

Corticosteroids for tuberculous pleurisy (Review)

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[Intervention Review]

Corticosteroids for tuberculous pleurisy

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ABSTRACT

Background

Corticosteroids used in addition to antituberculous therapy have been reported to benefit people with tuberculous pleurisy. However, research findings are inconsistent, raising doubt as to whether such treatment is worthwhile. Concern also exists regarding the potential adverse effects of corticosteroids, especially in HIV-positive people.

Objectives

To evaluate the effects of adding corticosteroids to drug regimens for tuberculous pleural effusion.

Search strategy

In May 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 2), MEDLINE, EMBASE, LILACS, Current Controlled Trials, and reference lists of articles.

Selection criteria

Randomized and quasi-randomized controlled trials comparing any corticosteroid with no treatment, placebo, or other active treatment (both groups should receive the same antituberculous drug regimen) in people diagnosed with tuberculous pleurisy.

Data collection and analysis

Two authors independently assessed trial methodological quality and extracted data. Data were analysed using relative risks (RR) and mean difference (MD) with 95% confidence intervals (CI). The fixed-effect model was applied in the absence of statistically significant heterogeneity.

Main results

Six trials with 633 participants met the inclusion criteria; one trial included only HIV-positive people. Compared to control, corticosteroid use was associated with less residual pleural fluid at four weeks (RR 0.76, 95% CI 0.62 to 0.94; 394 participants, 3 trials) and reduced pleural thickening (RR 0.69, 95% CI 0.51 to 0.94; 309 participants, 4 trials). We found no evidence of an effect of corticosteroids on death from any cause (194 participants, 1 trial), respiratory function (191 participants, 2 trials), residual pleural fluid at eight weeks (399 participants, 4 trials), or pleural adhesions (123 participants, 2 trials). Although discontinuation of treatment due to adverse events was more frequent in participants receiving corticosteroids than placebo (RR 2.80, 95% CI 1.12 to 6.98; 586 participants, 6 trials), the effects were generally mild. The risk of Kaposi sarcoma may be increased in HIV-positive people receiving corticosteroids (RR 13.00, 95% CI 0.74 to 227.63; 194 participants, 1 trial).

Authors' conclusions

There are insufficient data to support evidence-based recommendations regarding the use of adjunctive corticosteroids in people with tuberculous pleurisy. Randomized controlled trials that are sufficiently powered to evaluate the effects of corticosteroids on both morbidity and mortality are needed. The effects of corticosteroids on HIV-related complications, such as Kaposi sarcoma, should be assessed in people co-infected with HIV.

PLAIN LANGUAGE SUMMARY

No clear evidence that corticosteroids are effective for tuberculous

Tuberculous pleural effusion results from tuberculous infection of the membrane covering of the lungs. This results in a build up of fluid around the lung that impairs breathing and may lead to restriction of lung function in the long term. Some clinicians believe that corticosteroids used in combination with antituberculous drugs can help to prevent these complications. We found no clear evidence supporting the use of corticosteroids in people with tuberculous pleural effusion, regardless of HIV status. However, only one trial evaluated the balance between benefit and harm of corticosteroids in people infected with HIV.

BACKGROUND

Tuberculosis is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. It is a major contributor to global morbidity and mortality causing close to an estimated two million deaths each year (WHO 2005). While tuberculosis infection of the lung (pulmonary tuberculosis) is most common, tissues outside of the lungs, such as pericardium (membrane lining the heart) and meninges (membrane lining the brain), may also be infected (extrapulmonary tuberculosis). Extrapulmonary tuberculosis has occurred more frequently in recent years (Harries 1990), and this increase is believed to be attributable to co-infection with human immunodeficiency virus (HIV) (Song 2003; Yang 2004).

Definition and incidence

Pleurisy is the name given to an inflammation of the pleura, a semi-permeable membrane covering the lungs and lining the chest wall. The form of pleurisy caused by tuberculosis infection usually results in an abnormal accumulation of fluid in the pleural space between the lungs and chest wall (pleural effusion). Tuberculous pleural effusion is thought to be a delayed hypersensitivity reaction following a recent mycobacterial infection of the pleura (Rossi 1987). Apart from lymph node tuberculosis, tuberculous pleural effusion is the most frequent extrapulmonary manifestation of tuberculosis, representing about 20% of extrapulmonary tuberculosis (Sharma 2004). In one series of 1700 tuberculosis

patients, 70 cases of tuberculous pleural effusion were identified (Seibert 1991). Batungwanayo 1993 reported that a high percentage (83%) of people with tuberculous pleural effusion were also HIV infected. This association is thought to be a function of the higher burden of micro-organisms resulting from an impaired host response (Relkin 1994), though detection bias resulting from more opportunity for diagnosis of tuberculous pleural effusion in HIV-positive individuals may also be a contributory factor (Frye 1997).

Prognosis

Clinically, tuberculous pleural effusion presents as an acute illness consisting of cough, fever, chest pain, and dyspnoea (Morehead 1998). Although it can resolve spontaneously within a few weeks or months, medical treatment is believed to speed resolution of the effusion and reduce long-term complications such as fibrosis and thickening of the pleura that can further restrict lung function. Therapeutic options for pleural space infections include intravenous antibiotic administration, chest tube drainage, intrapleural administration of a fibrinolytic agent to dissolve fibrous adhesions, thoracotomy to remove fibrinous and infected tissue, and steroid therapy (Chapman 2004). The theoretical basis for using corticosteroids is that they suppress the inflammatory response believed to be responsible for tuberculous pleural effusion. One corticosteroid is prednisone, which is converted in the liver into the active drug, prednisolone. Prednisone or prednisolone is recommended

at a daily dose of about 1 mg/kg gradually reducing after one to two weeks, with a total treatment course sometimes being as long as three months (Lemaistre 1951; Mathur 1960; Morehead 1998; Blumberg 2003).

Debates

Studies of adjunctive corticosteroids for the treatment of tuberculous pleural effusion show conflicting results. Non-randomized studies in the pre-HIV era found that corticosteroids led to more rapid resolution of the effusion and reduced likelihood of residual pleural thickening and pleural adhesions (Menon 1964; Singh 1965). An observational study of 165 HIV-positive participants with tuberculous pleural effusion found that prednisolone was associated with decreasing rates of lymphadenopathy and cough as well as improved survival (Elliott 1992; Elliott personal communication).

In contrast, a critical appraisal of published studies demonstrated beneficial effects of corticosteroids on acute symptoms, but it found no benefit for chronic endpoints such as fibrosis, irrespective of dose (Dooley 1997). The authors noted that many of the studies lacked rigour and clinical correlations. Furthermore, the previous version of this Cochrane Review, which included three randomized controlled trials (with a total of 236 participants), concluded that there was insufficient evidence for the effectiveness of adjunctive corticosteroids on lung function, pleural adhesions, residual pleural thickening, residual fluid, and acute clinical symptoms (Matchaba 2000). No HIV-related data were available at the time.

In addition to the uncertainty about benefits of corticosteroid therapy, there is concern about potential risks. In immunocompromized patients, such as those infected with HIV, corticosteroids may further constrain the immune system leading to an increased frequency of opportunistic infections and tumours such as Kaposi sarcoma, a vascular tumour accompanied by numerous unconnected lesions of the skin and thought to be associated with human herpes virus-8 infection (Ensoli 2001). More generally, adverse effects of corticosteroids such as fluid retention and gastrointestinal disturbances have also been documented in people with tuberculosis (Anonymous 1983).

Our review aimed to appraise the existing evidence on the benefits and harms of corticosteroids regardless of HIV status. The study hypothesis was that in people with tuberculous pleurisy, there was no difference in the effects of corticosteroid therapy and placebo on mortality and morbidity.

OBJECTIVES

To evaluate the effects of adding corticosteroids to drug regimens for tuberculous pleural effusion.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

People diagnosed with tuberculous pleurisy by chest x-ray (as defined by trial authors) *plus* any of the following: pleural biopsy for histology; Ziehl-Neelsen staining and/or culture of sputum; pleural fluid; or pleural biopsy.

Types of interventions

Intervention

Any corticosteroid.

Control

No treatment, placebo, or other active treatment. Both groups should receive the same antituberculous drug regimen.

Types of outcome measures

Primary

- Death from any cause.
- Improvement in respiratory function.

Secondary

- Reabsorption of pleural effusion (as defined by authors).
- Presence of pleural thickening.
- Presence of pleural adhesions.
- Improvement in clinical symptoms and signs.
- Adverse events.
- HIV-associated events.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

We searched the following databases using the search terms and strategy described in [Appendix 1](#): Cochrane Infectious Diseases Group Specialized Register (May 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 2); MEDLINE (1966 to May 2007); EMBASE (1974 to May 2007) and LILACS (1982 to May 2007). We also searched Current Controlled Trials (May 2007) using 'tuberculosis' and 'pleur*' as search terms.

We also checked the reference lists of all studies identified with the above methods.

Data collection and analysis

Selection of studies

ME and JV screened the results of the search for potentially relevant studies. We independently applied eligibility criteria and resolved differences in opinion through discussion. Where the abstracts were unclear or if there was any other reason for uncertainty, we obtained the full article before making a decision on study eligibility. We obtained the assistance of translators when abstracts were not available in English. We excluded studies that did not meet our criteria and stated the reason.

Data extraction and management

Using a specially designed data extraction form, ME extracted information for each trial with JV independently cross checking the data. For each trial, we collected information regarding trial characteristics, intervention characteristics, participant characteristics, and outcome measures. We resolved differences in the extracted data by referring to the original articles and through discussion. ME entered the data into [Review Manager 5](#).

Assessment of risk of bias in included studies

ME and JV independently assessed the quality of included trials. We evaluated the generation of the allocation sequence and allocation concealment as adequate, unclear, or inadequate ([Jüni 2001](#)). We indicated who was blinded (patients, clinicians, or outcome assessors) in each of the trials. Inclusion of randomized participants was considered adequate if greater than 80% of all participants randomized into the trial were included in the analysis. We presented the results of the quality assessment in a table.

Data synthesis

ME analysed the data using [Review Manager 5](#), and JV checked the analysis. We pooled estimates of effect using risk ratio (RR) as a measure of effect for dichotomous outcomes and mean difference (MD) for continuous outcomes, and presented these with 95% confidence intervals (CI). We assessed heterogeneity by visually examining the forest plot and by the statistical chi-square test for heterogeneity using a 10% level of significance. We used the fixed-effect model for the meta-analysis, except for instances of statistical heterogeneity when we used the random-effects model.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Trial selection

Forty-eight studies were screened of which 26 published trials were identified for possible inclusion into the review. Six trials met our inclusion criteria (see 'Characteristics of included studies'). The reasons for excluding studies, initially considered relevant, are provided in the 'Characteristics of excluded studies'.

Participants and location

The six trials included 633 participants, with a range of 45 to 197 per trial. They were conducted in Taiwan (1 trial), Spain (1 trial), South Africa (1 trial), Korea (2 trials), and Uganda (1 trial). Participants were adults except in one trial ([Galarza 1995](#)), which studied people aged 11 years and older. All trials included participants of both sexes; 59% were male, with a range of 51% to 64% across trials. One trial included only HIV-positive participants ([Elliott 2004](#)), two excluded HIV-positive participants ([Galarza 1995](#); [Wyser 1996](#)), while the other trials reported HIV status as negative or not determined. In all of the trials, participants with pleural effusion had tuberculosis confirmed by a laboratory diagnosis; in one trial only 63% of participants had a confirmatory pathological or microbiological diagnosis ([Galarza 1995](#)).

Follow up

The follow-up period varied, ranging from 24 weeks ([Wyser 1996](#)) to 46 months ([Galarza 1995](#)). [Bang 1997](#) and [Lee 1999](#) did not mention the length of follow up.

Interventions

Four trials compared either prednisone or prednisolone with placebo as an adjunct to an established antituberculous regimen containing isoniazid and rifampicin. [Bang 1997](#) and [Lee 1999](#) did not use any comparative treatment.

All but two trials gave corticosteroids orally in different daily doses ranging from 0.75 to 1.0 mg/kg/day for two weeks; [Bang 1997](#) and [Lee 1999](#) used injection but did not clearly state the dosages. Pleural fluid was aspirated before randomization in all but one trial ([Galarza 1995](#)) in which aspiration was conducted before patient discharge.

Outcomes

None of the trials reported on all eight outcome measures chosen for this review. The outcome measures reported included death from any cause (1 trial), improvement in respiratory function (2 trials), reabsorption of pleural effusion (3 trials examined the outcome at 4 weeks; 4 trials examined the outcome at 8 weeks), presence of pleural thickening (4 trials) and adhesions (2 trials), improvement in clinical symptoms and signs (3 trials), adverse events (6 trials), and HIV-associated events (1 trial).

Risk of bias in included studies

See 'Characteristics of included studies' for details of individual trials.

Generation of allocation sequence

All trials were reported as randomized. [Elliott 2004](#) explicitly stated that random numbers were computer-generated, which we considered as adequate. The other trials did not indicate how the sequence was generated.

Allocation concealment

One trial gave a detailed report the method it used, which we considered to be adequate; briefly, prednisolone and matching placebo tablets were packaged in identical sequentially numbered plastic bags labelled with the randomization code by two people unrelated to the trial ([Elliott 2004](#)). The rest did not provide sufficient information to assess this aspect of study quality.

Blinding

Four trials were described as double blind and placebo controlled. The remaining two trials did not mention blinding ([Bang 1997](#); [Lee 1999](#)). [Wyser 1996](#) and [Elliott 2004](#) specifically mentioned that those assessing outcomes had been blinded.

Inclusion of all randomized participants

The trials included all participants in the analysis ([Galarza 1995](#); [Lee 1999](#)) or included most participants (all adequate): 98.8% ([Bang 1997](#)), 98.5% ([Elliott 2004](#)), 89% ([Lee 1988](#)), and 95% ([Wyser 1996](#)).

Effects of interventions

Primary outcomes

Death from any cause

Only [Elliott 2004](#) assessed the risk of death, finding no reduction in mortality with corticosteroids (194 participants, [Analysis 1.1](#)).

Improvement in respiratory function

Two trials with 191 participants measured improvement in respiratory function and found no difference between the groups. In [Galarza 1995](#), mean forced vital capacity (FVC) was 95% in both the treatment and control groups at the end of treatment. [Wyser 1996](#) reported no significant difference in the degree of improvement in pulmonary function between the prednisone and placebo groups, (total lung capacity: $P = 0.39$; FVC: $P = 0.65$) up to six months. A meta-analysis could not be performed due to insufficient reported data.

Reabsorption of pleural effusion

At 4 weeks

Three trials reported results for this outcome ([Galarza 1995](#); [Bang 1997](#); [Elliott 2004](#)). Corticosteroid use resulted in a reduced risk of residual fluid being present at four weeks (RR 0.76, 95% CI 0.62 to 0.94; 394 participants, [Analysis 1.2](#)).

At 8 weeks

Given that there was heterogeneity in the effects across the four trials that measured this outcome at eight weeks (chi-squared test = 18.71, $P = 0.0003$), we used the random-effects model and found no statistically significant benefit with corticosteroids (399 participants, [Analysis 1.3](#).) In [Wyser 1996](#), complete drainage of pleural fluid was undertaken on admission and effusions did not recur in either group during the course of the study.

Presence of pleural thickening

Corticosteroids were associated with a statistically significant reduction in residual pleural thickening (RR 0.69, 95% CI 0.51 to 0.94; 309 participants, 4 trials, [Analysis 1.4](#)).

Presence of pleural adhesions

We found no statistically significant reduction in the risk of pleural adhesions (123 participants, 2 trials, [Analysis 1.5](#)).

Improvement in clinical symptoms and signs

Time to disappearance of symptoms was significantly shorter in participants receiving corticosteroids (MD -4.32 days, 95% CI -7.44 to -1.20; 123 participants, 2 trials, [Analysis 01.06](#)). Furthermore, [Lee 1988](#) demonstrated that fever, chest pain, and dyspnoea were more likely to be resolved by day seven post-treatment in participants on corticosteroids compared to placebo (RR 0.06, 95% CI 0.00 to 0.99; 40 participants, [Analysis 1.7](#)). In this trial, all participants were asymptomatic within 14 days. [Wyser 1996](#) reported no differences in the degree of improvement in symptoms (individual or combined Visual Analogue Scores) or in mean weight gain at regular follow-up evaluations over a 24-week period.

Adverse events

Overall, more people in the corticosteroid group experienced adverse events leading to the discontinuation of treatment (RR 2.80, 95% CI 1.12 to 6.98; 586 participants, 6 trials, [Analysis 1.8](#)). In [Elliott 2004](#), nine of 97 participants in the treatment group and two of 97 participants in the placebo group required stoppage of treatment due to hyperglycaemia, hypertension, herpes zoster, or candida infections. Epigastric pain was reported by [Wyser 1996](#) (4/34 participants on corticosteroid therapy and 3/36 on placebo), [Lee 1988](#) (1/21 participants on corticosteroids and 0/19 in the placebo group), and [Bang 1997](#) (1/33 participants on corticosteroids and 0/50 participants in the control group). The same participant in [Lee 1988](#) developed a 'moon' face and lower limb oedema.

HIV-associated events

[Elliott 2004](#), which included only HIV-positive participants, reported a trend towards an increase in the incidence of Kaposi's sarcoma in participants receiving corticosteroids (RR 13.00, 95% CI 0.74 to 227.63; 194 participants, [Analysis 1.9](#)). This trial found no evidence of an effect of corticosteroids on HIV-associated infections including cryptococcal meningitis, oesophageal candidiasis, herpes simplex, herpes zoster, oral thrush, and gastroenteritis.

DISCUSSION

The evidence base on the effects of corticosteroids administered to people with tuberculous pleurisy remains small, with only six trials evaluating 633 participants.

Only the trial of HIV-positive people evaluated mortality ([Elliott 2004](#)). Due to the small number of events in this trial, the confidence interval around the effect estimate is wide thus precluding firm conclusions about the effect of corticosteroids on death. The other primary outcome we aimed to assess was improvement in respiratory function, but neither trial that focused on this endpoint provided evidence for benefit with corticosteroids, and there was insufficient information to allow us to perform a meta-analysis.

Compared to placebo or no corticosteroids, adjunctive corticosteroids appear to hasten the reabsorption of pleural fluid with trials finding an overall reduction of 24% in the risk of residual fluid four weeks after the start of treatment. Similarly, there is evidence that corticosteroids reduce the likelihood of pleural thickening at the end of treatment. The clinical importance of these findings is unclear particularly in view of the lack of outcome data on respiratory function and the mixed findings with respect to resolution of symptoms and signs in the acute phase of the condition.

Concern has been expressed that corticosteroid-induced immunosuppression may increase the risk of opportunistic infections in HIV-infected participants ([Lionakis 2003](#)). To date only one trial has investigated corticosteroid use in this group ([Elliott 2004](#)). In this trial there was a trend towards an increase in oesophageal candidiasis, but no statistically important differences were found for any of the opportunistic infections assessed. Also, the risk of Kaposi sarcoma was found to be substantially higher in the corticosteroid group – a potentially important finding that requires confirmation in future trials.

In interpreting the above findings a number of issues need to be kept in mind. Firstly, all six included trials are small and it is possible that clinically significant differences may have been missed. For example, in the trial reporting on mortality ([Elliott 2004](#)), 356 participants per study arm would be needed to ensure sufficient power to demonstrate a 10% reduction in mortality from the baseline rate of 39/97. Secondly, while the methodological quality of the available trials seems reasonably good, we did not have sufficient information to assess the completeness of allocation concealment in five of the six trials, a factor known to have a substantial influence on internal validity. A third issue concerns the diagnosis of tuberculous pleural effusion: in the [Galarza 1995](#) trial, one-third of participants had no microbiological confirmation with no indication as to the distribution of unconfirmed diagnoses in the study arms. Fourthly, the optimal dose of adjunctive corticosteroids is not known. Rifampicin induces the liver metabolism of corticosteroids, thus increasing their plasma clearance ([McAllister 1983](#)). It has been suggested that higher than usual doses be used to compensate for the reduced availability of corticosteroids to the

tissues (Commerford 1991). Finally, all but one of the trials were carried out in the pre-HIV era and thus the generalizability of the current evidence to most participants with tuberculous pleural effusion in low- and middle-income countries who are co-infected with HIV is limited.

AUTHORS' CONCLUSIONS

Implications for practice

The included randomized controlled trials provide insufficient data to support evidence-based recommendations regarding the use of corticosteroids on risk of death or improvement in lung function in participants with tuberculous pleural effusion, regardless of HIV status. There is also no rigorous evidence to support the use of corticosteroids in people co-infected with HIV, in whom there is some cause for concern that corticosteroids may increase the risk of Kaposi sarcoma.

Implications for research

Randomized controlled trials with sufficient statistical power to evaluate the effects of corticosteroids on mortality and key morbidity outcomes are needed. Careful attention should be given to adverse effects, particularly in HIV-positive people.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bang 1997

Methods	<p>Generation of allocation sequence: not stated</p> <p>Allocation concealment: not stated</p> <p>Blinding: not stated</p> <p>Inclusion of all randomized participants in the analysis: 98.8%</p> <p>Mean duration of follow up: no fixed duration</p>
Participants	<p>Number: 118 randomized; mean age 34 years; 59% men</p> <p>Inclusion criteria: "Proper condition for tuberculous pleurisy after the pleura tissue test, positive for cultivation of tuberculous bacilli and anti-bacteria from pleura fluid, pleura tissue and etc."</p> <p>Exclusion criteria: people with "diabetes, high blood pressure, digestive ulcer, pneumonia, malignant tumor, cardiac insufficiency and etc."; HIV-negative</p>
Interventions	<p>1. Prednisolone plus standard regimen</p> <p>2. Standard regimen only</p> <p>Prednisolone: single dose per injection of 1 mg/kg twice weekly (period not stated) thereafter tapered off by 10 mg/week</p> <p>Standard regimen: isoniazid (400 mg/day), rifampicin (600 mg/day; 450 mg if < 50 kg), pyrazinamide (1500 mg/day), ethambutol (800 mg/day) for 2 months followed by same regimen minus pyrazinamide for 7 months</p>
Outcomes	<p>1. Mean duration to relief from symptoms</p> <p>2. Rate of reabsorption of pleural fluid</p> <p>3. Pleural adhesions and thickening</p> <p>4. Adverse effects</p>
Notes	<p>Location: Korea</p> <p>Date: June 1991 to September 1994</p>

Elliott 2004

Methods	<p>Generation of allocation sequence: computer-generated allocation sequence in block size of 20 participants</p> <p>Allocation concealment: unclear</p> <p>Blinding: providers, participants and assessors</p> <p>Inclusion of all randomized participants in the analysis: 98.5</p> <p>Mean duration of follow up: 1.65 years for intervention group; 1.48 years for control group</p>
Participants	<p>Number: 197 randomized; mean age 34 years; 58% men</p> <p>Inclusion criteria: HIV-positive; clinical features suggesting tuberculous pleurisy with pleural effusion > 1/3 of 1 hemithorax; age > 18 years; no previous treatment or prophylaxis for tuberculosis; no recent treatment with glucocorticoids; not pregnant or breastfeeding;</p> <p>Exclusion criteria: HIV-negative failed to complete screening procedures; failure to obtain pleural fluid for diagnostic purposes; empyema; a second, major HIV-related disease; risk factors for serious steroid-related adverse events; standard doses of antituberculous drugs could not be used (as in participants with concurrent liver disease)</p>

Elliott 2004 (Continued)

Interventions	<ol style="list-style-type: none"> 1. Prednisolone plus standard regimen 2. Placebo plus standard regimen <p>Prednisolone: single oral dose of 50 mg/day for 14 days, 40 mg/day for 14 days, 25 mg/day for 14 days, 15 mg/day for 14 d</p> <p>Standard regimen: isoniazid (5 mg/kg/day; max 300 mg/day); rifampicin (10 mg/kg/day; max 600 mg/day); pyrazinamide (18 to 26 mg/kg/day); ethambutol (14 to 21 mg/kg/day for 2 months); followed by 4 months of isoniazid and rifampicin</p>
Outcomes	<ol style="list-style-type: none"> 1. All-cause mortality 2. Adverse effects related to steroid use 3. Resolution of tuberculosis 4. HIV-related events
Notes	<p>Location: Uganda</p> <p>Date: November 1998 with recruitment until January 2002</p> <p>Pleural aspiration and, if possible, biopsy for all participants on admission</p>

Galarza 1995

Methods	<p>Generation of allocation sequence: unclear</p> <p>Allocation concealment: unclear</p> <p>Blinding: providers, participants, and assessors</p> <p>Inclusion of all randomized participants in the analysis: 100%; intention-to-treat analysis done</p> <p>Mean duration of follow up: 46 months</p>
Participants	<p>Number: 117 randomized; mean age 27 years; 51% men</p> <p>Inclusion criteria: admitted to hospital for a pleural effusion of tuberculous aetiology</p> <p>Exclusion criteria: HIV-positive; other criteria not stated</p>
Interventions	<ol style="list-style-type: none"> 1. Prednisone plus standard regimen 2. Placebo plus standard regimen <p>Prednisone: single oral dose of 1 mg/kg/day for 15 d tapering off over the next 15 d</p> <p>Standard regimen: isoniazid (5 mg/kg/day; max 300 mg/day); rifampicin (10 mg/kg/day; max 600 mg/day); once daily as a combination tablet for 6 months</p>
Outcomes	<ol style="list-style-type: none"> 1. Time to normal temperature 2. Lung function assessed by forced vital capacity (FVC) at end of treatment 3. Pleural thickening at baseline and at 1, 6, and 12 months after start of treatment 4. Rate of reabsorption of pleural fluid on chest x-ray at baseline and at 1, 6, and 12 months after start of treatment 5. Adverse effects
Notes	<p>Location: Spain</p> <p>Date: January 1985 with recruitment until January 1992</p> <p>Definite microbiological or pathological diagnosis in 63% of participants</p> <p>Before discharge pleural fluid was drained to 1/3 of hemithorax in all participants</p>

Lee 1988

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: participants only Inclusion of all randomized participants in the analysis: 89% Duration of follow up: up to 24 months
Participants	Number: 45 randomized; mean age 29 years; 60% men Inclusion criteria: age < 45 years with pleural effusion with no previous treatment; no past history of pulmonary tuberculosis Exclusion criteria: congestive heart failure; pneumonia; malignancy; other pulmonary diseases and conditions that contraindicated the use of corticosteroids
Interventions	1. Prednisolone plus standard regimen 2. Placebo plus standard regimen Prednisolone: initially given as a single oral dose (0.75 mg/kg/day), tapered gradually over 2 to 3 months once radiological improvement was seen Standard regimen: isoniazid (300 mg/day); rifampicin (450 mg/day for 9 to 12 months); and ethambutol (20 mg/kg/day for 3 months)
Outcomes	1. Resolution of clinical symptoms and signs 2. Rate of reabsorption of pleural fluid on chest x-ray 3. Pleural adhesions and thickening 4. Adverse effects
Notes	Location: Taiwan Date: October 1983 with recruitment until June 1987 HIV status: not stated Diagnostic thoracentesis (< 50 mL) on first day for all participants

Lee 1999

Methods	Generation of allocation sequence: not stated Allocation concealment: not stated Blinding: not stated Inclusion of all randomized participants in the analysis: 100% Mean duration of follow up: 9 months for intervention group; 12 months for control group
Participants	Number: 82 randomized; mean age of 32 years; 64% men Inclusion criteria: "Proper condition for tuberculous pleurisy after the pleura tissue test, positive for cultivation of tuberculous bacilli and anti-bacteria from pleura fluid, pleura tissue and etc." Exclusion criteria: "diabetes, high blood pressure, digestive ulcer, pneumonia, malignant tumor, cardiac insufficiency and etc."; HIV-negative
Interventions	1. Prednisolone plus standard regimen 2. Standard regimen only Prednisolone: single dose per injection of 30 mg/day for 30 days, followed by a tapering off over a further 30 days Standard regimen: isoniazid, rifampicin, pyrazinamide, ethambutol for 6 months OR isoniazid, rifampicin, pyrazinamide, and streptomycin for 2 months followed by same regimen minus streptomycin for 4 months; dosage not stated

Lee 1999 (Continued)

Outcomes	1. Rate of reabsorption of pleural fluid 2. Pleural adhesions and thickening 3. Adverse effects
Notes	Location: Korea Date: February 1990 to February 1997

Wyser 1996

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: participants and assessors Inclusion of all randomized participants in the analysis: 95% Duration of follow up: 6 months
Participants	Number: 74 randomized; mean age of 33 years; 61% men Inclusion criteria: exudative pleural effusions with biopsy specimen proven tuberculous pleurisy Exclusion criteria: other causes of pleural exudates including pneumonia or malignancy; other diseases and conditions that contraindicated use of corticosteroids, including diabetes mellitus, uncontrolled hypertension, peptic ulcer disease, and empyema; neoplastic disease; HIV-positive
Interventions	1. Prednisone plus standard regimen 2. Placebo plus standard regimen Prednisone: oral dose of 0.75 mg/kg/day for 2 to 4 weeks; dose tapered by 5 mg/day over 2 weeks after clinical and radiological improvement Standard regimen: isoniazid (8 mg/kg/day), rifampicin (10 mg/kg/day), and pyrazinamide (25 mg/kg/day) as a fixed combination tablet (Rifater); and pyridoxine (25 mg/kg/day) for 6 months
Outcomes	1. Resolution of symptoms: dyspnoea, cough, night sweats, tiredness, appetite, pleuritic chest pain, and general well-being were each graded from 0 to 100 using a visual analogue scale and combined index with a maximum score of 700 was calculated 2. Lung function at end of treatment as assessed by total lung capacity and forced vital capacity (FVC) 3. Recurrence of effusion 4. Residual pleural thickening at 24 weeks 5. Adverse effects
Notes	Location: South Africa Date: April 1994 with recruitment until January 1995 Thoracoscopy, bronchoscopy, and complete aspiration of pleural fluid for all participants on admission

HIV: human immunodeficiency virus.

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

Aspin 1958	No randomization
Bilaceroglu 1999	Participants did not have pleurisy - cases of pulmonary tuberculosis
Cherednikova 1973	Case series
Cisneros 1996	Review
Damany 1968	Numbers of participants in each arm not clearly stated
Filler 1963	No randomization
Fleishman 1960	Diagnosis of tuberculosis not confirmed
Grewal 1969	No randomization
Khomenko 1990	Participants did not have pleurisy - cases of pulmonary tuberculosis
Manresa 1997	Letter referring to included trial (Galarza 1995)
Mathur 1960	No randomization
Mathur 1965	No randomization
Mayanja-Kizza 2005	Participants did not have pleurisy - cases of pulmonary tuberculosis
Menon 1964	No randomization
Paheco 1973	Compared prednisolone to another steroid (cortivazol)
Paley 1959	No randomization
Porsio 1966	Participants did not have pleurisy - cases of pulmonary tuberculosis
Singh 1965	No randomization
Starostenko 1989	No randomization
Tani 1964	No randomization
Tanzj 1965	No randomization

DATA AND ANALYSES

Comparison 1. Corticosteroids versus control (placebo or no steroids)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from any cause	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Residual fluid at 4 weeks	3	394	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.62, 0.94]
3 Residual fluid at 8 weeks	4	399	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.46, 1.12]
4 Presence of pleural thickening	4	309	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.51, 0.94]
5 Presence of pleural adhesions	2	123	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.51, 1.11]
6 Days to improvement in symptoms	2	123	Mean Difference (IV, Fixed, 95% CI)	-4.32 [-7.44, -1.20]
7 Clinical symptoms after 7 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Adverse events leading to treatment discontinuation	6	586	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [1.12, 6.98]
9 HIV-associated events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Cryptococcal meningitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Oesophageal candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3 Gastroenteritis	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.4 Herpes simplex	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.5 Herpes zoster	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.6 Kaposi sarcoma	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.7 Oral thrush	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Corticosteroids versus control (placebo or no steroids), Outcome 1 Death from any cause.

Review: Corticosteroids for tuberculous pleurisy

Comparison: 1 Corticosteroids versus control (placebo or no steroids)

Outcome: 1 Death from any cause

Study or subgroup	Corticosteroid n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Elliott 2004	36/97	39/97		0.92 [0.65, 1.32]

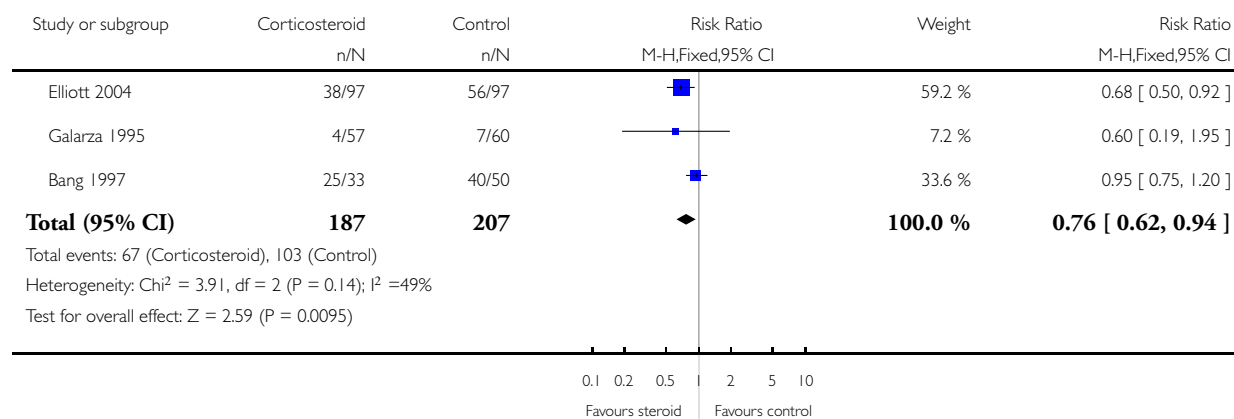
0.5 0.7 1.5 2
Favours steroid Favours placebo

Analysis 1.2. Comparison 1 Corticosteroids versus control (placebo or no steroids), Outcome 2 Residual fluid at 4 weeks.

Review: Corticosteroids for tuberculous pleurisy

Comparison: 1 Corticosteroids versus control (placebo or no steroids)

Outcome: 2 Residual fluid at 4 weeks

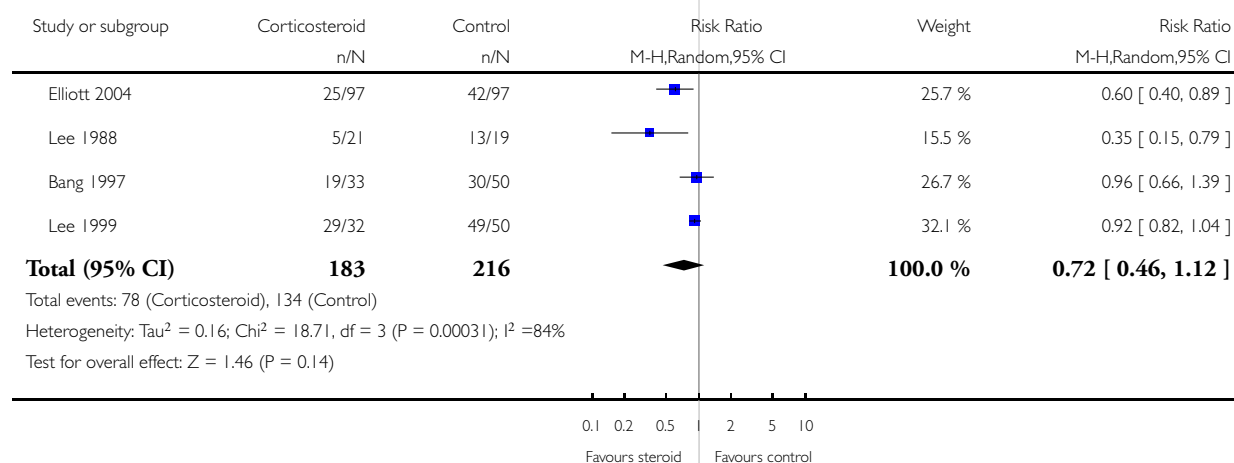


Analysis 1.3. Comparison 1 Corticosteroids versus control (placebo or no steroids), Outcome 3 Residual fluid at 8 weeks.

Review: Corticosteroids for tuberculous pleurisy

Comparison: 1 Corticosteroids versus control (placebo or no steroids)

Outcome: 3 Residual fluid at 8 weeks

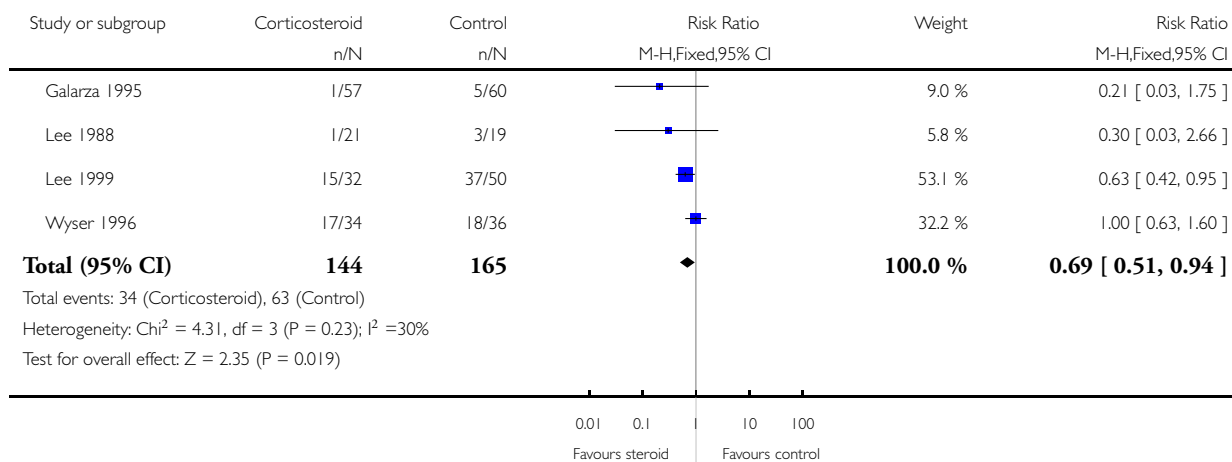


Analysis I.4. Comparison I Corticosteroids versus control (placebo or no steroids), Outcome 4 Presence of pleural thickening.

Review: Corticosteroids for tuberculous pleurisy

Comparison: I Corticosteroids versus control (placebo or no steroids)

Outcome: 4 Presence of pleural thickening

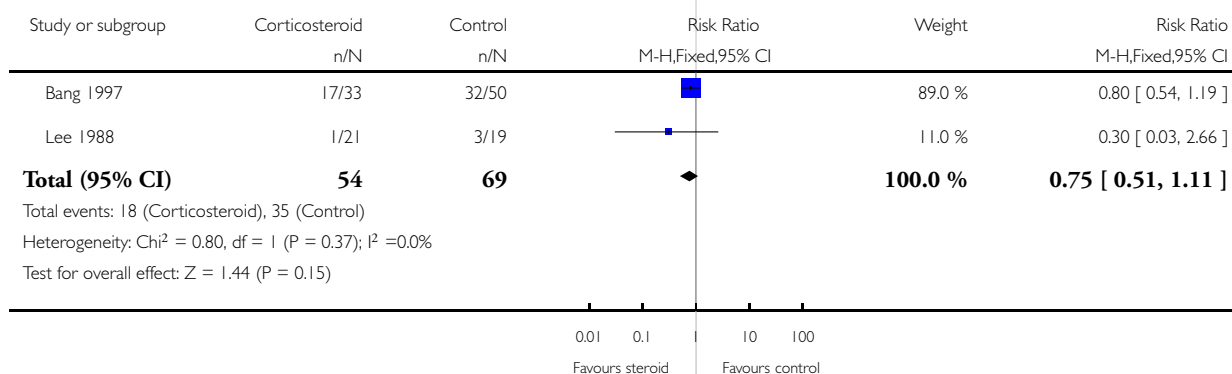


Analysis I.5. Comparison I Corticosteroids versus control (placebo or no steroids), Outcome 5 Presence of pleural adhesions.

Review: Corticosteroids for tuberculous pleurisy

Comparison: I Corticosteroids versus control (placebo or no steroids)

Outcome: 5 Presence of pleural adhesions

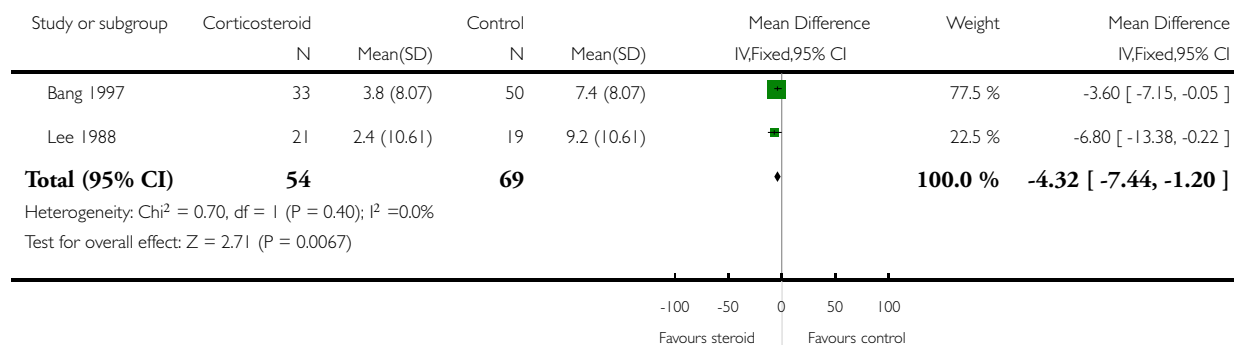


Analysis 1.6. Comparison 1 Corticosteroids versus control (placebo or no steroids), Outcome 6 Days to improvement in symptoms.

Review: Corticosteroids for tuberculous pleurisy

Comparison: 1 Corticosteroids versus control (placebo or no steroids)

Outcome: 6 Days to improvement in symptoms

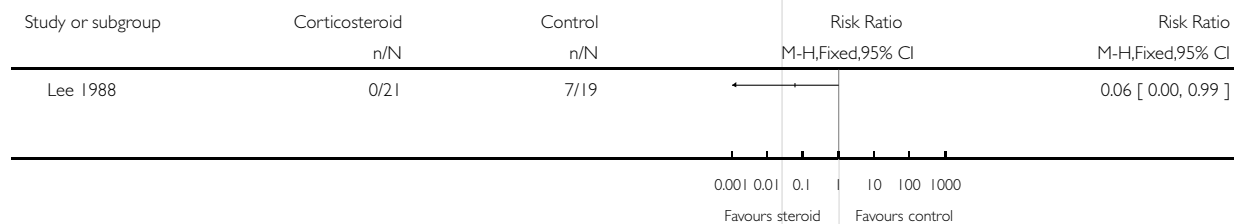


Analysis 1.7. Comparison 1 Corticosteroids versus control (placebo or no steroids), Outcome 7 Clinical symptoms after 7 days.

Review: Corticosteroids for tuberculous pleurisy

Comparison: 1 Corticosteroids versus control (placebo or no steroids)

Outcome: 7 Clinical symptoms after 7 days

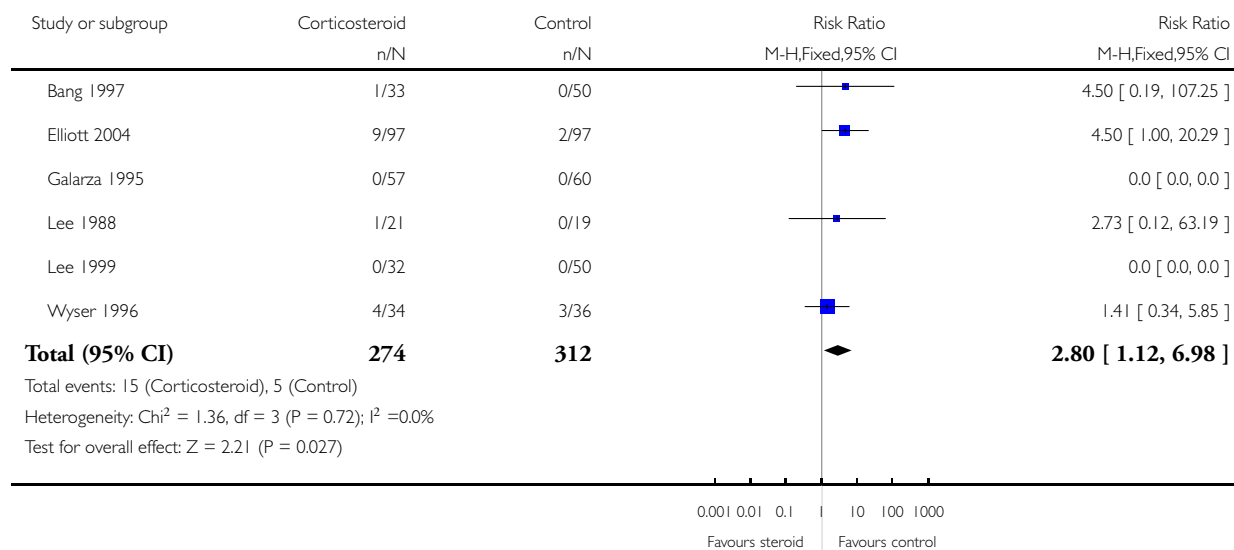


Analysis 1.8. Comparison 1 Corticosteroids versus control (placebo or no steroids), Outcome 8 Adverse events leading to treatment discontinuation.

Review: Corticosteroids for tuberculous pleurisy

Comparison: 1 Corticosteroids versus control (placebo or no steroids)

Outcome: 8 Adverse events leading to treatment discontinuation

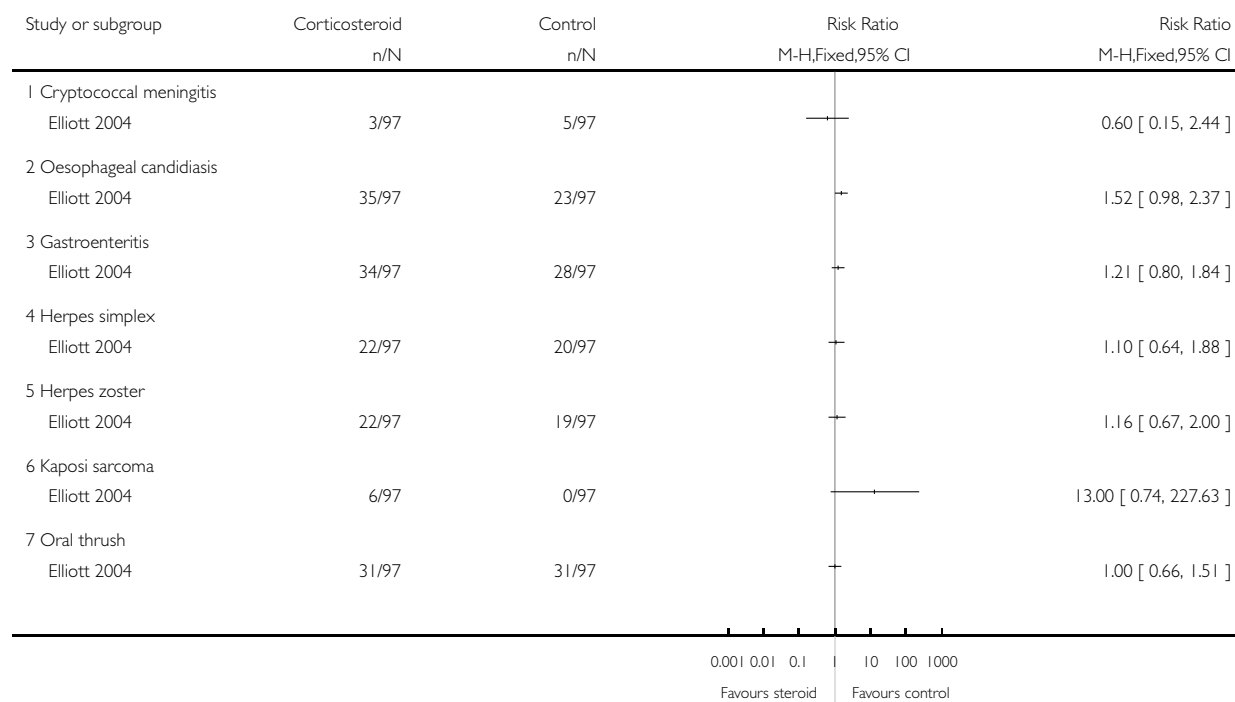


Analysis 1.9. Comparison 1 Corticosteroids versus control (placebo or no steroids), Outcome 9 HIV-associated events.

Review: Corticosteroids for tuberculous pleurisy

Comparison: 1 Corticosteroids versus control (placebo or no steroids)

Outcome: 9 HIV-associated events



APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR ^a	CENTRAL	MEDLINE ^b	EMBASE ^b	LILACS ^b
1	tuberculosis	tuberculosis	TUBERCULOSIS	TUBERCULOSIS	tuberculosis
2	TB	steroids	tuberculosis	tuberculosis	TB
3	steroids	corticosteroids	TB	TB	1 or 2
4	corticosteroids	glucocorticoids	1 or 2 or 3	1 or 2 or 3	steroids

(Continued)

5	dexamethasone	hydrocortisone	steroid*	steroids	hydrocortisone
6	hydrocortisone	prednisolone	STEROIDS	STEROIDS	dexamethasone
7	prednisolone	dexamethasone	corticosteroids	corticosteroids	prednisolone
8	-	2 or 3 or 4 or 5 or 6 or 7	glucocorticoids	glucocorticoids	4 or 5 or 6 or 7
9	-	1 and 8	hydrocortisone	hydrocortisone	3 and 8
10	-	-	dexamethasone	dexamethasone	-
11	-	-	prednisolone	prednisolone	-
12	-	-	prednisone	methylprednisone	-
13	-	-	methylprednisone	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	-
14	-	-	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	4 and 13	-
15	-	-	4 and 14	Limit 13 to human	-
16	-	-	Limit 15 to human	-	-

*Cochrane Infectious Diseases Group Specialized Register.

^bSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Higgins 2006](#)); upper case: MeSH or Emtree heading; lower case: free text term.

WHAT'S NEW

Last assessed as up-to-date: 23 July 2007.

10 September 2008	Amended	Converted to new review format with minor editing.
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HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 3, 1998

24 July 2007	New citation required and conclusions have changed	Review title changed from 'Steroids for treating tuberculous pleurisy'; search updated to May 2007; general updates and modifications were made to most sections with the methods and results sections of the review entirely revised; 'Types of interventions' modified to include any corticosteroid used in combination with antituberculous treatment; 'Types of outcome measures' modified to evaluate death from any cause and improvement in respiratory function as primary outcomes, secondary outcomes updated to include HIV-associated events, "worsening of the parenchymal disease" excluded, and adverse drug effects changed to adverse events. Three new trials added, one of which consisted exclusively of HIV-positive participants. Despite all this, the conclusions remain unchanged.
28 April 2006	Amended	New studies sought but none found.
28 February 2005	Amended	New studies found and included or excluded.

CONTRIBUTIONS OF AUTHORS

Mark Engel (ME) took responsibility for the update of this review. ME developed the data extraction forms with Jimmy Volmink (JV) providing input. ME and JV selected the trials for inclusion in the review, extracted the data, and assessed trial quality. ME contacted authors for additional information. ME entered the data and conducted the analysis. ME wrote the first draft of the review with JV contributing to the final text and analysis. Patrice Matchaba (PM) contributed to the discussion. ME and JV are responsible for maintaining the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- South African Medical Research Council, South Africa.
- University of Cape Town, South Africa.

External sources

- Department for International Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Randomized Controlled Trials as Topic; Tuberculosis, Pleural [*drug therapy]; Tuberculosis, Pulmonary [drug therapy]

MeSH check words

Humans