry, 6-minute walking distance, duration of hospitalisation, PaO_2, $PaCO_2$, visual analogue scale of breathlessness (100-mm scale, more breathless represented by a higher number), treatment failure, mortality, adverse events Reported or data available: spirometry, 6-minute walking distance, duration of hospitalisation, visual analogue scale of breathlessness Mortality: 1 death in the placebo arm. Morbidity: no adverse biochemical effects
Notes	Likelihood of COPD: aged > 40 years, > 10 pack-years' smoking history, diagnosis of asthma not exclusion, FEV_1 < 50% predicted Funding: no funding source disclosed Data analysed by review authors in 3 groups. Data from 14 day treatment group used in review Study published as abstract. Protocol and study data available to review authors

Wood-Baker 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers table
Allocation concealment (selection bias)	Unclear risk	Information not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants blinded to allocation until completion. Use of identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants withdrew from follow-up (6%), no details on group allocation
Selective reporting (reporting bias)	Low risk	Study outcome data supplied to review authors
Free of other potential confounders?	Low risk	Characteristics of both groups were similar at baseline

Zheng 2011

Methods	Design: parallel RCT Duration: not reported Setting: not reported
Participants	Number screened: not reported Number randomised: 153 Number completed: not reported Number withdrawals: not reported Baseline details: not reported Gender: not reported Age: not reported Diagnosis COPD: not reported AE criteria: not reported Inclusion criteria: not reported Exclusion criteria: not reported

Zheng 2011 *(Continued)*

Interventions	Group 1 (n = 53): 2 mg/4 mL nebulised budesonide, every 6 hours and normal saline 10 mL IV 4 times daily Group 2 (n = 54): methylprednisolone 40 mg, IV and nebulised normal saline 4 mL every 6 hours Group 3 (n = 46): nebulised normal saline 4 mL every 6 hours and normal saline 10 mL IV 4 times daily Treatment period: 7 days Follow-up period: not reported
Outcomes	Treatment failure, FEV_1, dyspnoea score, use of rescue medication and systemic glucocorticoids, length of hospital stay, adverse events
Notes	Likelihood of COPD: age limit for inclusion unknown, unknown pack- years' smoking, unknown if asthma an exclusion, fixed airflow obstruction criteria for COPD unknown. Funding: no sources disclosed Protocol: not available (abstract only). No trial registration located Emailed data request to authors - 9 August 2013, 30 September 2013 (Zheng). No response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, method for randomisation not known
Allocation concealment (selection bias)	Unclear risk	Allocation method not known
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, double-dummy and parallel controlled trial. Each group used nebulised medication (active or placebo) and had IV medication (active or saline) over same period and frequency
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Results data incomplete in abstract
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Free of other potential confounders?	Unclear risk	No data on baseline characteristics

ABG: arterial blood gas; ACCP: American College of Chest Physicians; AE: acute exacerbation; ATS: American Thoracic Society; CCQ: Clinical COPD Questionnaire; CI: confidence interval; COPD: chronic obstructive pulmonary disease; ED: emergency department; F: female; FEV_1 : forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICU: intensive care unit; IQR: interquartile range; IV: intravenous; LTOT: long-term oxygen therapy; LVF: left ventricular failure; M: male; MDI: metered-dose inhaler; NIV: non-invasive ventilation; $PaCO_2$: partial pressure of carbon dioxide dissolved in arterial blood; PaO_2 : partial pressure of oxygen dissolved in arterial blood; PEF: peak expiratory flow; QoL: quality of life; SD: standard deviation; SGRQ: St. George Respiratory Questionnaire.

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

Study	Reason for exclusion
Bafadhel 2012	Parallel group, double-blind trial, with randomisation to a biomarker-directed arm (peripheral blood eosinophil count at exacerbation was used to guide corticosteroid treatment) or standard treatment control group receiving prednisolone 30 mg capsule once daily (irrespective of the blood eosinophil biomarker results)
Bingol 2005	Participants did not have an acute exacerbation of COPD
Dahlen 2001	Purpose of study was to analyse the changes seen in inflammatory markers after treatment with 1 of 2 corticosteroids, 1 given orally, the other inhaled. The study was not placebo-controlled. Comparison between the effects of oral and inhaled corticosteroids
Gerogianni 2002	Not reported to be randomised. Study published as abstract only. Comparison of people with COPD divided into 2 groups. 1 group received prednisolone 12 mg daily plus SABA and the other SABA only during exacerbations and for 12 weeks after. Not clear how participants allocated to groups. Sent letter requesting details - no response within 4 months
Ghanei 2005	Participants with exposure to mustard gas inducing "chronic bronchitis", all non-smokers. Lung function indicates restriction present low FVC. Comparison of IV methylprednisolone and oral prednisolone in "acute exacerbation" of symptoms. Excluded as COPD not confirmed in participants
GSK FLIT98	Mild or moderate stable COPD. group comparison. Group 1: placebo 14 days + inhaled fluticasone 500 mcg 12/52; group 2:prednisolone 20-40 mg/day 14 days + placebo diskus 14 days and fluticasone 500 mcg 10/52; group 3: placebo 14 days + placebo diskus 12/52 .
Kunter 2006	Consecutive participants with exacerbations enrolled without randomisation to treatment. No placebo used in control group
Li 2003	RCT comparison of 2 corticosteroids, methylprednisolone and dexamethasone in hospital for 7-14 days. Dose regimen was 3 steps. IV/oral/inhaled methylprednisolone and dexamethasone and matched co-interventions. No placebo control group
Mirici 2002	Systemic (IV) corticosteroids versus nebulised budesonide in acute exacerbations of COPD, no placebo group
Murata 1990	Not an RCT. Retrospective study of 45 visits in which IV and oral corticosteroids were given (T visits) were compared with an equal number of matched visits in which they were withheld (N visits)
Plant 1999	Abstract for conference paper not obtainable
Rahman 2004	Oral corticosteroids 7 days versus 14 days in acute exacerbations of COPD, no placebo group
Rizzato 1998	The aim of study was to evaluate and compare clinical tolerability and relative potency of a new corticosteroid drug, deflazacort against that of methylprednisolone. No placebo control

Study	Reason for exclusion
Roede 2008	Cluster RCT of general practices, comparing high-dose oral corticosteroid course + antibiotics in accordance with the national guideline versus treatment 'as usual' (general practitioner could use oral corticosteroid and 75% of participants received oral corticosteroid)
Sayiner 2001	This study compared the likelihood of a link between duration of treatment with corticosteroids in COPD exacerbations and efficacy of treatment. Not a placebo-controlled trial
Shortall 2002	Participants screened with acute exacerbation COPD (n = 117), 50 recruited but 1 participant was admitted and included twice and 1 patent was admitted and included 3 times. Data not reported for participants on 1 occasion only. Comparison of oral corticosteroid methylprednisolone 40 mg + metered-dose inhaler bronchodilators with IV methylprednisolone 40 mg until wheeze-free then oral corticosteroid)/nebulised bronchodilators
Sin 2004	Comparison of inhaled corticosteroids, oral corticosteroids and placebo in stable COPD
Wang 2011	Observational study of high-dose (60 mg) and, lower- dose (< 60 mg) corticosteroid treatment in exacerbations (protocol clinicaltrials.gov/show/NCT01215825)

COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; IV: intravenous; RCT: randomised controlled trial; SABA: short-acting beta agonist.

DATA AND ANALYSES

Comparison 1. Systemic corticosteroid (SCS) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	9	917	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.35, 0.67]
1.1 Inpatient (treatment > 3 days)	6	680	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.30, 0.69]
1.2 Inpatient (treatment 1 day)	1	70	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [0.51, 6.89]
1.3 Outpatient	2	167	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.19, 0.72]
2 Rate of relapse to 30 days	2		Hazard ratio (Fixed, 95% CI)	0.78 [0.63, 0.97]
2.1 Inpatient (treatment > 3 days)	1		Hazard ratio (Fixed, 95% CI)	0.81 [0.50, 1.30]
2.2 Outpatient	1		Hazard ratio (Fixed, 95% CI)	0.78 [0.61, 0.99]
3 Relapse	5	582	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.42, 1.07]
3.1 Inpatient (treatment > 3 days)	4	439	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.45, 1.31]
3.2 Outpatient	1	143	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.18, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Mortality	12	1319	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.60, 1.66]
4.1 Inpatient (treatment > 3 days)	7	749	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.36, 1.92]
4.2 In patient (treatment 1 day)	1	96	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Outpatient	2	174	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 16.07]
4.4 ICU	2	300	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.58, 2.16]
5 Early FEV_1 (L) - absolute or change	7	649	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.09, 0.20]
5.1 Inpatient (treatment > 3 days)	7	649	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.09, 0.20]
5.2 Outpatient	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Early FEV_1 (% predicted)	3	231	Mean Difference (IV, Fixed, 95% CI)	3.85 [0.18, 7.52]
6.1 Inpatient (treatment > 3 days)	2	135	Mean Difference (IV, Fixed, 95% CI)	4.52 [-0.38, 9.42]
6.2 Inpatient (treatment 1 day)	1	96	Mean Difference (IV, Fixed, 95% CI)	3.00 [-2.54, 8.54]
7 Early FVC (L) - absolute or change	3	123	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.05, 0.45]
7.1 Inpatient (treatment > 3 days)	3	123	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.05, 0.45]
8 Early FVC (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Inpatient (treatment > 3 days)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Early FEV_1/FVC (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Inpatient (treatment > 3 days)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Early PEF (L/minute) - absolute or change	2	137	Mean Difference (IV, Fixed, 95% CI)	22.52 [5.02, 40.03]
10.1 Inpatient (treatment > 3 days)	1	113	Mean Difference (IV, Fixed, 95% CI)	16.19 [-2.27, 34.65]
10.2 Outpatient	1	24	Mean Difference (IV, Fixed, 95% CI)	78.96 [23.86, 134.06]
11 Early dyspnoea score	3	178	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [0.05, 0.64]

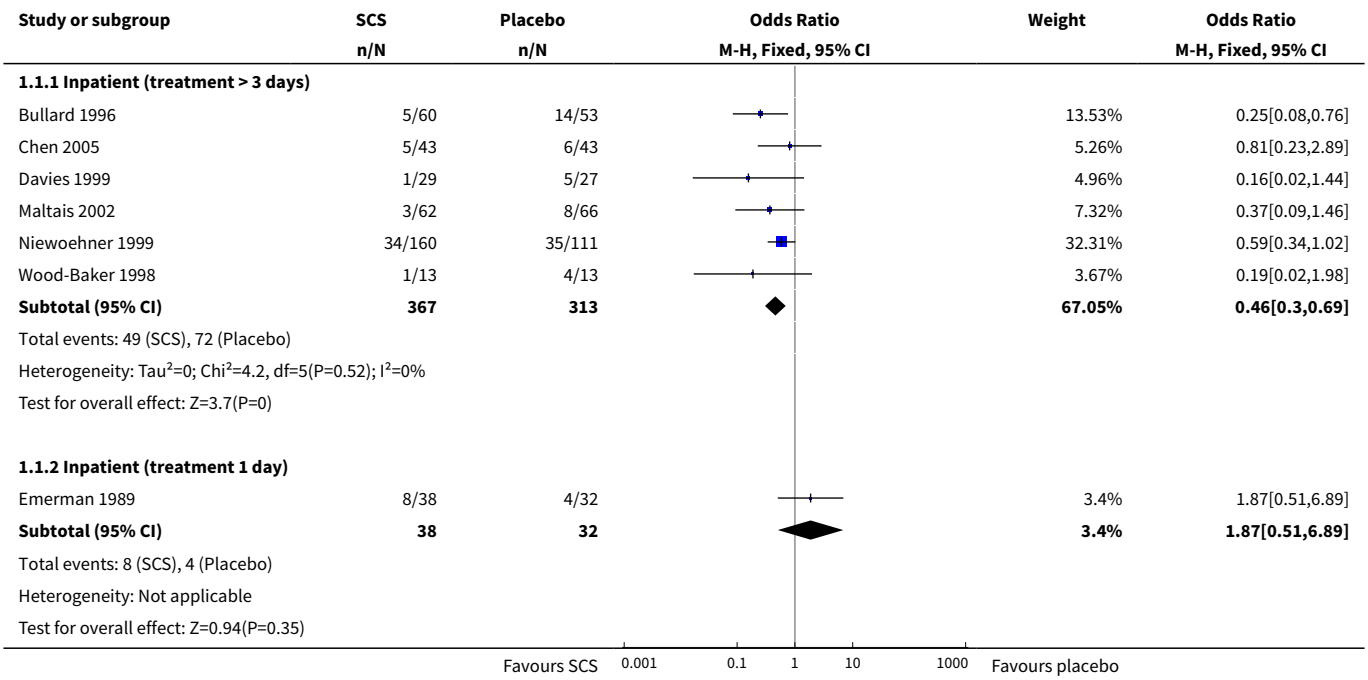
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Inpatient (treatment > 3 days)	3	178	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [0.05, 0.64]
12 Early PaO_2 (mmHg) - absolute or change	3	233	Mean Difference (IV, Fixed, 95% CI)	3.71 [0.55, 6.88]
12.1 Inpatient (treatment > 3 days)	3	233	Mean Difference (IV, Fixed, 95% CI)	3.71 [0.55, 6.88]
13 Early $PaCO_2$ (mmHg) - absolute or change	4	316	Mean Difference (IV, Fixed, 95% CI)	-2.21 [-3.84, -0.58]
13.1 Inpatient (treatment > 3 days)	3	233	Mean Difference (IV, Fixed, 95% CI)	-1.71 [-3.41, -0.01]
13.2 ICU	1	83	Mean Difference (IV, Fixed, 95% CI)	-7.90 [-13.61, -2.19]
14 FEV_1 (L) - absolute or change	7	669	Mean Difference (IV, Random, 95% CI)	0.09 [-0.01, 0.19]
14.1 Inpatient (treatment > 3 days)	5	522	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]
14.2 Outpatient	2	147	Mean Difference (IV, Random, 95% CI)	0.21 [-0.03, 0.45]
15 FEV_1 (% predicted)	2	129	Mean Difference (IV, Fixed, 95% CI)	6.14 [1.32, 10.96]
15.1 Inpatient (treatment > 3 days)	2	129	Mean Difference (IV, Fixed, 95% CI)	6.14 [1.32, 10.96]
16 FVC (L) - absolute or change	2	74	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.28, 0.32]
16.1 Inpatient (treatment > 3 days)	2	74	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.28, 0.32]
17 FVC (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Inpatient (treatment > 3 days)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 FEV_1/FVC (%)	3	189	Mean Difference (IV, Fixed, 95% CI)	1.07 [-2.11, 4.26]
18.1 Inpatient (treatment > 3 days)	3	189	Mean Difference (IV, Fixed, 95% CI)	1.07 [-2.11, 4.26]
19 PEF (L/minute) - absolute	2	112	Mean Difference (IV, Fixed, 95% CI)	119.06 [64.39, 173.73]
19.1 Inpatient (treatment > 3 days)	1	86	Mean Difference (IV, Fixed, 95% CI)	198.0 [81.58, 314.42]
19.2 Outpatient	1	26	Mean Difference (IV, Fixed, 95% CI)	96.72 [34.79, 158.65]

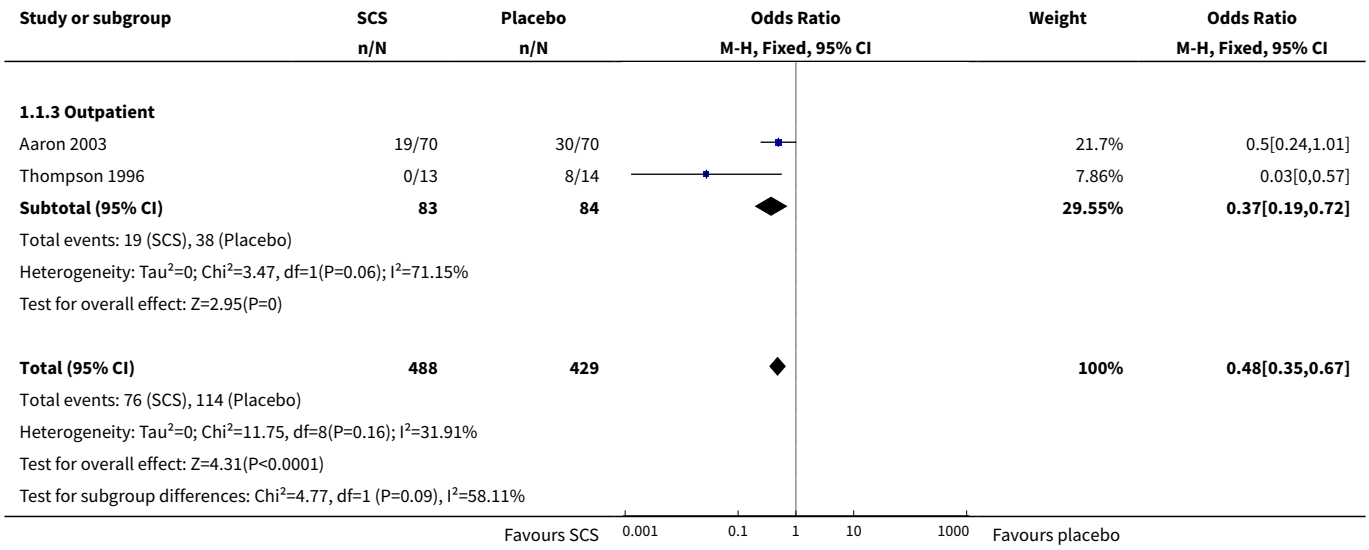
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 Transitional dyspnoea index (change)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20.1 Outpatient	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Dyspnoea score walking (change, VAS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Inpatient (treatment > 3 days)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Overall dyspnoea score	4	301	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.05, 0.41]
22.1 Inpatient (treatment > 3 days)	3	154	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.31, 0.32]
22.2 Outpatient	1	147	Std. Mean Difference (IV, Fixed, 95% CI)	0.37 [0.04, 0.69]
23 PaO_2 (mmHg) - change or absolute	4	200	Mean Difference (IV, Fixed, 95% CI)	6.86 [2.75, 10.96]
23.1 Inpatient (treatment > 3 days)	4	200	Mean Difference (IV, Fixed, 95% CI)	6.86 [2.75, 10.96]
24 $PaCO_2$ (mmHg) - absolute	3	188	Mean Difference (IV, Fixed, 95% CI)	-1.81 [-5.06, 1.44]
24.1 Inpatient (treatment > 3 days)	2	105	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-4.17, 2.97]
24.2 ICU	1	83	Mean Difference (IV, Fixed, 95% CI)	-7.60 [-15.41, 0.21]
25 Overall quality of life score (CRQ) (change)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
25.1 Outpatient	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 Physical capacity (m) (6-minute walk distance)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
26.1 Inpatient (treatment > 3 days)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Length of stay (days)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
27.1 Inpatient (treatment > 3 days)	2	296	Mean Difference (IV, Fixed, 95% CI)	-1.22 [-2.26, -0.18]
27.2 ICU	2	300	Mean Difference (IV, Fixed, 95% CI)	0.65 [-0.84, 2.15]
28 Duration of mechanical ventilation (days)	2	300	Mean Difference (IV, Random, 95% CI)	-1.03 [-3.44, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 ICU	2	300	Mean Difference (IV, Random, 95% CI)	-1.03 [-3.44, 1.38]
29 Adverse drug effects	8	736	Odds Ratio (M-H, Fixed, 95% CI)	2.33 [1.59, 3.43]
29.1 Inpatient (treatment > 3 days)	6	613	Odds Ratio (M-H, Fixed, 95% CI)	2.33 [1.59, 3.43]
29.2 Inpatient (treatment 1 day)	1	96	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.3 Outpatient	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
30 Adverse effect - hyperglycaemia (30 days)	6	804	Odds Ratio (M-H, Fixed, 95% CI)	2.79 [1.86, 4.19]
30.1 Inpatient (treatment > 3 days)	3	369	Odds Ratio (M-H, Fixed, 95% CI)	8.00 [2.96, 21.63]
30.2 Outpatient	1	135	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.14, 7.43]
30.3 ICU	2	300	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [1.33, 3.43]
31 Adverse effect - hypertension	2	274	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.44, 3.25]
31.1 Inpatient (treatment > 3 days)	1	191	Odds Ratio (M-H, Fixed, 95% CI)	2.17 [0.59, 7.95]
31.2 ICU	1	83	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.08, 2.54]
32 Adverse effect - gastrointestinal bleeding	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
32.1 ICU	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33 Adverse effect - dyspepsia	2	185	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.45, 3.21]
33.1 Inpatient (treatment > 3 days)	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.2 [0.18, 7.89]
33.2 Outpatient	1	135	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.38, 3.79]
34 Adverse effect - weight gain	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
34.1 Outpatient	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
35 Adverse effect - depression	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
35.1 Outpatient	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36 Adverse effect - anxiety	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

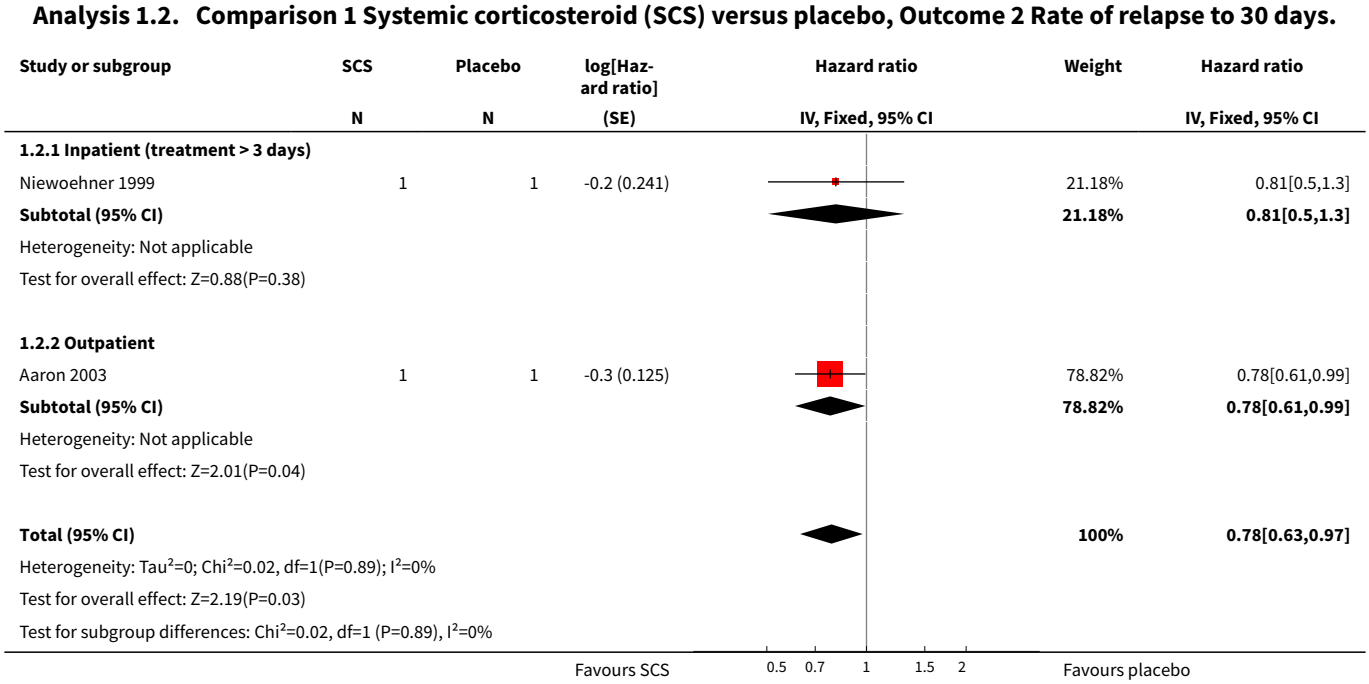
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.1 Outpatient	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37 Adverse effect - psychiatric disorder	2	331	Odds Ratio (M-H, Fixed, 95% CI)	2.15 [0.95, 4.88]
37.1 Inpatient (treatment > 3 days)	1	191	Odds Ratio (M-H, Fixed, 95% CI)	2.4 [0.56, 10.35]
37.2 Outpatient	1	140	Odds Ratio (M-H, Fixed, 95% CI)	2.05 [0.77, 5.50]
38 Adverse effect - insomnia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
38.1 Outpatient	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
39 Adverse effect - delirium	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
39.1 ICU	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
40 Adverse effect - secondary infection	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
40.1 ICU	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
41 Adverse effect - ventilator-associated pneumonia	2	300	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.44, 3.40]
41.1 ICU	2	300	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.44, 3.40]

Analysis 1.1. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 1 Treatment failure.

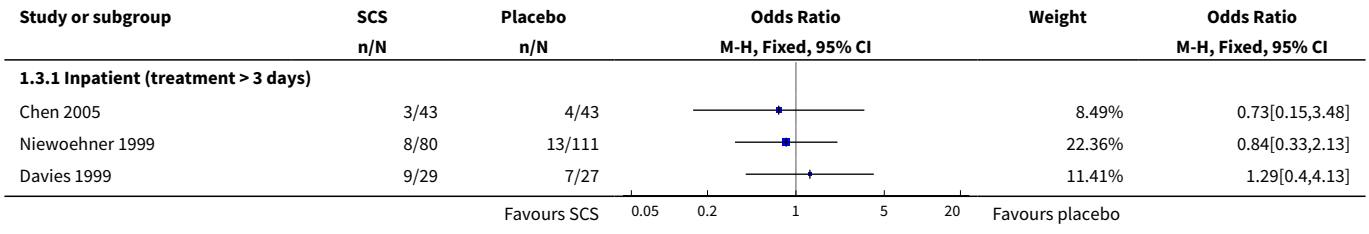


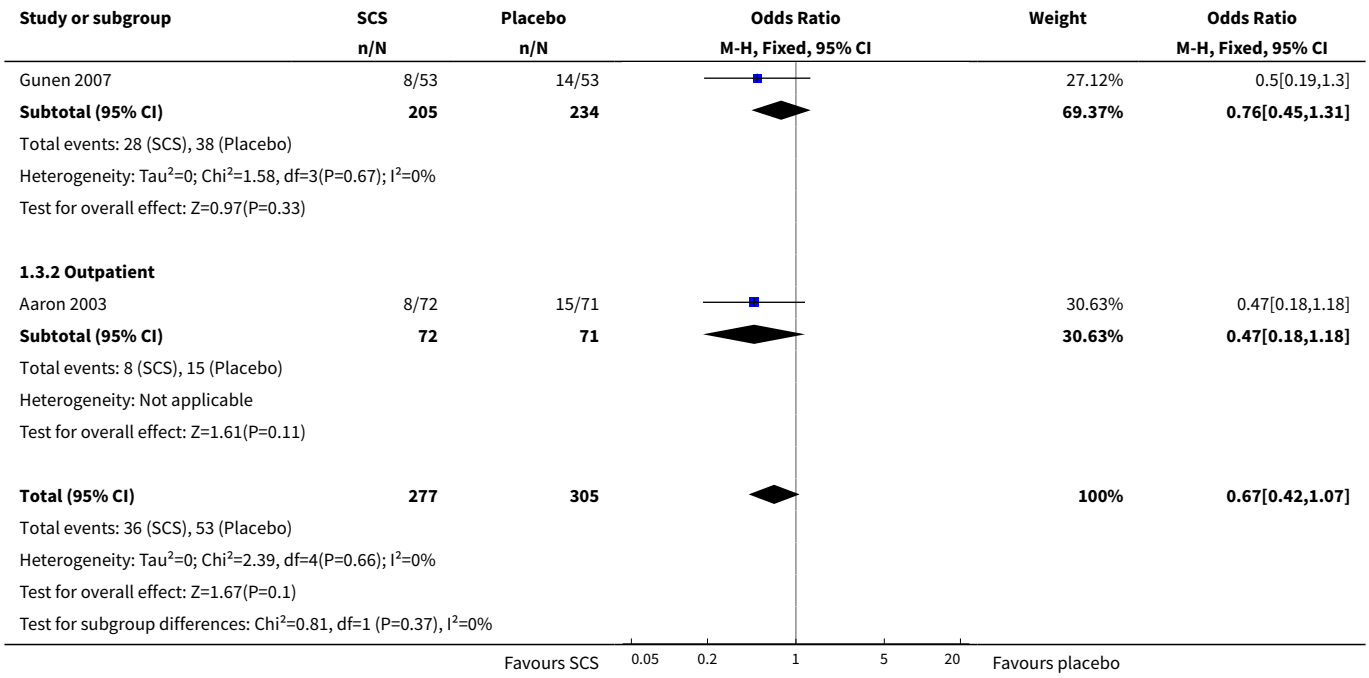


Analysis 1.2. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 2 Rate of relapse to 30 days.

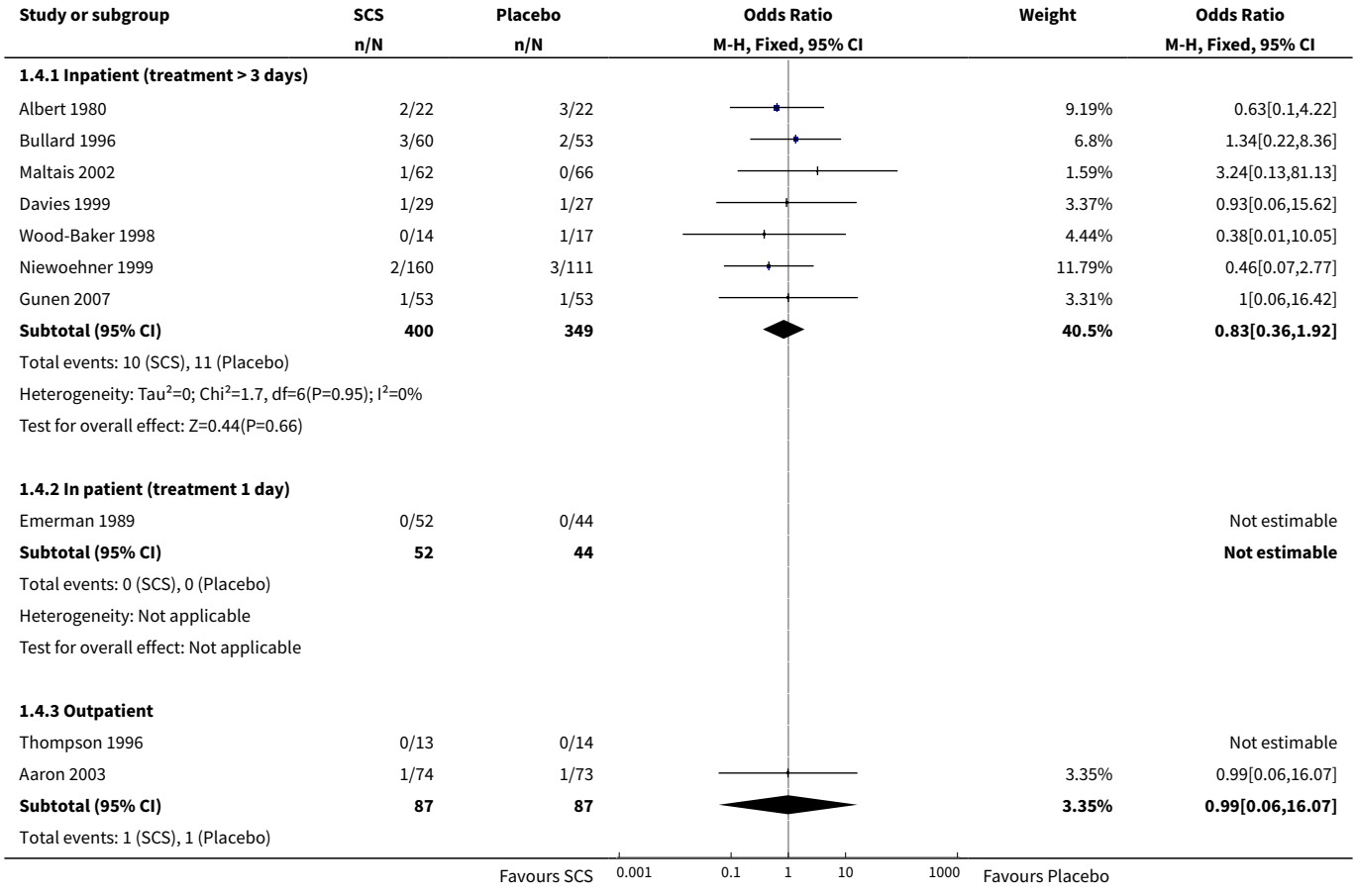


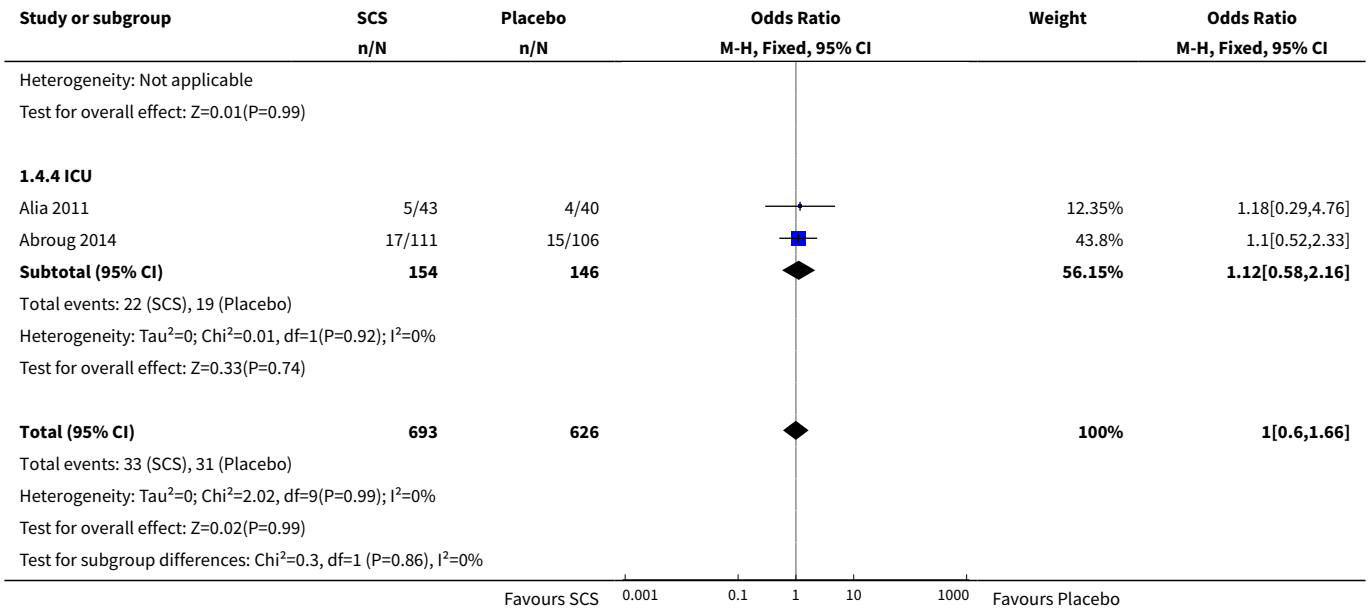
Analysis 1.3. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 3 Relapse.



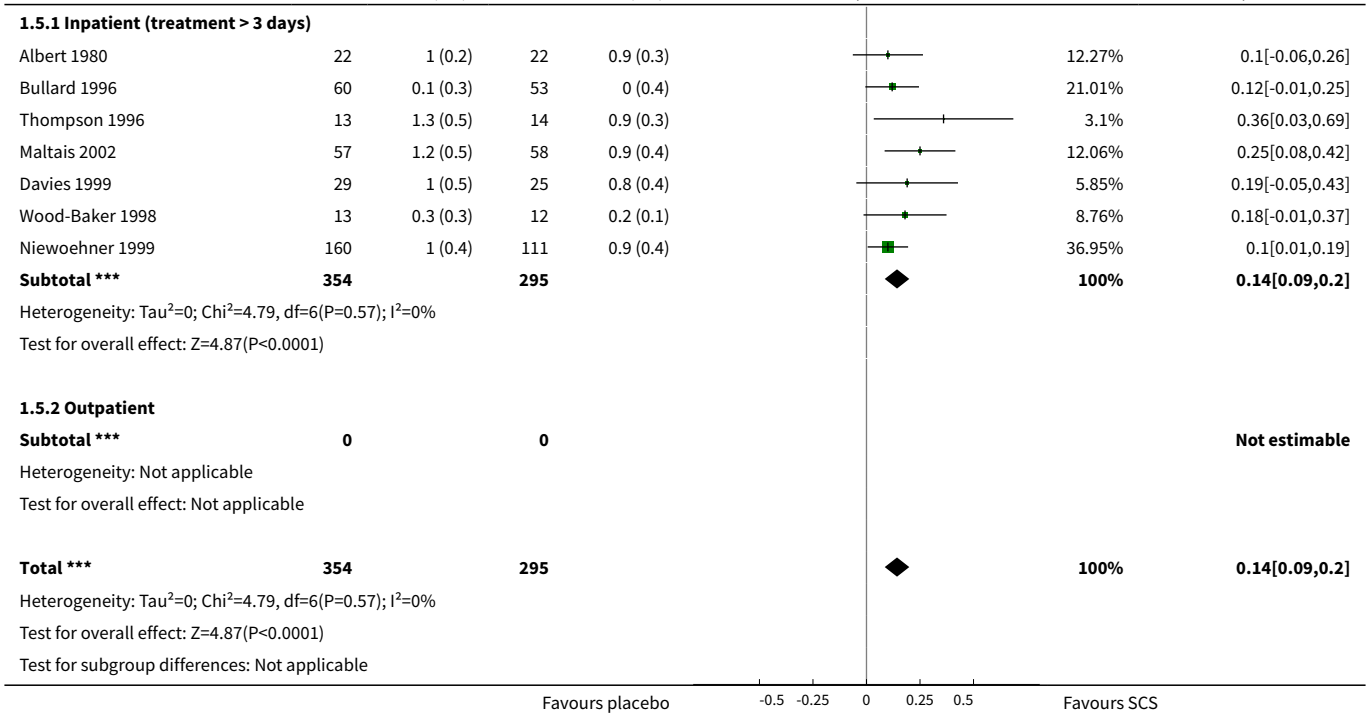


Analysis 1.4. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 4 Mortality.

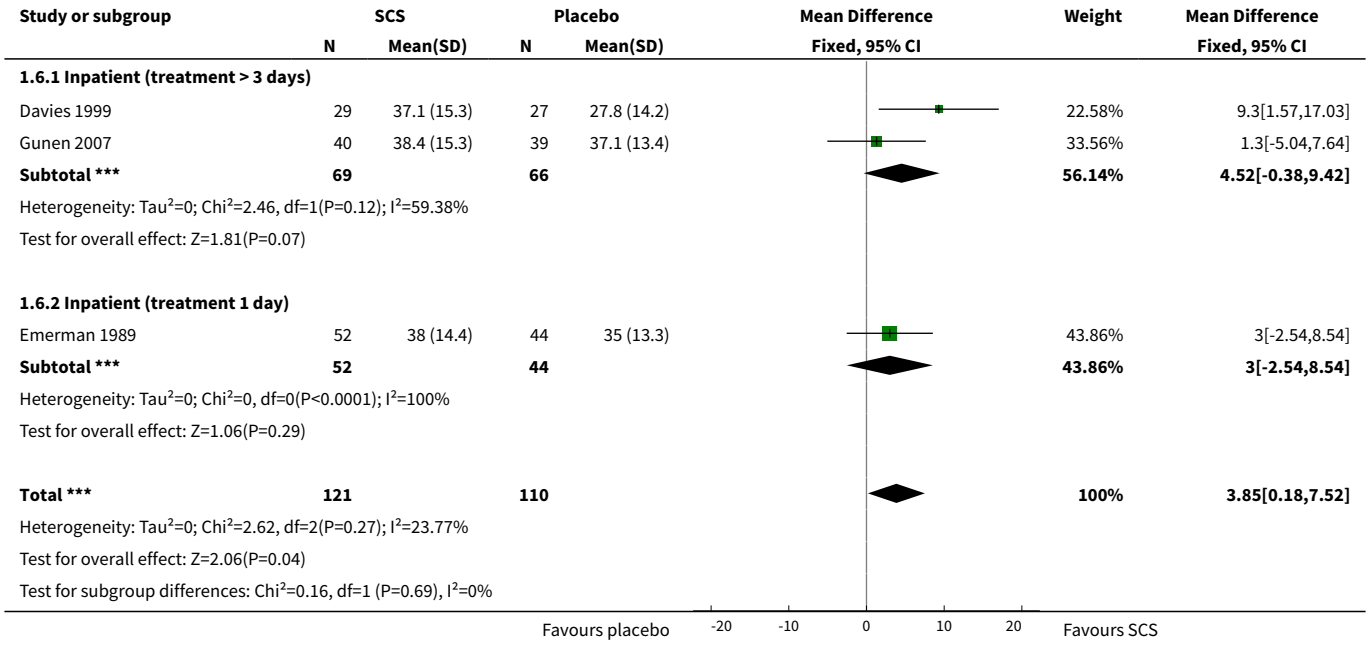




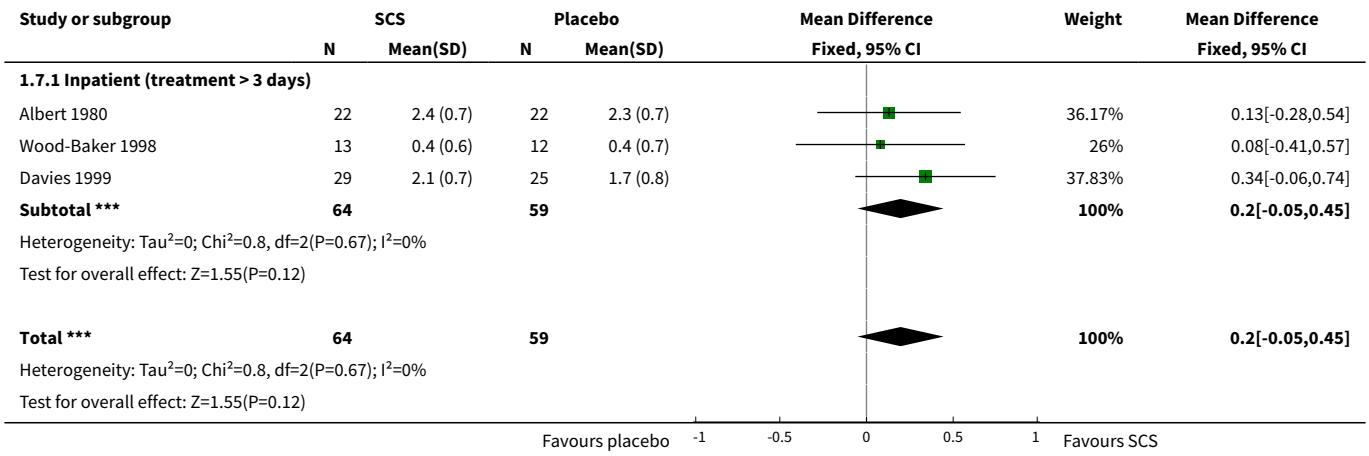
Analysis 1.5. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 5 Early FEV_1 (L) - absolute or change.



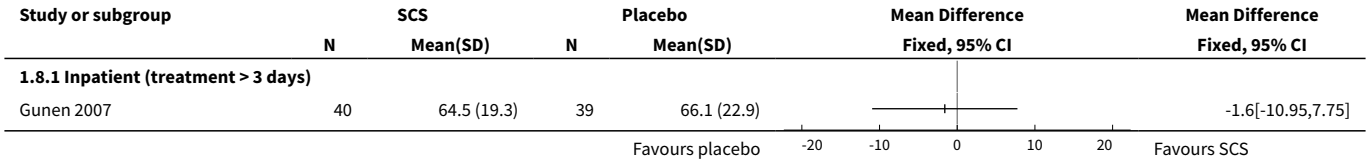
Analysis 1.6. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 6 Early FEV_1 (% predicted).



Analysis 1.7. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 7 Early FVC (L) - absolute or change.

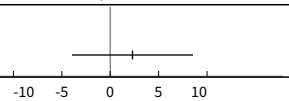


Analysis 1.8. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 8 Early FVC (% predicted).



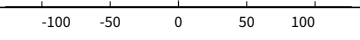
Analysis 1.9. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 9 Early FEV_1/FVC (%).

Study or subgroup	SCS N	SCS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.9.1 Inpatient (treatment > 3 days)						
Gunen 2007	40	48.4 (13.7)	39	46.1 (14.6)		2.3[-3.95,8.55]



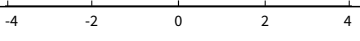
Analysis 1.10. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 10 Early PEF (L/minute) - absolute or change.

Study or subgroup	SCS N	SCS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.10.1 Inpatient (treatment > 3 days)							
Bullard 1996	60	21.7 (54.5)	53	5.5 (45.6)		89.91%	16.19[-2.27,34.65]
Subtotal ***	**60**		**53**			**89.91%**	**16.19[-2.27,34.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.72(P=0.09)							
1.10.2 Outpatient							
Thompson 1996	12	273.5 (81.8)	12	194.5 (52.8)		10.09%	78.96[23.86,134.06]
Subtotal ***	**12**		**12**			**10.09%**	**78.96[23.86,134.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.81(P=0)							
Total ***	**72**		**65**			**100%**	**22.52[5.02,40.03]**
Heterogeneity: Tau^2=0; Chi^2=4.48, df=1(P=0.03); I^2=77.69%							
Test for overall effect: Z=2.52(P=0.01)							
Test for subgroup differences: Chi^2=4.48, df=1 (P=0.03), I^2=77.69%							

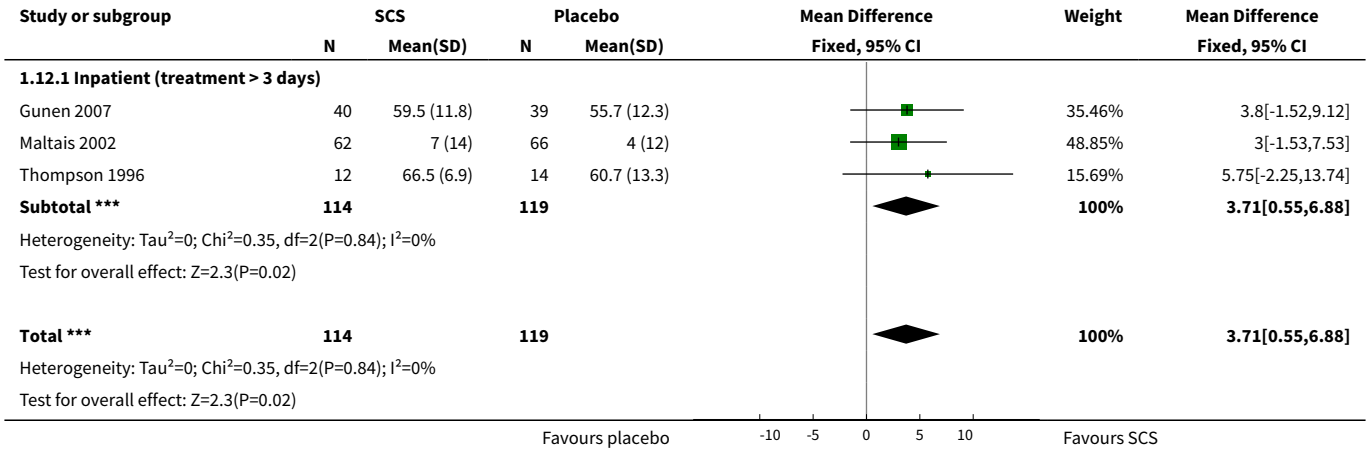


Analysis 1.11. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 11 Early dyspnoea score.

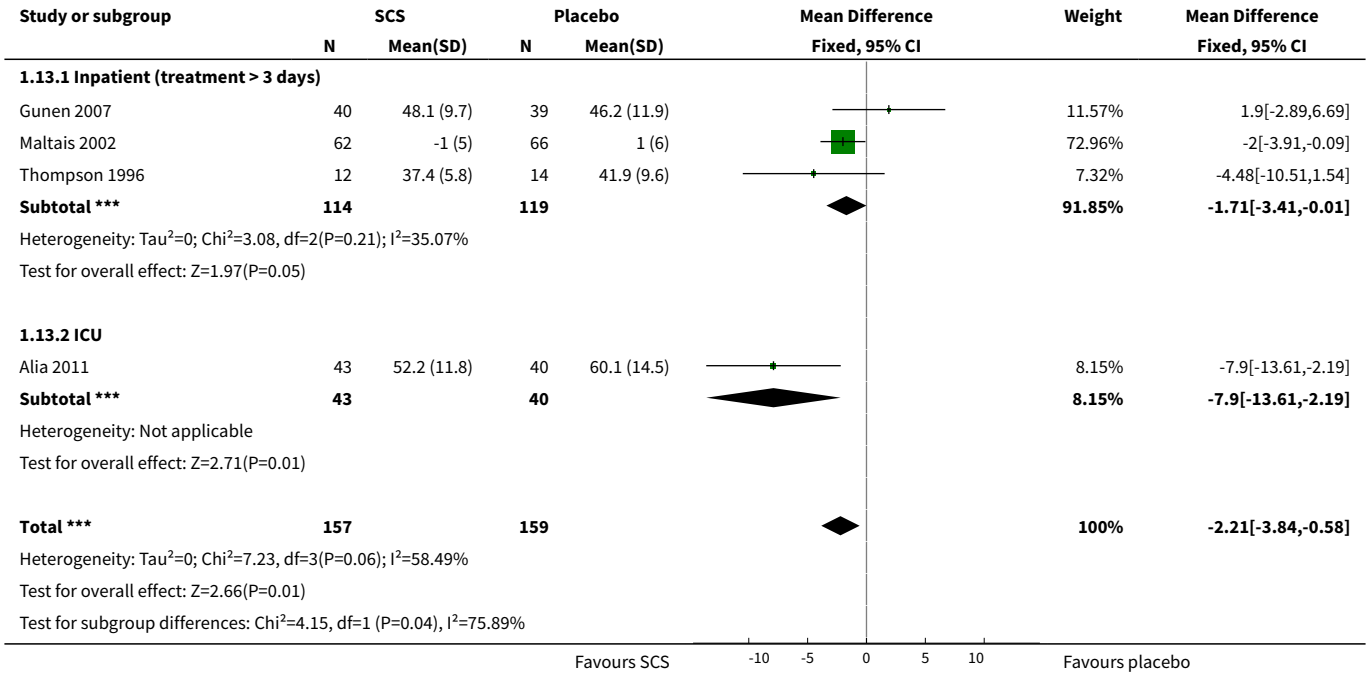
Study or subgroup	SCS N	SCS Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.11.1 Inpatient (treatment > 3 days)							
Thompson 1996	13	18.4 (14.4)	14	5 (15)		13.97%	0.88[0.09,1.68]
Maltais 2002	62	2.6 (2.3)	66	1.8 (2.6)		72.81%	0.32[-0.03,0.67]
Wood-Baker 1998	11	1.3 (2.9)	12	1.5 (2.2)		13.23%	-0.1[-0.92,0.72]
Subtotal ***	**86**		**92**			**100%**	**0.35[0.05,0.64]**
Heterogeneity: Tau^2=0; Chi^2=2.89, df=2(P=0.24); I^2=30.87%							
Test for overall effect: Z=2.28(P=0.02)							
Total ***	**86**		**92**			**100%**	**0.35[0.05,0.64]**
Heterogeneity: Tau^2=0; Chi^2=2.89, df=2(P=0.24); I^2=30.87%							
Test for overall effect: Z=2.28(P=0.02)							



Analysis 1.12. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 12 Early PaO_2 (mmHg) - absolute or change.

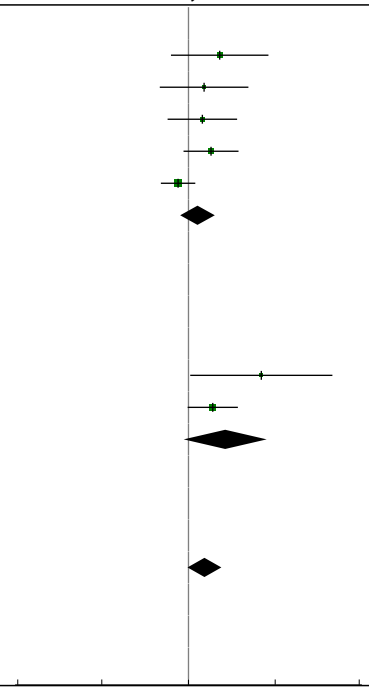


Analysis 1.13. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 13 Early $PaCO_2$ (mmHg) - absolute or change.



Analysis 1.14. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 14 FEV_1 (L) - absolute or change.

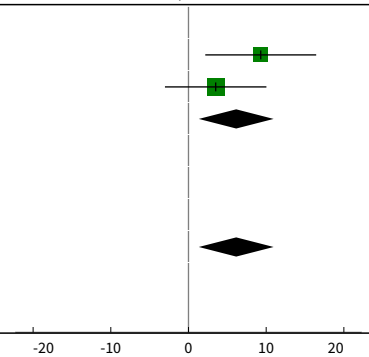
Study or subgroup	SCS N	SCS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.14.1 Inpatient (treatment > 3 days)							
Davies 1999	28	1.1 (0.6)	22	0.9 (0.4)		8.88%	0.18[-0.1,0.46]
Chen 2005	43	0.2 (0.5)	43	0.1 (0.7)		10.18%	0.09[-0.17,0.35]
Maltais 2002	48	1.2 (0.5)	43	1.1 (0.5)		13.92%	0.08[-0.12,0.28]
Wood-Baker 1998	12	0.3 (0.2)	12	0.2 (0.2)		17.84%	0.13[-0.03,0.29]
Niewoehner 1999	160	1 (0.4)	111	1.1 (0.4)		24.98%	-0.06[-0.16,0.04]
Subtotal * **	**291**		**231**			**75.8%**	**0.05[-0.05,0.15]**
Heterogeneity: Tau^2=0; Chi^2=6.21, df=4(P=0.18); I^2=35.57%							
Test for overall effect: Z=1.02(P=0.31)							
1.14.2 Outpatient							
Thompson 1996	13	1.4 (0.6)	14	1 (0.5)		4.85%	0.42[0.01,0.83]
Aaron 2003	57	0.3 (0.4)	63	0.2 (0.4)		19.35%	0.14[-0,0.28]
Subtotal * **	**70**		**77**			**24.2%**	**0.21[-0.03,0.45]**
Heterogeneity: Tau^2=0.01; Chi^2=1.59, df=1(P=0.21); I^2=37.26%							
Test for overall effect: Z=1.73(P=0.08)							
Total * **	**361**		**308**			**100%**	**0.09[-0.01,0.19]**
Heterogeneity: Tau^2=0.01; Chi^2=11.28, df=6(P=0.08); I^2=46.79%							
Test for overall effect: Z=1.85(P=0.06)							
Test for subgroup differences: Chi^2=1.46, df=1 (P=0.23), I^2=31.34%							



Favours placebo — Favours SCS

Analysis 1.15. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 15 FEV_1 (% predicted).

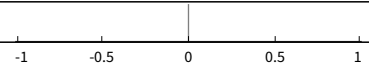
Study or subgroup	SCS N	SCS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.15.1 Inpatient (treatment > 3 days)							
Davies 1999	28	41.5 (14.6)	22	32.2 (11.1)		45.56%	9.3[2.16,16.44]
Gunen 2007	40	44.2 (14.6)	39	40.7 (15)		54.44%	3.5[-3.03,10.03]
Subtotal * **	**68**		**61**			**100%**	**6.14[1.32,10.96]**
Heterogeneity: Tau^2=0; Chi^2=1.38, df=1(P=0.24); I^2=27.58%							
Test for overall effect: Z=2.5(P=0.01)							
Total * **	**68**		**61**			**100%**	**6.14[1.32,10.96]**
Heterogeneity: Tau^2=0; Chi^2=1.38, df=1(P=0.24); I^2=27.58%							
Test for overall effect: Z=2.5(P=0.01)							



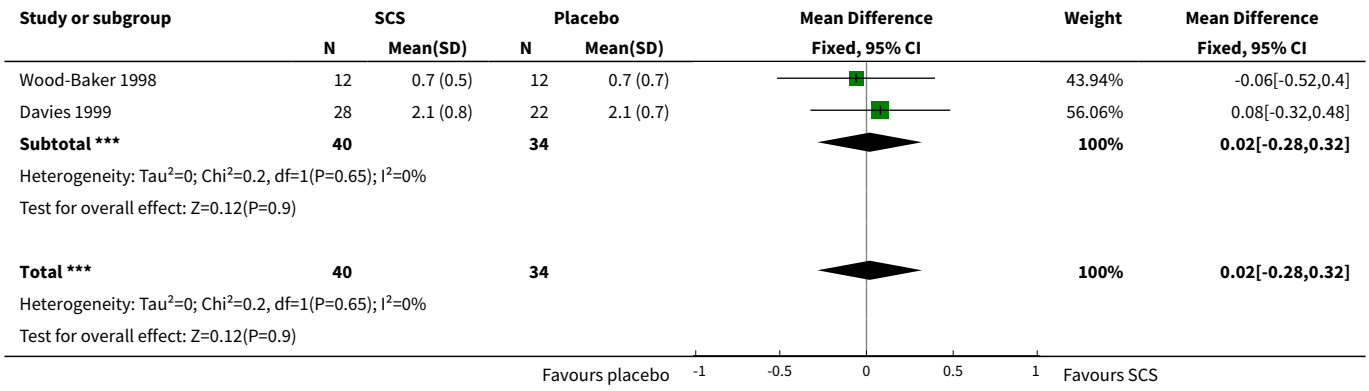
Favours placebo — Favours SCS

Analysis 1.16. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 16 FVC (L) - absolute or change.

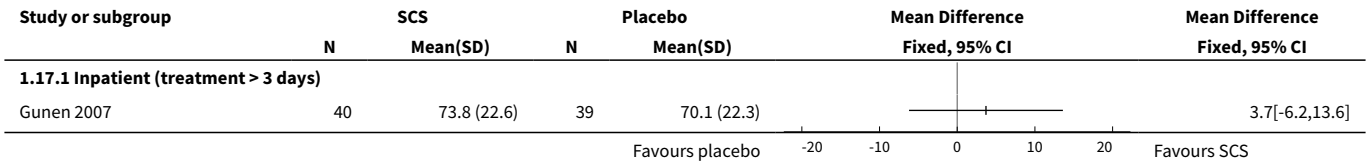
Study or subgroup	SCS N	SCS Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.16.1 Inpatient (treatment > 3 days)							



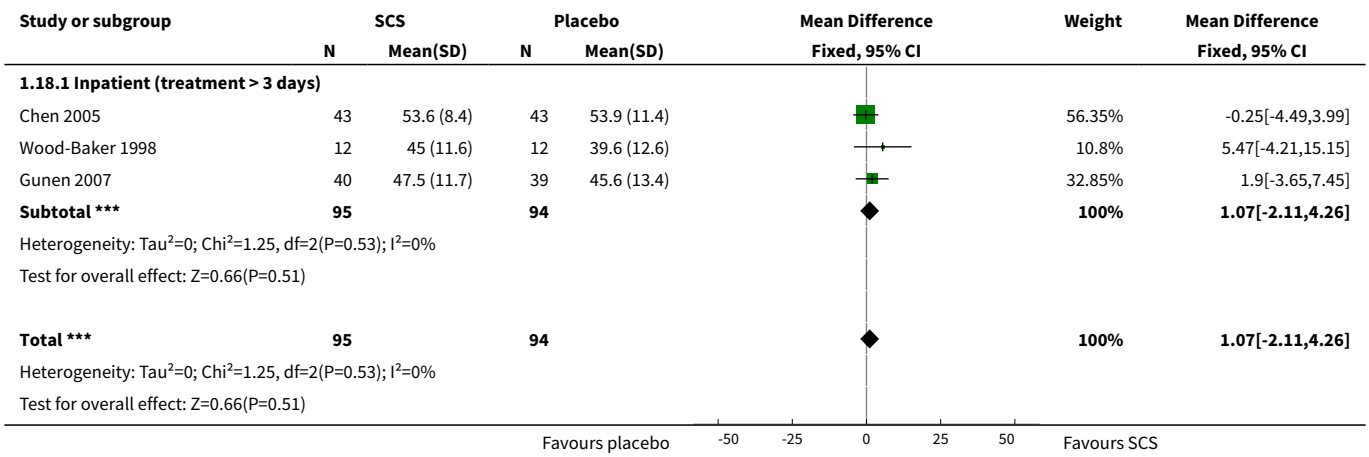
Favours placebo — Favours SCS



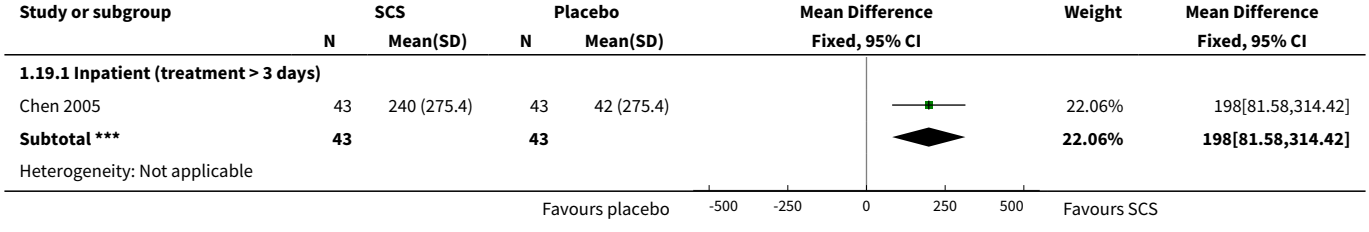
Analysis 1.17. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 17 FVC (% predicted).

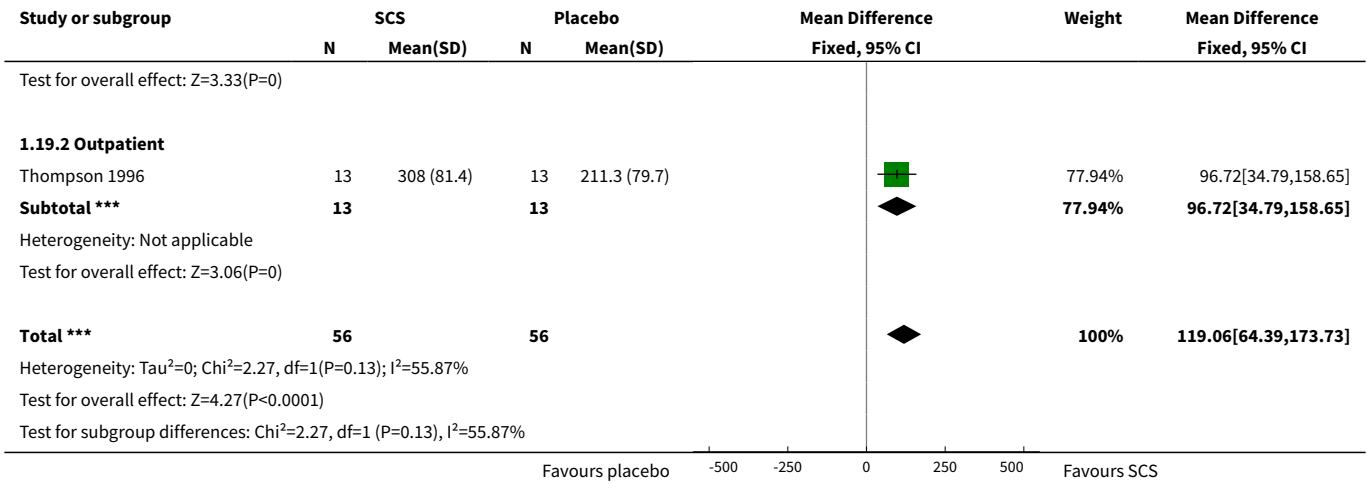


Analysis 1.18. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 18 FEV_1/FVC (%).

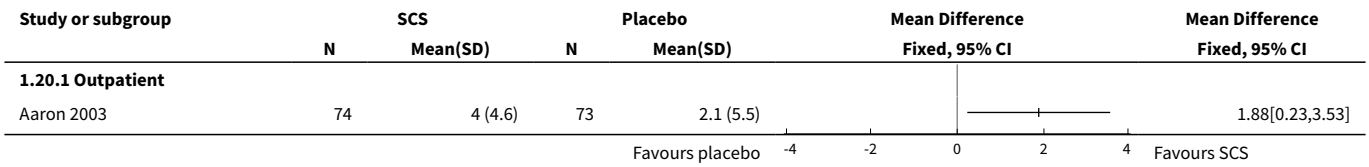


Analysis 1.19. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 19 PEF (L/minute) - absolute.

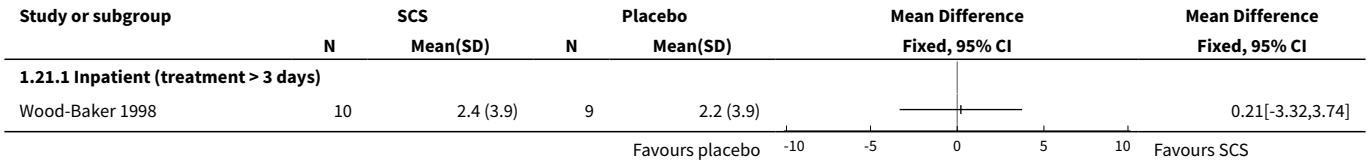




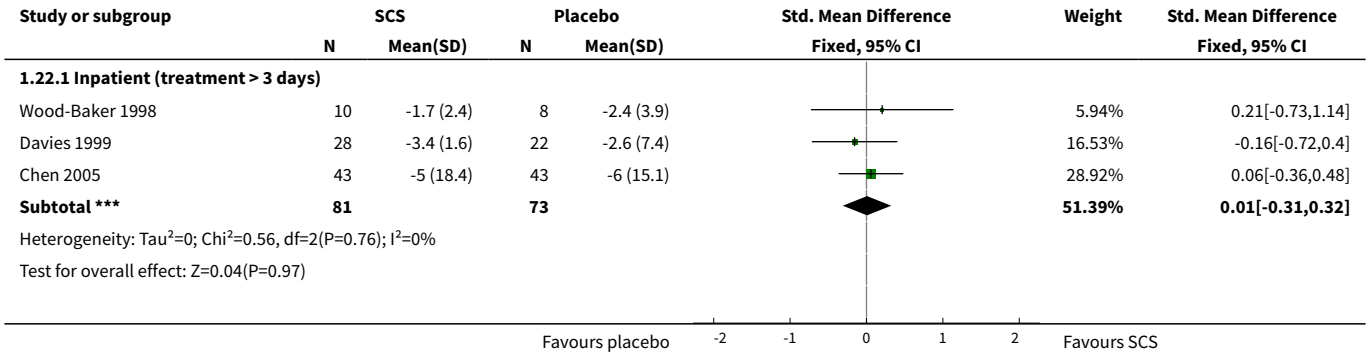
Analysis 1.20. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 20 Transitional dyspnoea index (change).

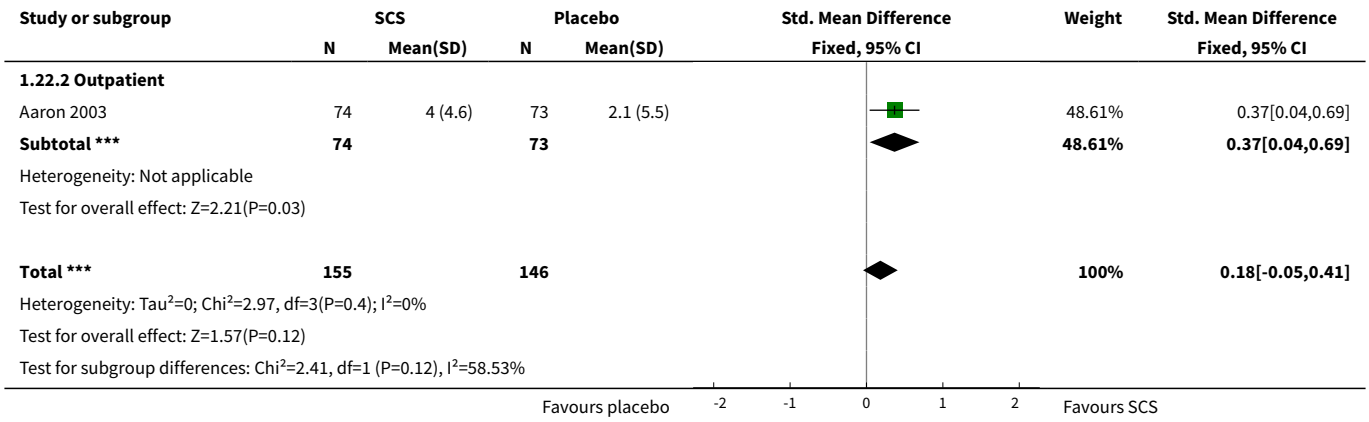


Analysis 1.21. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 21 Dyspnoea score walking (change, VAS).

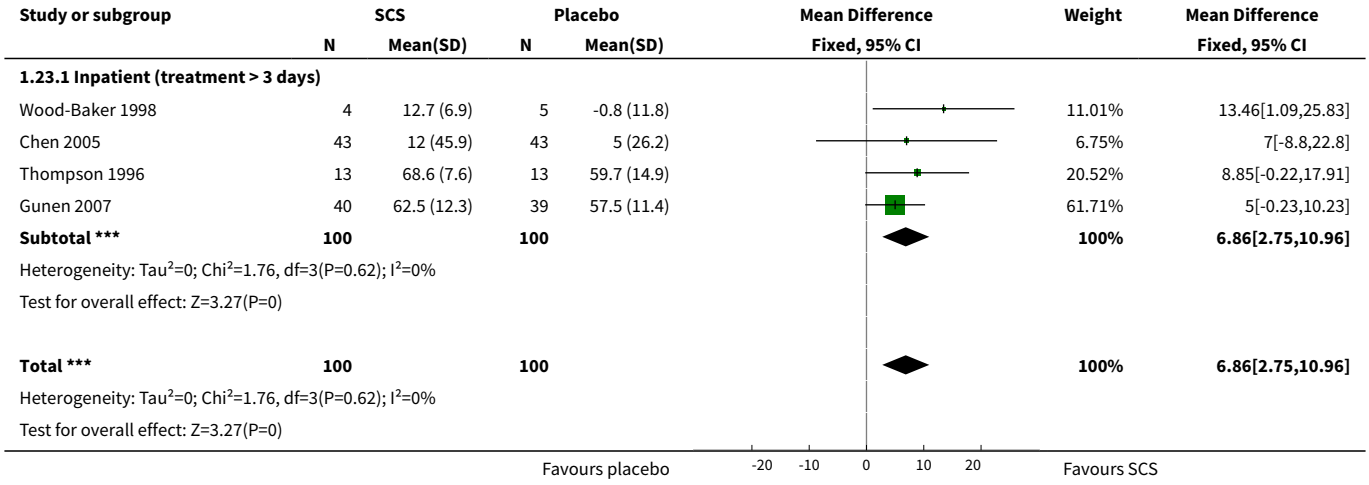


Analysis 1.22. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 22 Overall dyspnoea score.

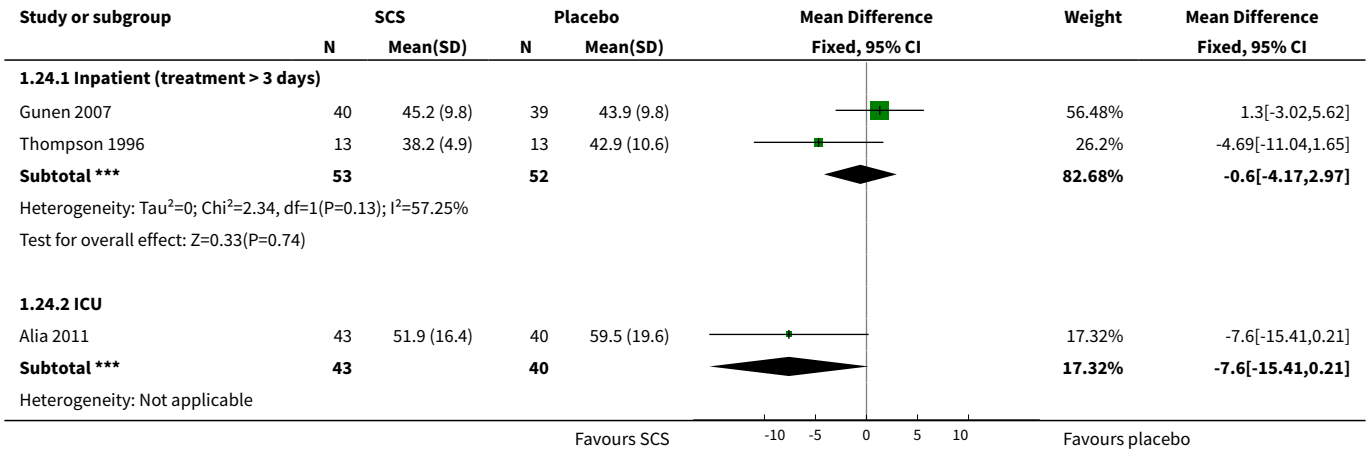


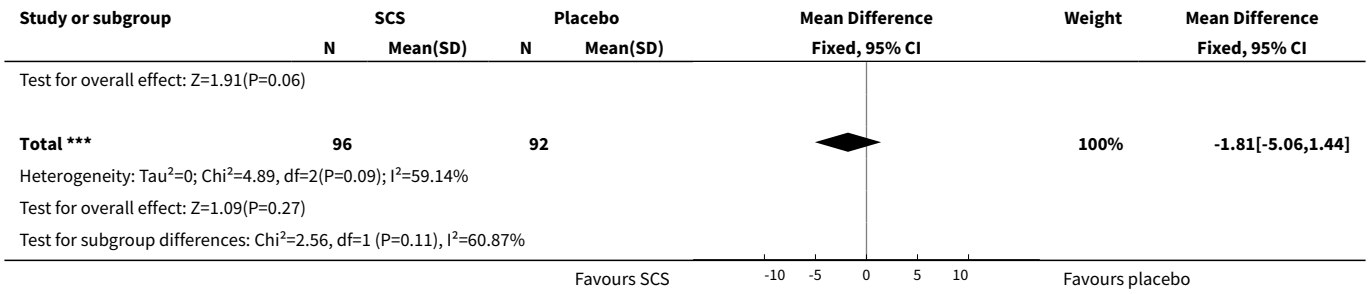


Analysis 1.23. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 23 PaO_2 (mmHg) - change or absolute.

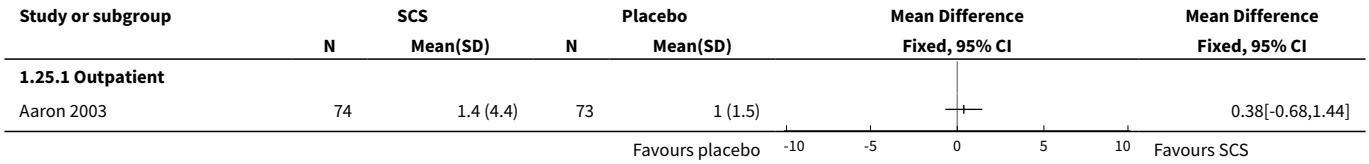


Analysis 1.24. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 24 $PaCO_2$ (mmHg) - absolute.

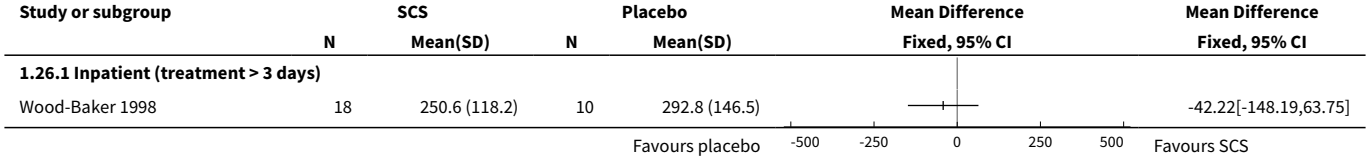




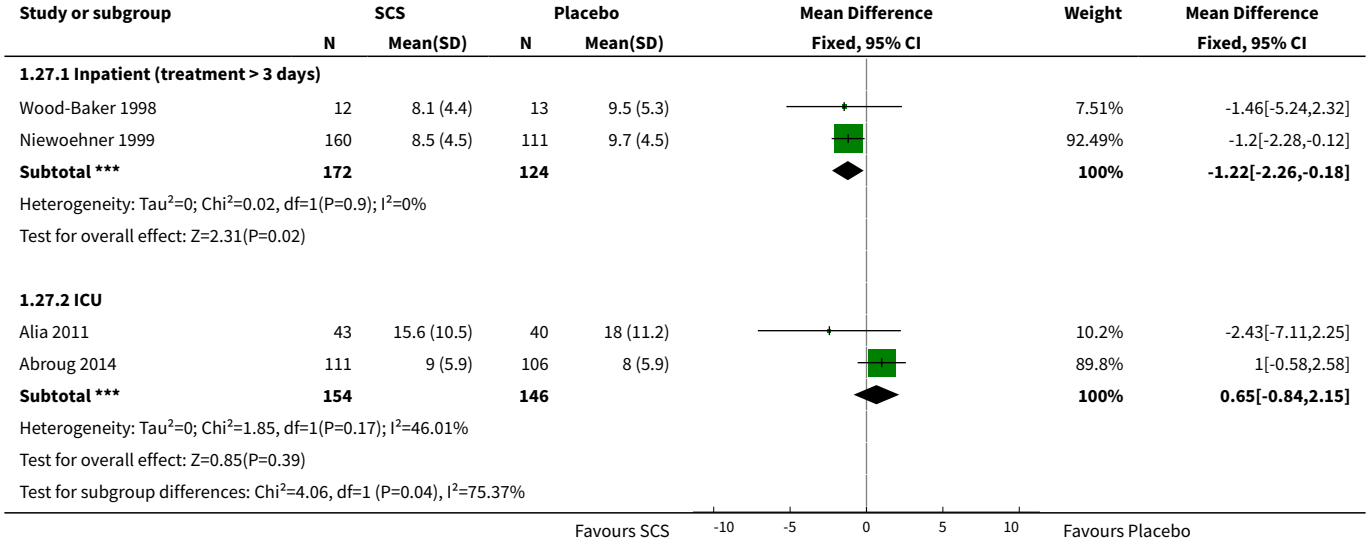
Analysis 1.25. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 25 Overall quality of life score (CRQ) (change).



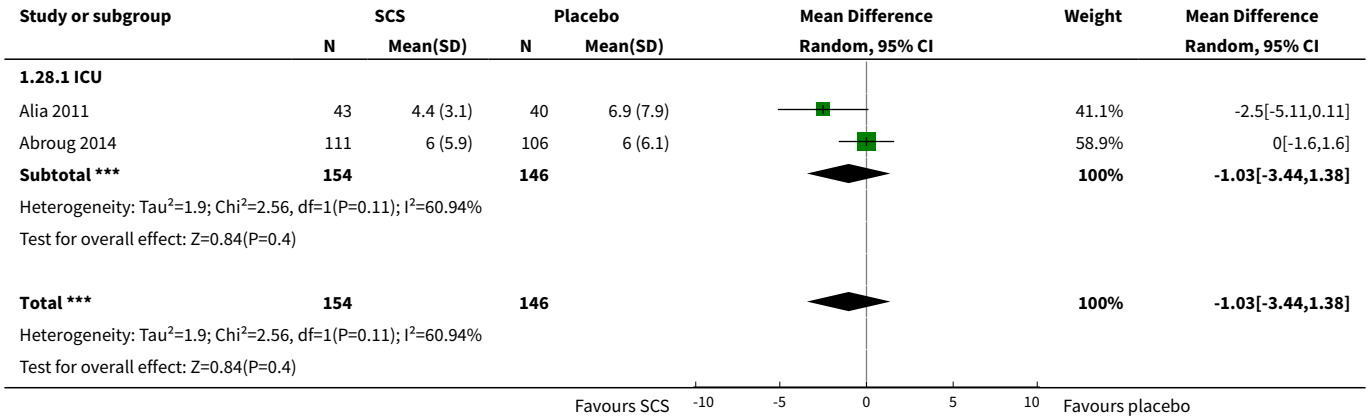
Analysis 1.26. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 26 Physical capacity (m) (6-minute walk distance).



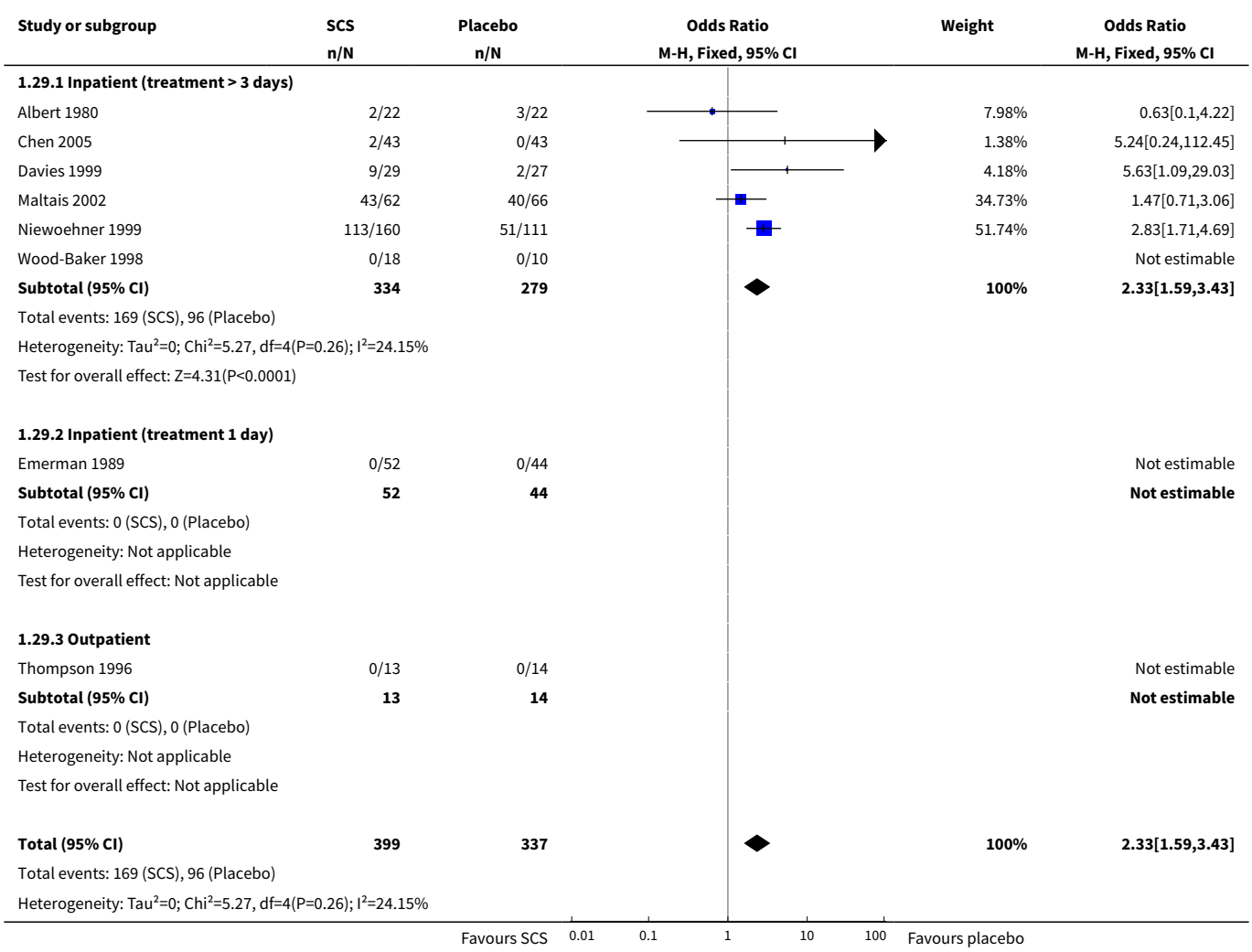
Analysis 1.27. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 27 Length of stay (days).

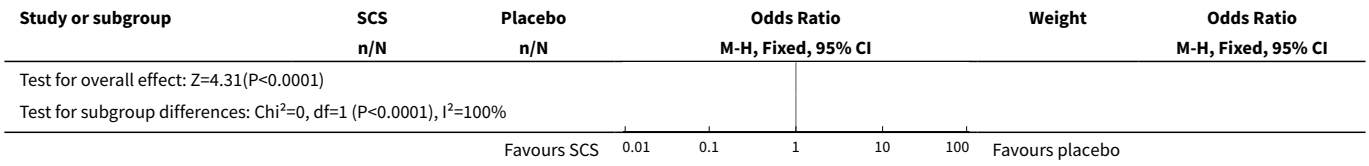


Analysis 1.28. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 28 Duration of mechanical ventilation (days).

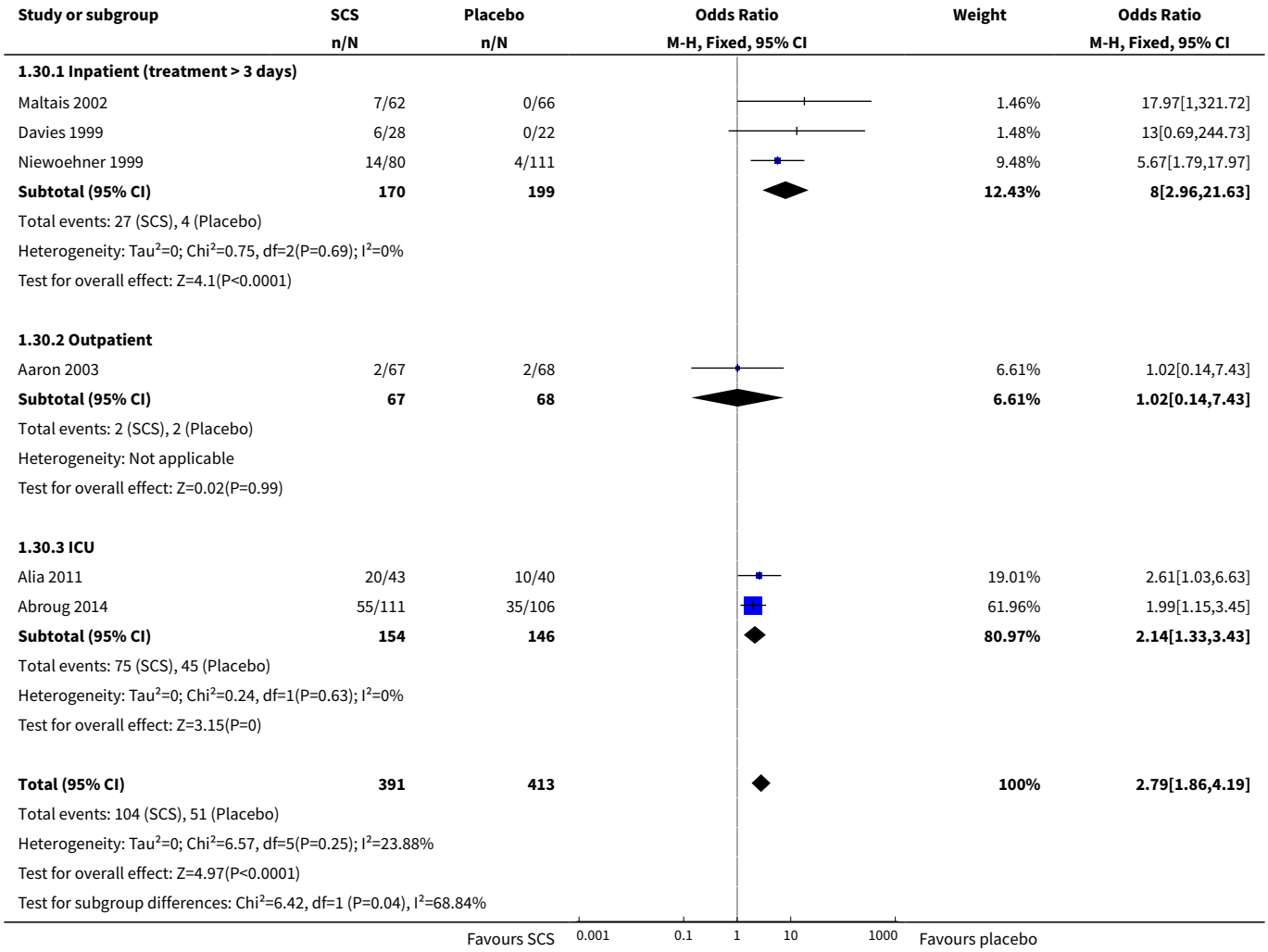


Analysis 1.29. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 29 Adverse drug effects.

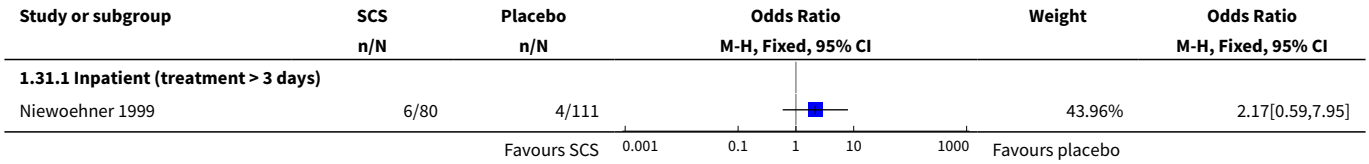


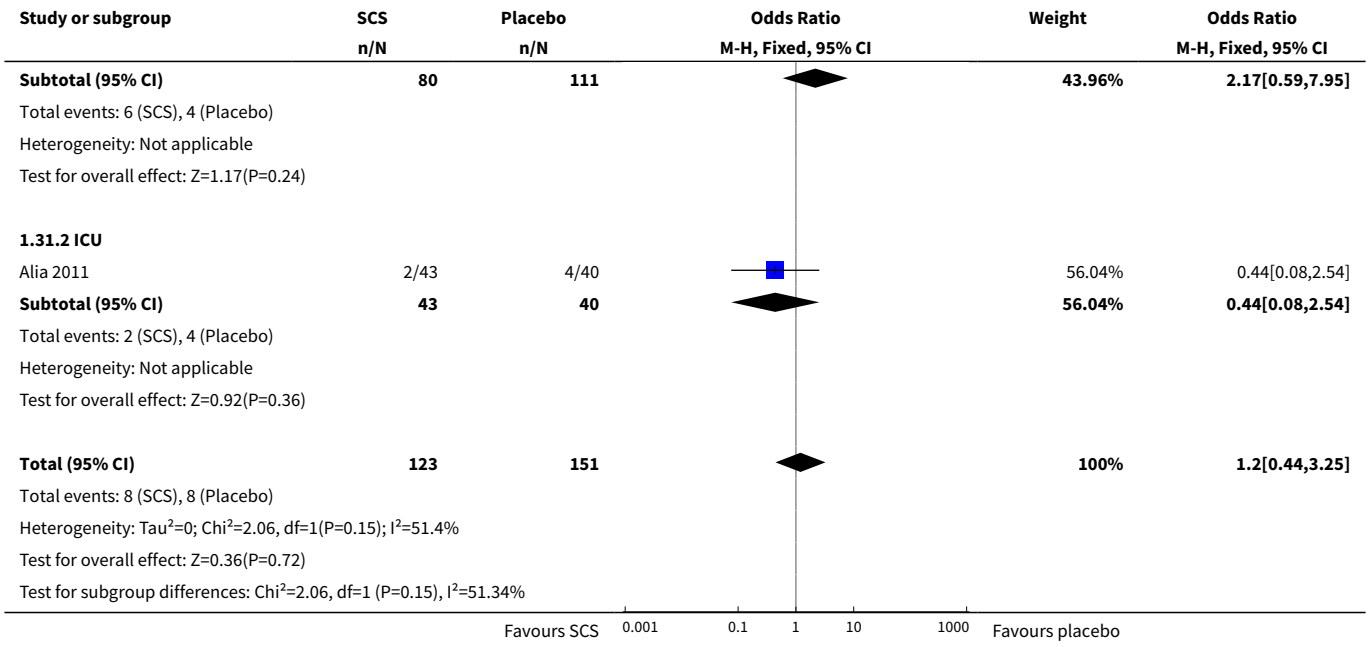


Analysis 1.30. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 30 Adverse effect - hyperglycaemia (30 days).

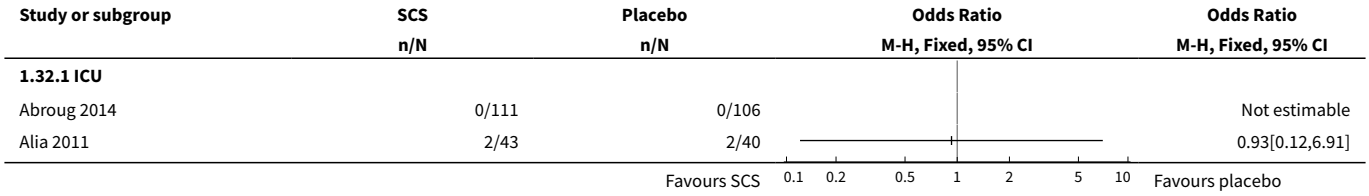


Analysis 1.31. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 31 Adverse effect - hypertension.

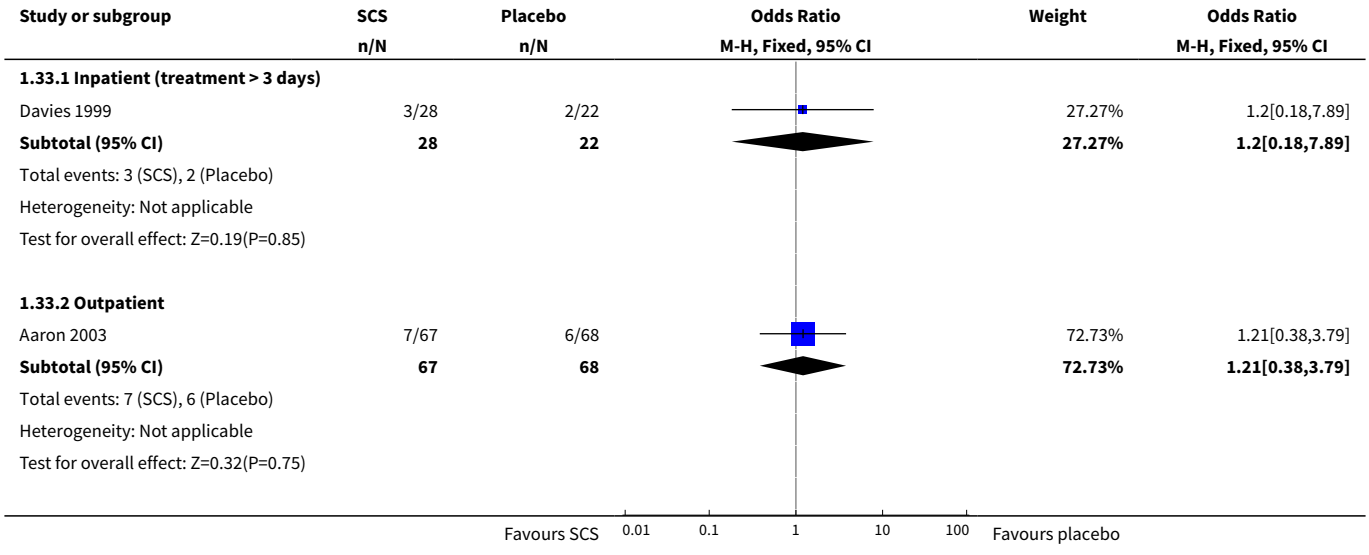


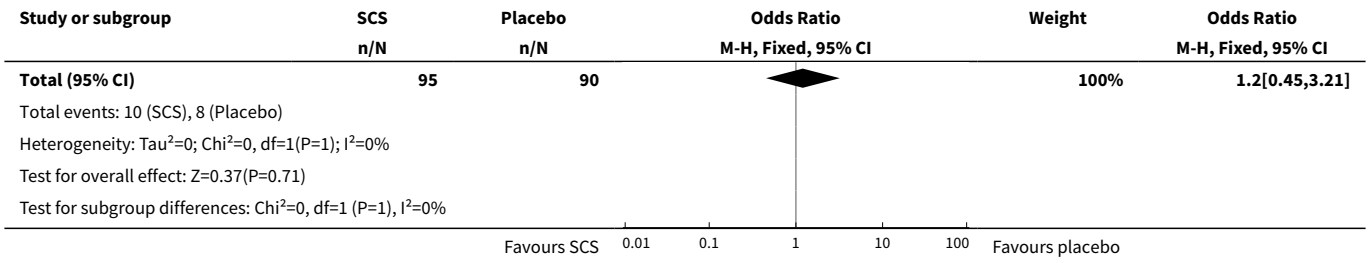


Analysis 1.32. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 32 Adverse effect - gastrointestinal bleeding.

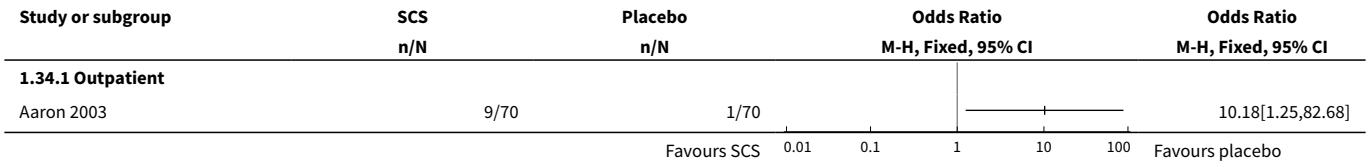


Analysis 1.33. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 33 Adverse effect - dyspepsia.

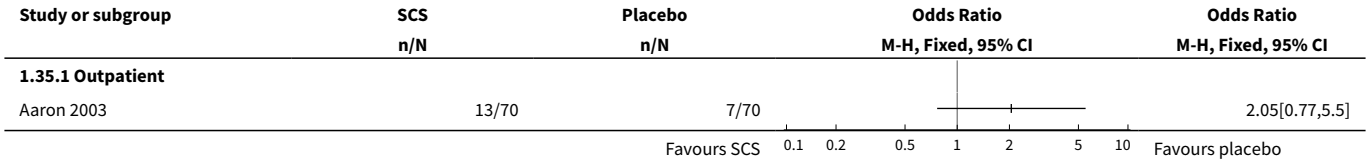




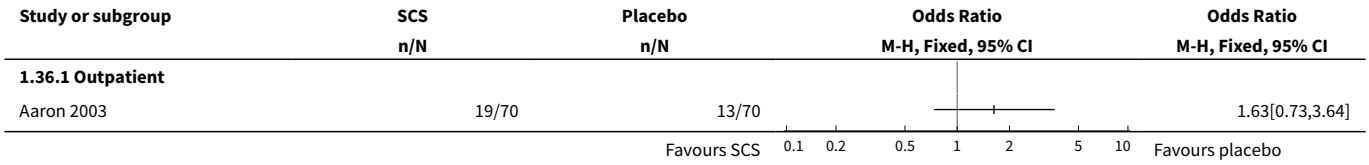
Analysis 1.34. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 34 Adverse effect - weight gain.



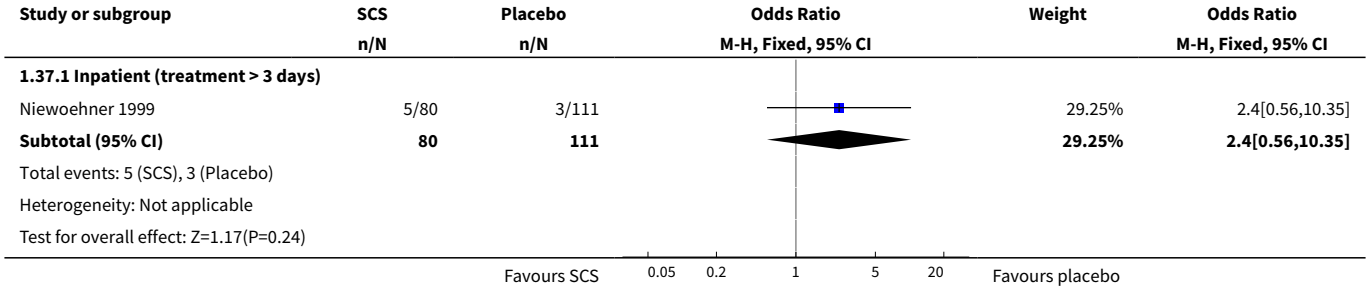
Analysis 1.35. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 35 Adverse effect - depression.

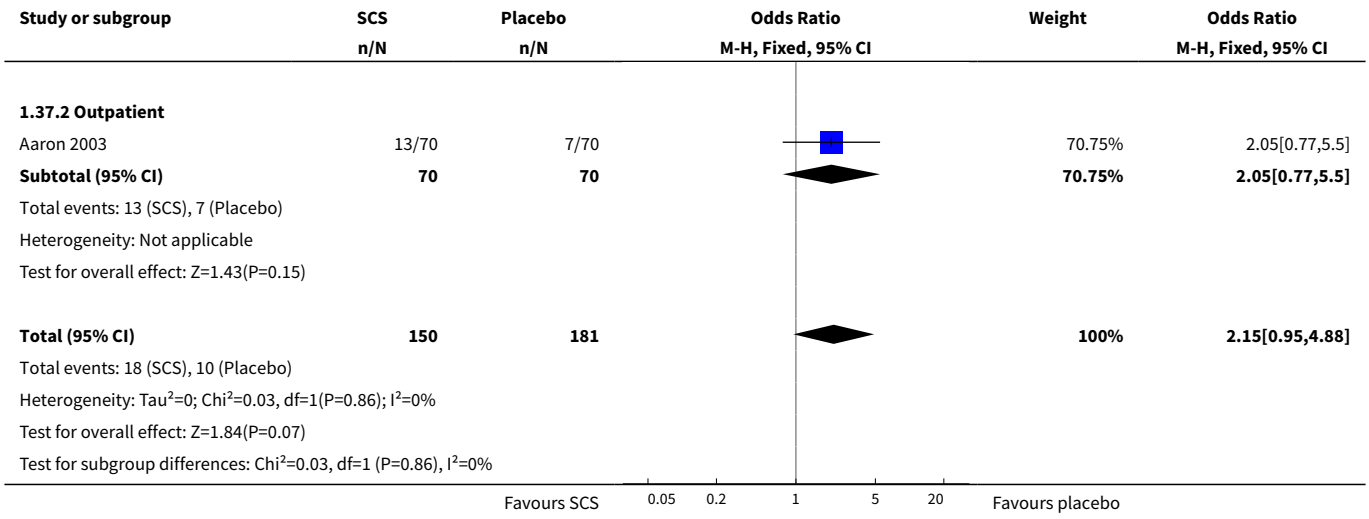


Analysis 1.36. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 36 Adverse effect - anxiety.

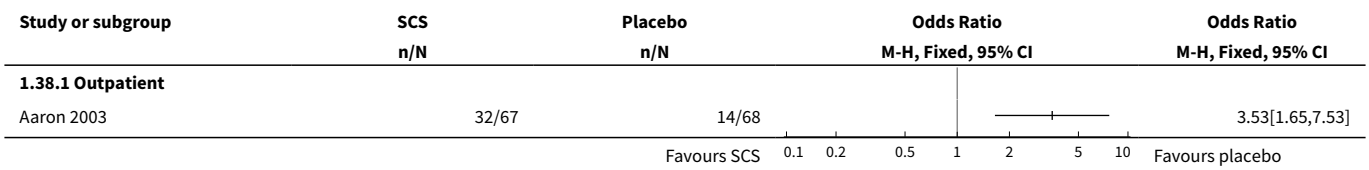


Analysis 1.37. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 37 Adverse effect - psychiatric disorder.

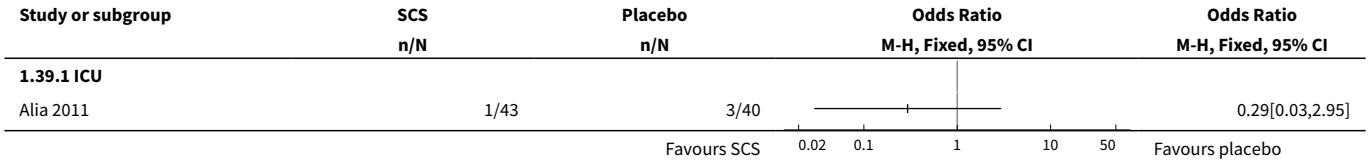




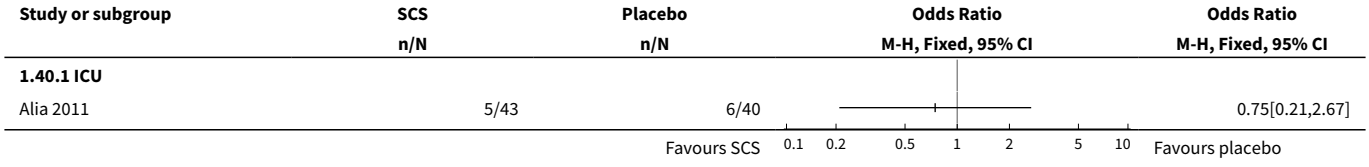
Analysis 1.38. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 38 Adverse effect - insomnia.



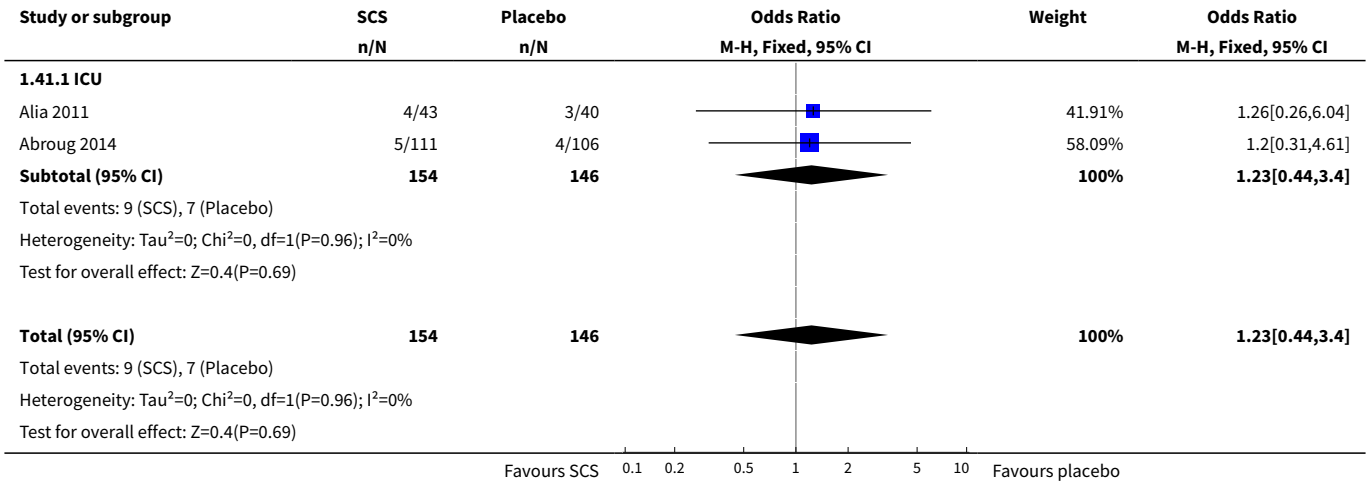
Analysis 1.39. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 39 Adverse effect - delirium.



Analysis 1.40. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 40 Adverse effect - secondary infection.



Analysis 1.41. Comparison 1 Systemic corticosteroid (SCS) versus placebo, Outcome 41 Adverse effect - ventilator-associated pneumonia.



Comparison 2. Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	3	298	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.30]
1.1 Inpatient treatment	3	298	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.30]
2 Relapse	3	298	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.50, 1.80]
2.1 Inpatient treatment	3	298	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.50, 1.80]
3 Mortality after discharge (1-3 months)	3	298	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.44, 4.51]
3.1 Inpatient treatment	3	298	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.44, 4.51]
4 Early FEV_1 (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Early FVC (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Early dyspnoea score (VAS)	2	75	Mean Difference (IV, Fixed, 95% CI)	0.62 [-0.55, 1.78]
6.1 Inpatient treatment	2	75	Mean Difference (IV, Fixed, 95% CI)	0.62 [-0.55, 1.78]

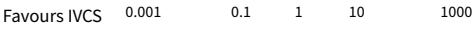
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Early cough score (VAS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Early sputum volume score (VAS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 FEV_1 (L) - absolute or change	3	285	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.08, 0.03]
9.1 Inpatient treatment (absolute)	2	75	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.24, 0.17]
9.2 Inpatient treatment (change)	1	210	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.08, 0.04]
10 FVC (L) - absolute	2	75	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.33, 0.22]
10.1 Inpatient treatment	2	75	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.33, 0.22]
11 FEV_1/FVC ratio	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Dyspnoea score (VAS) at 7-10 days	2	75	Mean Difference (IV, Fixed, 95% CI)	1.28 [-0.24, 2.80]
12.1 Inpatient treatment	2	75	Mean Difference (IV, Fixed, 95% CI)	1.28 [-0.24, 2.80]
13 Cough score (VAS) at 7 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Sputum volume score (VAS) at 7 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 PaO_2 (mmHg) at 7 days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 $PaCO_2$ (mmHg) at 7 days	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16.1 Inpatient treatment	1	38	Mean Difference (IV, Fixed, 95% CI)	5.5 [-0.79, 11.79]
17 Health status: Clinical COPD Questionnaire (change at 1 week)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Inpatient treament	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Quality of life: SGRQ (change at 7 days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Inpatient treament	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Quality of life: CRQ Dyspnoea (change at 4 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Quality of life: CRQ Fatigue (change at 4 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Quality of life: CRQ Mastery (change at 4 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Quality of life: CRQ Emotion (change at 4 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 Inpatient treatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Duration of hospitalisation (days)	3	298	Mean Difference (IV, Fixed, 95% CI)	1.54 [-0.09, 3.17]
23.1 Inpatient treatment	3	298	Mean Difference (IV, Fixed, 95% CI)	1.54 [-0.09, 3.17]
24 Adverse effect - hyperglycaemia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Inpatient treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Adverse effect - hypertension	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
25.1 Inpatient treatment	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

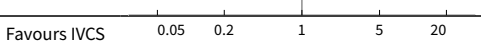
Analysis 2.1. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 1 Treatment failure.

Study or subgroup	IVCS n/N	OCS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Inpatient treatment					
Willaert 2002	3/23	6/25		23.51%	0.48[0.1,2.18]
Ceviker 2014	2/20	4/20		16.93%	0.44[0.07,2.76]
de Jong 2007	12/107	14/103		59.56%	0.8[0.35,1.83]
Subtotal (95% CI)	**150**	**148**		**100%**	**0.67[0.34,1.3]**
Total events: 17 (IVCS), 24 (OCS)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=2(P=0.75); I^2=0%					
Test for overall effect: Z=1.19(P=0.23)					
Total (95% CI)	**150**	**148**		**100%**	**0.67[0.34,1.3]**
Total events: 17 (IVCS), 24 (OCS)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=2(P=0.75); I^2=0%					
Test for overall effect: Z=1.19(P=0.23)					



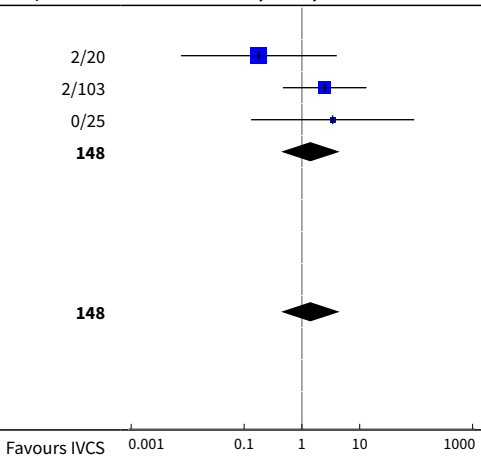
Analysis 2.2. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 2 Relapse.

Study or subgroup	IVCS n/N	OCS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Inpatient treatment					
Ceviker 2014	5/20	4/20		15.64%	1.33[0.3,5.93]
de Jong 2007	13/107	11/103		51.34%	1.16[0.49,2.71]
Willaert 2002	4/23	8/25		33.02%	0.45[0.11,1.76]
Subtotal (95% CI)	**150**	**148**		**100%**	**0.95[0.5,1.8]**
Total events: 22 (IVCS), 23 (OCS)					
Heterogeneity: Tau^2=0; Chi^2=1.57, df=2(P=0.46); I^2=0%					
Test for overall effect: Z=0.16(P=0.88)					
Total (95% CI)	**150**	**148**		**100%**	**0.95[0.5,1.8]**
Total events: 22 (IVCS), 23 (OCS)					
Heterogeneity: Tau^2=0; Chi^2=1.57, df=2(P=0.46); I^2=0%					
Test for overall effect: Z=0.16(P=0.88)					



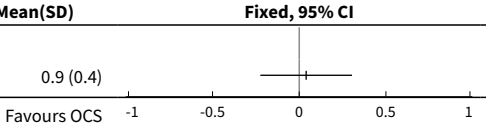
Analysis 2.3. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 3 Mortality after discharge (1-3 months).

Study or subgroup	IVCS n/N	OCS n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Inpatient treatment					
Ceviker 2014	0/20	2/20		50.49%	0.18[0.01,4.01]
de Jong 2007	5/107	2/103		40.2%	2.48[0.47,13.06]
Willaert 2002	1/23	0/25		9.31%	3.4[0.13,87.72]
Subtotal (95% CI)	**150**	**148**		**100%**	**1.4[0.44,4.51]**
Total events: 6 (IVCS), 4 (OCS)					
Heterogeneity: Tau^2=0; Chi^2=2.41, df=2(P=0.3); I^2=17.12%					
Test for overall effect: Z=0.57(P=0.57)					
Total (95% CI)	**150**	**148**		**100%**	**1.4[0.44,4.51]**
Total events: 6 (IVCS), 4 (OCS)					
Heterogeneity: Tau^2=0; Chi^2=2.41, df=2(P=0.3); I^2=17.12%					
Test for overall effect: Z=0.57(P=0.57)					



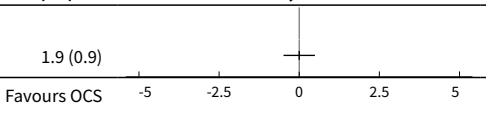
Analysis 2.4. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 4 Early FEV_1 (L).

Study or subgroup	IVCS N	IVCS Mean(SD)	OCS N	OCS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.4.1 Inpatient treatment						
Willaert 2002	19	0.9 (0.4)	18	0.9 (0.4)		0.04[-0.22,0.3]



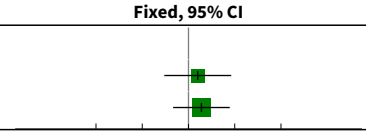
Analysis 2.5. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 5 Early FVC (L).

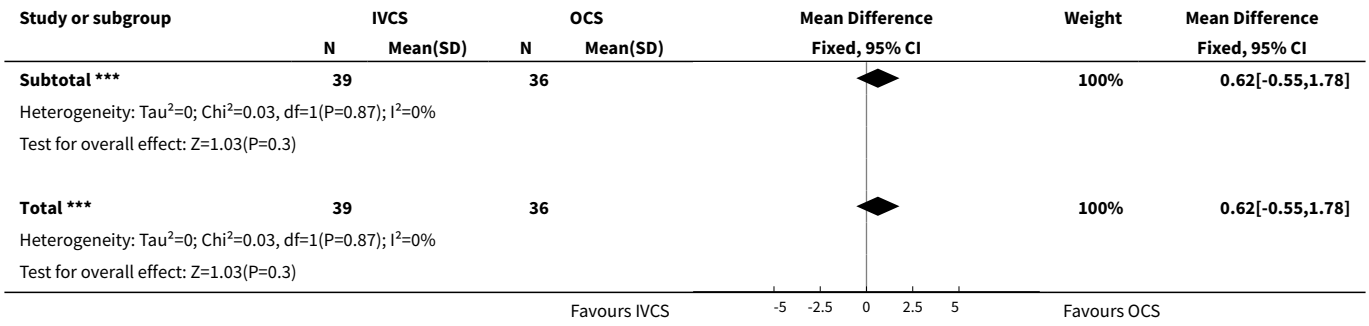
Study or subgroup	IVCS N	IVCS Mean(SD)	OCS N	OCS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.5.1 Inpatient treatment						
Willaert 2002	19	1.9 (0.7)	18	1.9 (0.9)		0[-0.49,0.49]



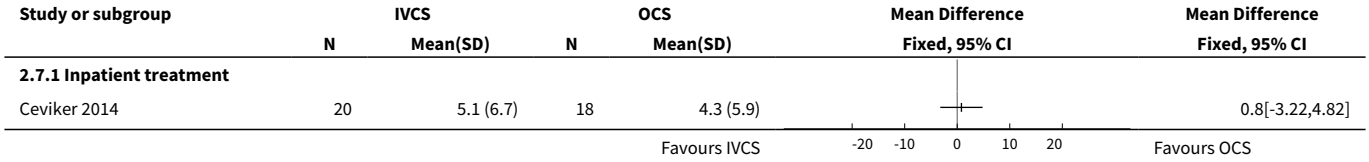
Analysis 2.6. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 6 Early dyspnoea score (VAS).

Study or subgroup	IVCS N	IVCS Mean(SD)	OCS N	OCS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.6.1 Inpatient treatment							
Willaert 2002	19	4.9 (2.6)	18	4.4 (3)		41.74%	0.5[-1.31,2.31]
Ceviker 2014	20	8.2 (2.2)	18	7.5 (2.5)		58.26%	0.7[-0.83,2.23]

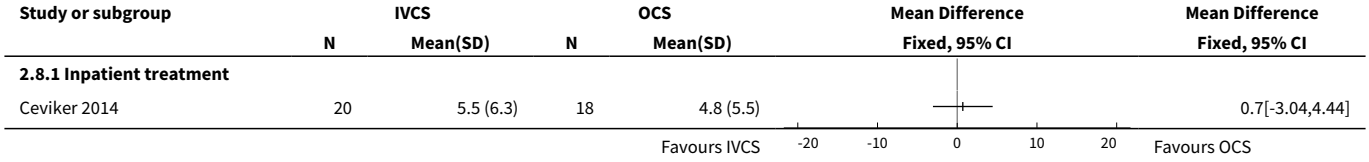




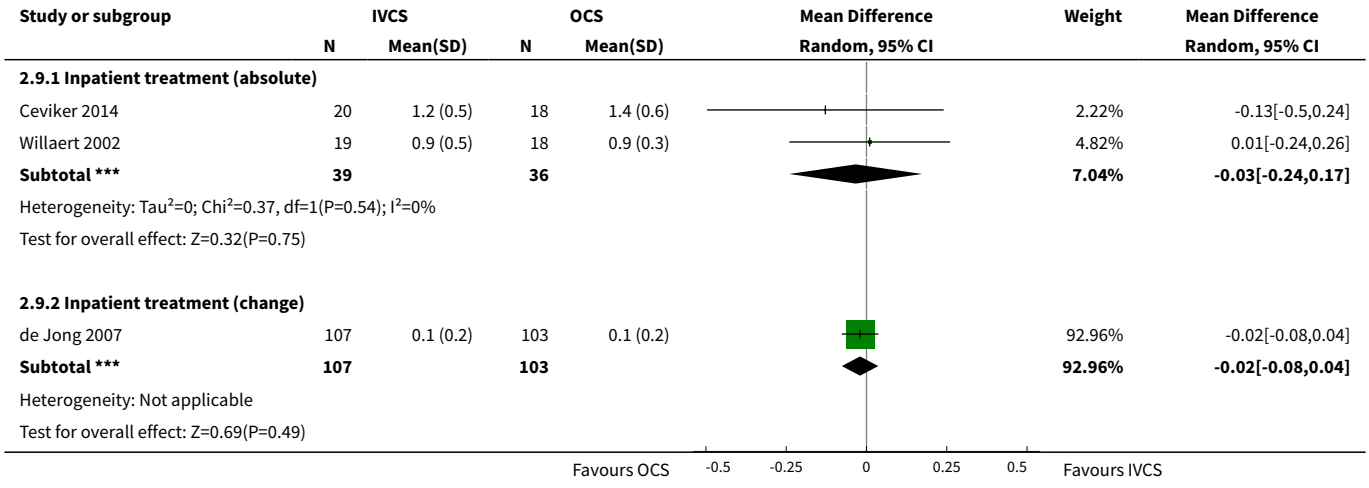
Analysis 2.7. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 7 Early cough score (VAS).

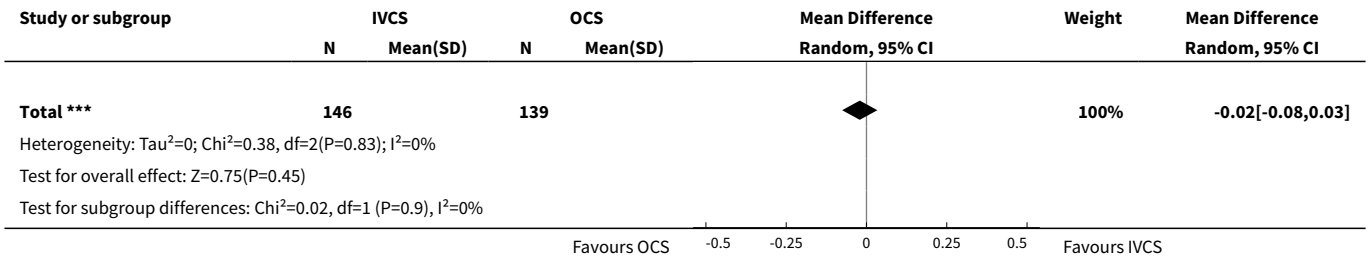


Analysis 2.8. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 8 Early sputum volume score (VAS).

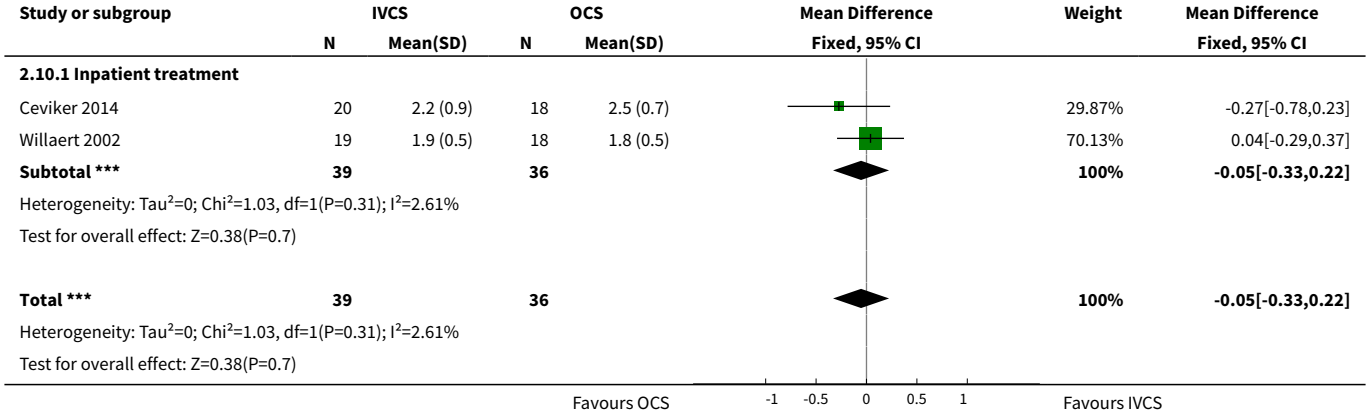


Analysis 2.9. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 9 FEV_1 (L) - absolute or change.

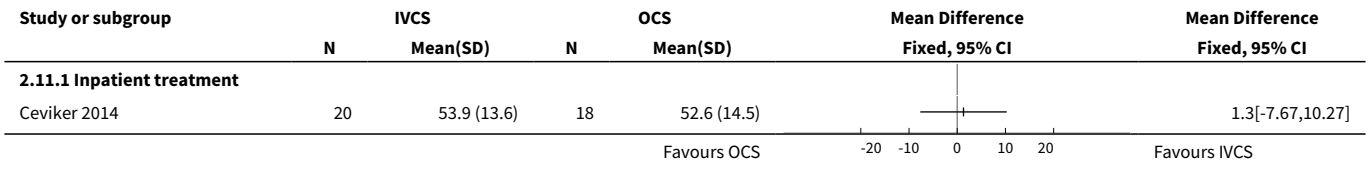




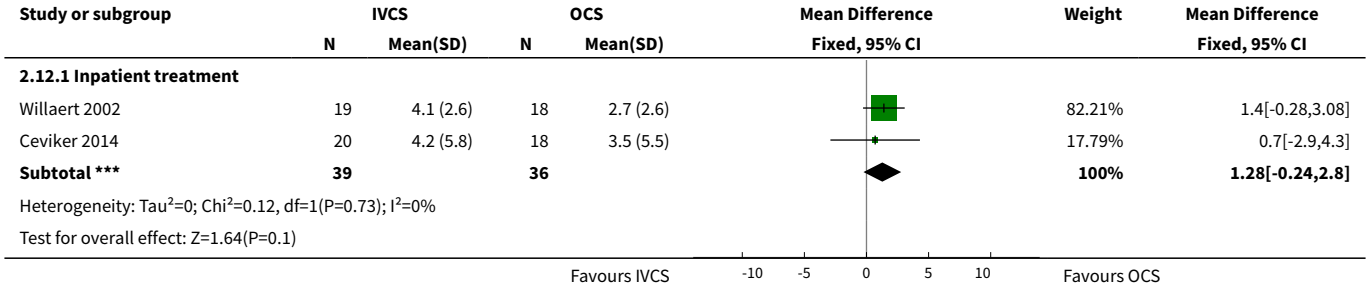
Analysis 2.10. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 10 FVC (L) - absolute.

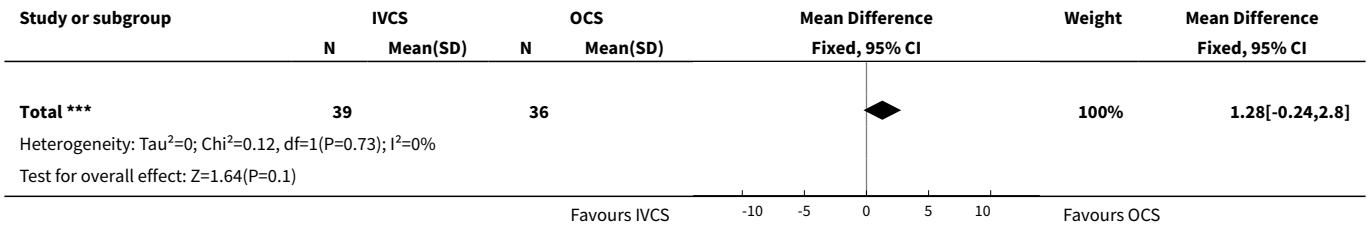


Analysis 2.11. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 11 FEV_1/FVC ratio.

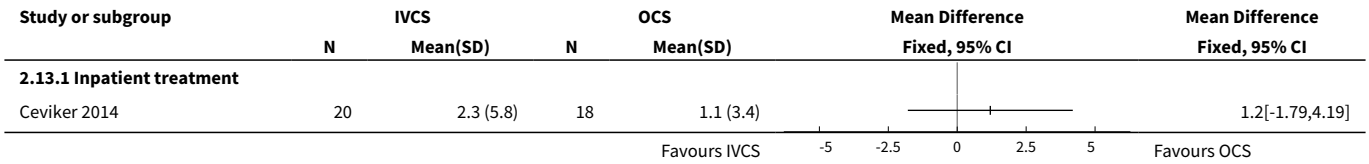


Analysis 2.12. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 12 Dyspnoea score (VAS) at 7-10 days.

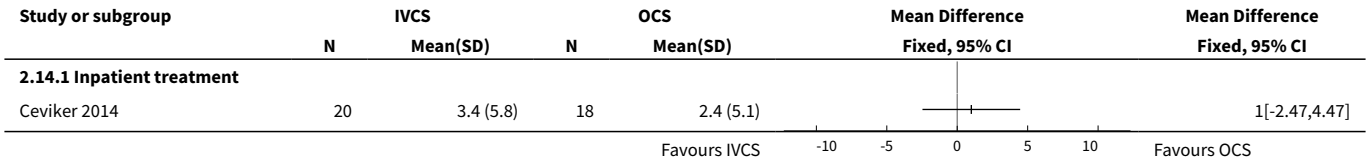




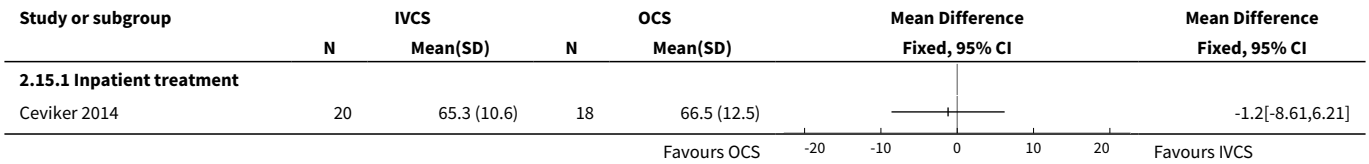
Analysis 2.13. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 13 Cough score (VAS) at 7 days.



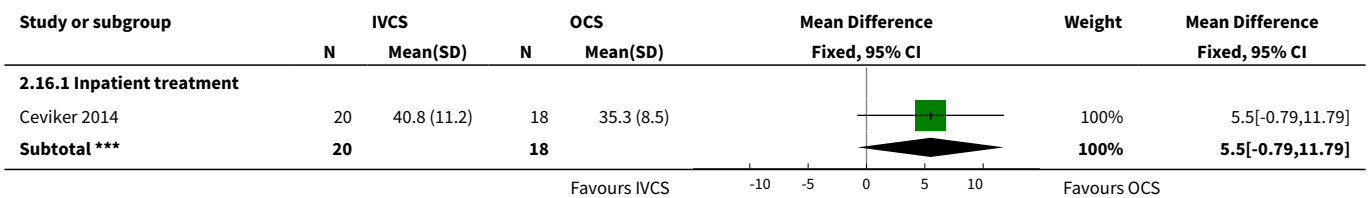
Analysis 2.14. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 14 Sputum volume score (VAS) at 7 days.



Analysis 2.15. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 15 PaO_2 (mmHg) at 7 days.



Analysis 2.16. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 16 $PaCO_2$ (mmHg) at 7 days.



Study or subgroup	IVCS N	IVCS Mean(SD)	OCS N	OCS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=1.71(P=0.09)							

Favours IVCS -10 -5 0 5 10 Favours OCS

Analysis 2.17. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 17 Health status: Clinical COPD Questionnaire (change at 1 week).

Study or subgroup	IVCS N	IVCS Mean(SD)	OCS N	OCS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.17.1 Inpatient treament						
de Jong 2007	107	-1 (1)	103	-1.1 (1)		0.1[-0.17,0.37]

Favours IVCS -0.5 -0.25 0 0.25 0.5 Favours OCS

Analysis 2.18. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 18 Quality of life: SGRQ (change at 7 days).

Study or subgroup	IVCS N	IVCS Mean(SD)	OCS N	OCS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.18.1 Inpatient treament						
de Jong 2007	107	-4.4 (14.2)	103	-3.7 (12.6)		-0.7[-4.33,2.93]

Favours IVCS -10 -5 0 5 10 Favours OCS

Analysis 2.19. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 19 Quality of life: CRQ Dyspnoea (change at 4 weeks).

Study or subgroup	IVCS N	IVCS Mean(SD)	OCS N	OCS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.19.1 Inpatient treatment						
Willaert 2002	12	3.2 (4.5)	9	4.9 (7.2)		-1.7[-7.05,3.65]

Favours OCS -20 -10 0 10 20 Favours IVCS

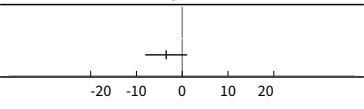
Analysis 2.20. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 20 Quality of life: CRQ Fatigue (change at 4 weeks).

Study or subgroup	IVCS N	IVCS Mean(SD)	OCS N	OCS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.20.1 Inpatient treatment						
Willaert 2002	12	2.4 (4.5)	9	5 (5.4)		-2.6[-6.95,1.75]

Favours OCS -10 -5 0 5 10 Favours IVCS

Analysis 2.21. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 21 Quality of life: CRQ Mastery (change at 4 weeks).

Study or subgroup	IVCS		OCS		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
2.21.1 Inpatient treatment						
Willaert 2002	12	1.1 (5.2)	9	4.6 (5.4)		-3.5[-8.09,1.09]

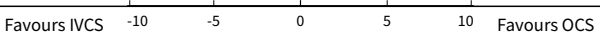


Analysis 2.22. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 22 Quality of life: CRQ Emotion (change at 4 weeks).

Study or subgroup	IVCS		OCS		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
2.22.1 Inpatient treatment						
Willaert 2002	12	3 (9.7)	9	7.2 (6.3)		-4.2[-11.06,2.66]

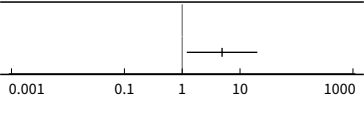
Analysis 2.23. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 23 Duration of hospitalisation (days).

Study or subgroup	IVCS		OCS		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
2.23.1 Inpatient treatment							
Ceviker 2014	20	12.7 (6.4)	20	11 (3.9)		24.62%	1.7[-1.58,4.98]
de Jong 2007	107	11.9 (8.6)	103	11.2 (6.7)		61.35%	0.7[-1.38,2.78]
Willaert 2002	23	15.5 (10.3)	25	10.6 (2.8)		14.04%	4.9[0.55,9.25]
Subtotal ***	**150**		**148**			**100%**	**1.54[-0.09,3.17]**
Heterogeneity: Tau^2=0; Chi^2=2.93, df=2(P=0.23); I^2=31.67%							
Test for overall effect: Z=1.85(P=0.06)							
Total ***	**150**		**148**			**100%**	**1.54[-0.09,3.17]**
Heterogeneity: Tau^2=0; Chi^2=2.93, df=2(P=0.23); I^2=31.67%							
Test for overall effect: Z=1.85(P=0.06)							



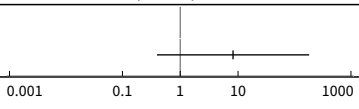
Analysis 2.24. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 24 Adverse effect - hyperglycaemia.

Study or subgroup	IVCS	OCS	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.24.1 Inpatient treatment				
Ceviker 2014	11/20	4/20		4.89[1.2,19.94]



Analysis 2.25. Comparison 2 Intravenous corticosteroid (IVCS) versus oral corticosteroid (OCS), Outcome 25 Adverse effect - hypertension.

Study or subgroup	IVCS n/N	OCS n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.25.1 Inpatient treatment				
Ceviker 2014	3/20	0/20		8.2[0.4,169.9]



ADDITIONAL TABLES

Table 1. Summary of study characteristics

Study ID	Setting/exacerbation definition	n (% male)	Systemic corticosteroid (treatment duration)	Age mean (SD)	FEV_1 mean (SD)	PYH smoking mean (SD)	Withdrawals (n/n)	History asthma excluded	Previous ICS use
Systemic corticosteroid vs. placebo									
Aaron 2003	Outpatient/AO criteria used	147 (57%)	Oral prednisone 40 mg (10 days)	69.4 (10.5)	1.0 (0.5)	50 (38)	3/147	Yes	52%
Abroug 2014	ICU/AO criteria used	217 (88%)	Prednisone 1 mg/kg daily until discharge or maximum 10 days	69 (9)	0.8 (0.4)	Not known	0/217	Not known	Not known
Albert 1980	Inpatient/AO criteria not used	45 (100%)	IV methylprednisolone 0.5 mg/kg 4 hourly x 72 hours (3 days)	61.5 (9)	0.8 (0.3)	80 (30)	3/45	Yes	Not known
Alia 2011	ICU/AO criteria not used	83 (80%)	IV methylprednisolone 0.5 mg/kg every 6 hours for first 72 hours, 0.5 mg/kg 12 hourly days 4-6, and 0.5 mg/kg days 7-10	68.4 (10.2)	Not known	Not known	0/83	Yes	Not known
Bullard 1996	ED-inpatient 76%/AO criteria used	138 (86%)	IV hydrocortisone x 96 hours + 4 days oral prednisone 40 mg (5-8 days)	66 (10.8)	0.53 (0.53)	Not known	27/138	Not known	Not known
Chen 2005	Inpatient/AO criteria not used	130 (75%)	1. Prednisolone 30 mg/day 7 days + placebo 7 days (7 days) vs. 2. prednisolone 30 mg/day 10 days + 15 mg/day 5 days vs. 3. placebo 14 days (14 days) (data from group 2 used)	72 (6.7)	0.73 (0.25)	Not known	9/130	Not known	Not known
Cordero 1996 [abstract only]	Outpatient/AO criteria used	30 (100%)	Oral prednisolone 40 mg/day for 10 days	Not known	Not known	Not known	Not known	Yes	Not known
Davies 1999	Inpatient/AO criteria used	60 (68%)	Oral prednisone 30 mg/day (14 days)	67 (8.5)	1.7	55 (35)	10/60	Yes	80%
Emerman 1989	ED-inpatient 63%/AO criteria used	100 (52%)	IV methylprednisolone 100 mg single dose (1 day)	64 (7.8)	64% (35)	59 (50)	4/100	Yes	Not known

Table 1. Summary of study characteristics *(Continued)*

Gunen 2007	Inpatient/AO criteria not used	159 (85%)	IV prednisolone 40 mg/day for days 1-15 if not discharged, oral methylprednisolone 32 mg/day for days 11-15 if discharged	64.1 (9)	37.2% (12.2)	45 (20.8)	38/159	Not known	Not known
Maltais 2002	Inpatient/AO criteria used	199 (82%)	Oral prednisone 40 mg x 3 days then 30 mg/day x 7 days (10 days)	70 (8)	0.91 (0.4)	56 (27)	28/199	Yes	59%
Niewoehner 1999	Inpatient/AO criteria not used	271 (99%)	IV methylprednisolone 72 hours + oral prednisolone 60 mg/day tapering over 57 days (group 1) or 12 days (group 2) or IV placebo + oral placebo 57 days (group 3) (15 or 60 days)	67.4 (10)	0.76 (0.27)	70 (33)	20/191	Yes	45%
Rostom 1994 [abstract only]	Inpatient/AO criteria not used	30 (not known)	IV methyl prednisolone 72 hours + oral prednisolone 15 days (19 days)	Not known	Not known	Not known	Not known	Not known	Not known
Thompson 1996	Outpatient/AO criteria specified	27 (96%)	Oral prednisone 60 mg tapering 9 days (9 days)	67.5 (8)	1.35 (0.5)	65 (30)	0	Yes	30%
Wood-Baker 1998 [abstract and data supplied]	Inpatient/AO criteria not used	47 (64%)	Oral prednisone high dose 2.5 mg/kg/day x 3 days OR medium dose 0.6-0.3 mg/kg/day x 14 days (14 days or 3 day high dose)	72 (6.3)	0.6	> 10	3/38	Yes	Not known
Zheng 2011 [abstract only]	Inpatient/not known	107 (not known)	Group 2 methylprednisolone 40 mg, IV and nebulised normal saline 4 mL 6 hourly x 7 days Group 3 (placebo): nebulised normal saline 4 mL and normal saline 10 mL IV 6 hourly x 7 days	Not known	Not known	Not known	Not known/107	Not known	Not known
IV corticosteroids vs. oral corticosteroids									
Ceviker 2014	Inpatient/AO criteria not used	40 (not known)	1. Oral methylprednisolone 32 mg/day 2. IV methylprednisolone 1 mg/kg/day for 4 days, then 0.5 mg/kg/day for 3 days	68 (9.4)	1.03 (0.37)	63 (38.7)	2/40	Not known	Not known

Table 1. Summary of study characteristics *(Continued)*

de Jong 2007	Inpatient/AO criteria used	157 (75%)	1. IV prednisolone 60 mg + placebo 5 days then tapering oral prednisolone 30 mg up to day 12 vs. 2. oral prednisolone 60 mg + placebo 5 days then tapering oral prednisolone 30 mg up to day 12	71 (8.4)	1.0 (0.4)	38 (21)	17/210	Yes	85%
Ridha 2006 [abstract only]	Not known/ not known	52 (not known)	1. Oral prednisone 40 mg/day for 10 days vs. 2. IV hydrocortisone 400 mg/day for 10 days	Not known	Not known	Not known	Not known	Not known	Not known
Willaert 2002	Inpatient/AO criteria not used	42 (87.5%)	1. IV methylprednisolone 40 mg/day days 1-10, decreased to 20 mg/day then to oral treatment 4 mg for 4 days vs. 2. oral methylprednisolone 32 mg/day days 1-7, decreased to 24 mg/day for days 8-11, then decrease in dosage by 4 mg/ week, 14 days total	71.5 (7)	1.12 (0.47)	31.7 (17.5)	11/48	Yes	Not known

AO: airflow obstruction; ED: emergency department; FEV_1: forced expiratory volume in 1 second; ICU: intensive care unit; IV: intravenous; PYH: pack-years' history; SD: standard deviation.

Table 2. Definition of treatment failure by study

Study ID	Treatment failure definition used in study	Time period	Data
Inpatient (treatment > 3 days)			
Bullard 1996	Returned to ED	< 14 days	5/60, 14/53
Chen 2005	Not known	Not known	5/43, 6/43
Davies 1999	Withdrawal due to unsatisfactory clinical improvement (specialist), or participant not satisfied with progress, or pH < 7.26	< 14 days	1/29, 5/27
Maltais 2002	Deterioration of COPD while participant hospitalised defined as need for treatment intensification according to the treating physician, the development of confusion, lethargy, acute respiratory acidosis ($PaCO_2$ > 70 mmHg with a pH < 7.30 or an increase in $PaCO_2$ > 10 mmHg) or need for ventilatory assistance	< 11 days	3/62, 8/66
Niewoehner 1999	Intubation and mechanical ventilation, re-admission because of COPD or intensification of pharmacological therapy	< 30 days	35/160, 37/111
Wood-Baker 1998	Lack of progress according to attending physician during treatment	< 7 days	1/13, 4/13
Inpatient (treatment 1 day)			
Emerman 1989	Required unscheduled visit to ED	< 2 days	8/38, 4/32
Outpatient			
Aaron 2003	Unscheduled visit to doctor's surgery or return to ED because of worsening dyspnoea	< 30 days	19/70, 30/70
Thompson 1996	Failure of outpatient therapy defined as hospitalisation for deteriorating respiratory status or lack of improvement of subjective dyspnoea requiring treatment with open-label prednisone	< 14 days	0/13, 8/14

COPD: chronic obstructive pulmonary disease; ED: emergency department; $PaCO_2$: partial pressure of carbon dioxide dissolved in arterial blood.

APPENDICES

Appendix 1. MEDLINE search strategy

#1 COPD[MeSH Terms]
#2 "adrenal cortex hormone*"
#3 steroid
#4 steroids
#5 glucocorticoid*
#6 corticoid*
#7 corticosteroid*
#8 beclomethasone
#9 betamethasone
#10 fluticasone
#11 cortisone
#12 dexamethasone

#13 hydrocortisone
#14 prednisolone
#15 prednisone
#16 methylprednisolone
#17 methylprednisone
#18 triamcinolone
#19 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)
#20 randomised controlled trial [pt]
#21 controlled clinical trial [pt]
#22 randomised [tiab]
#23 placebo [tiab]
#24 clinical trials as topic [mesh: noexp]
#25 randomly [tiab]
#26 trial [ti]
#27 (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
#28 (animals [mh] NOT humans [mh])
#29 (#27 NOT #28)
#30 ("2012/01/01"[Date - Publication] : "3000"[Date - Publication])
#31 (#1 AND #19 AND #29 AND #30)

Appendix 2. EMBASE search strategy

#1 chronic AND obstructive AND pulmonary AND 'disease'/exp AND [embase]/lim AND [2010-2013]/py

#2 'triamcinolone'/exp OR 'methylprednisone'/exp OR 'methylprednisolone'/exp OR 'prednisone'/exp OR 'prednisolone'/exp OR 'hydrocortisone'/exp OR 'dexamethasone'/exp OR 'cortisone'/exp OR 'fluticasone'/exp OR 'betamethasone'/exp OR 'beclomethasone'/exp OR 'corticosteroid'/exp OR 'corticoid'/exp OR 'glucocorticoid'/exp OR 'steroids'/exp OR 'steroid'/exp OR 'adrenal'/exp AND cortex AND 'hormone'/exp AND [embase]/lim AND [2010-2013]/py

#1 AND #2 AND ([controlled clinical trial]/lim OR [randomised controlled trial]/lim) AND [humans]/lim AND [embase]/lim AND [2010-2013]/py

WHAT'S NEW

Date	Event	Description
23 May 2014	New search has been performed	Literature search run.
23 May 2014	New citation required and conclusions have changed	Objectives of review amended. Participants: to include studies in which participants received assisted ventilation. Interventions: Comparison 1- corticosteroids, parenteral or oral administration versus placebo control injections or tablets as appropriate; Comparison 2- corticosteroids, parenteral versus oral administration.

HISTORY

Review first published: Issue 1, 1999

Date	Event	Description
22 August 2012	New search has been performed	Review updated. Changes to criteria for study inclusion; studies with participants requiring assisted ventilation included
1 August 2008	New search has been performed	Literature searches re-run

Date	Event	Description
11 July 2008	Amended	Converted to new review format.
2 January 2008	New citation required and conclusions have changed	This review, originally published in 1999 was updated in 2004 and for this version in 2007. One additional study (Chen 2005) has been added and additional data have been received from two authors (Aaron 2003 and Wood-Baker 1998). The conclusions of the previous version on the beneficial effect of treatment with systemic corticosteroids in acute exacerbations of COPD on the primary outcome of treatment failure have been strengthened. This update of the review found a significant reduction in length of hospital stay for treatment with systemic corticosteroids. The beneficial effects of treatment with systemic corticosteroids on the secondary outcomes of dyspnoea, blood gases and lung function, previously only significant at an early time point, have also been confirmed at the end of treatment. The increased risk of adverse effects associated with treatment, particularly the risk of hyperglycaemia, with systemic corticosteroids was confirmed.

CONTRIBUTIONS OF AUTHORS

JAEW: updates 2004, 2008, 2014: study selection, grading and data management, data entry, author correspondence, analysis, 'Summary of findings' table. Primary author first draft of results, discussion and conclusions.

DT: 2014 update: study selection, grading and data management, data entry, author correspondence, reviewing results and discussion, drafting abstract and plain language summary.

CW: 2014 update: study selection, grading and data management, data entry, author correspondence, reviewing results and discussion.

RWB: protocol development; data extraction and entry; data verification; writing first version of review; editing updates in 2004, 2008 and 2014.

EHW: protocol development; data extraction and entry; writing first version of review; editing updates 2004, 2008 and 2014.

PG: editing review drafts 2004, 2008 and 2014.

DECLARATIONS OF INTEREST

R Wood-Baker has undertaken research sponsored by a number of pharmaceutical companies including Marion Merrell Dow, ICI Australia, Pharmacia Upjohn, GlaxoSmithKline, Sanofi-Synthélabo and Novartis.

E H Walters has undertaken research sponsored by a number of pharmaceutical companies including Glaxo Wellcome, Novartis, Astra, Boehringer, Schering-Plough and Amgen. He has held consultancies for AstraZeneca, ICI Australia, Pfizer and GlaxoSmithKline.

SOURCES OF SUPPORT

Internal sources

- University of Tasmania, Australia.

External sources

- Commonwealth Department of Health and Aged Care, Australia.

  Through the National Health and Medical Research Council Cochrane funding (2013-2016)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We amended the objectives of the review in 2014 to include studies in which participants received assisted ventilation, and interventions to include: comparison 1: corticosteroid, parenteral or oral administration versus placebo control injections or tablets as appropriate; comparison 2: corticosteroid, parenteral versus oral administration. We changed the order of the secondary outcomes. We updated the methods, including using the latest version of the Cochrane 'Risk of bias' tool and added a 'Summary of findings' table. We added a subgroup analysis on setting of the exacerbations.

Two new review authors joined the team, DJT and CJW, and one review author stepped down, M Hannay.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Disease Progression; Glucocorticoids [*administration & dosage] [adverse effects]; Infusions, Intravenous; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male