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Corticosteroids for tuberculous pleurisy (Review)

Ryan H, Yoo J, Darsini P

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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 and raise doubt as to whether such treatment is worthwhile. There is also concern 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 methods

In April 2016, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (the Cochrane Library), MEDLINE, Embase, LILACS, Current Controlled Trials, and the reference lists of articles identified by the literature search.

Selection criteria

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

Data collection and analysis

Two review authors independently screened the search results, extracted data from the included trials, and assessed trial methodological quality using the Cochrane 'Risk of bias' tool. We analysed the data using risk ratios (RR) with 95% confidence intervals (CIs). We applied the fixed-effect model in the absence of statistically significant heterogeneity.

Main results

Six trials with 590 participants met the inclusion criteria, which were conducted in Asia (three trials), Africa (two trials), and Europe (one trial). Two trials were in HIV-negative people, one trial was in HIV-positive people, and three trials did not report HIV status.

Corticosteroids may reduce the time to resolution of pleural effusion. Risk of residual pleural effusion on chest X-ray was reduced by 45% at eight weeks (RR 0.54, 95% CI 0.37 to 0.78; 237 participants, 2 trials, *low certainty evidence*), and 65% at 24 weeks (RR 0.35, 95% CI 0.18 to 0.66; 237 participants, 2 trials, *low certainty evidence*).

Compared with control, corticosteroids may reduce the risk of having pleural changes (such as pleural thickening or pleural adhesions), on chest X-ray at the end of follow-up by almost one third (RR 0.72, 95% CI 0.57 to 0.92; 393 participants, 5 trials,*low certainty evidence*), which translates to an absolute risk reduction of 16%.

One trial reported deaths in people that were HIV-positive, with no obvious difference between the groups; the trial authors' analysis suggests that the deaths observed in this trial were related to HIV disease rather than pleural TB (RR 0.91, 95% CI 0.64 to 1.31; 197 participants, 1 trial).

We found limited data on long-term functional respiratory impairment on 187 people in two trials, which reported that average percentage predicted forced vital capacity was similar in the group receiving prednisolone and in the control group (*very low certainty evidence*).

The risk of adverse events that led to discontinuation of the trial drug was higher in people with pleural TB receiving corticosteroids (RR 2.78, 95% CI 1.11 to 6.94; 587 participants, 6 trials, *low certainty evidence*). The trial in HIV-positive people reported on six different HIV-related infections, with no obvious differences. However, cases of Kaposi's sarcoma were only seen in the corticosteroid group (with 6/99 cases in the steroid group compared to 0/98 in the control group) (*very low certainty evidence*).

Authors' conclusions

Long-term respiratory function is potentially the most important outcome for assessing the effects of adjunctive treatments for people with pleural TB. However, the information on the impact of pleural TB on long-term respiratory function is unknown and could be eclipsed by other risk factors, such as concurrent pulmonary TB, smoking, and HIV. This probably needs to be quantified to help decide whether further trials of corticosteroids for pleural TB would be worthwhile.

PLAIN LANGUAGE SUMMARY

What is tuberculous pleurisy and how might corticosteroids work?

Tuberculous pleurisy results from inflammation of the membrane that covers the lungs (the pleura) caused by exposure to *Mycobacterium tuberculosis* bacteria infecting the lungs. This results in a build up of fluid around the lung (pleural effusion) that causes pain and fever, impairs breathing, and may lead to impairment of lung function in the long term.

Some clinicians believe that corticosteroids used in combination with antituberculous drugs can speed up the recovery from TB pleurisy and help to prevent long-term complications.

What the evidence shows

We examined the available evidence up to 13 April 2016 and included six trials with 590 people, which evaluated prednisolone given with antituberculous treatment (ATT). One included trial was of high quality, while the rest had uncertainties regarding trial quality. All the included trials were in adults; one trial included only HIV-positive people, two included only HIV-negative people, and three did not report the HIV status of the participants.

Corticosteroids may reduce the time to resolution of the symptoms of TB pleurisy and the time to resolution of the pleural effusion on chest X-ray (*low certainty evidence).* Corticosteroids may also reduce the risk of having signs of pleural scarring on chest X-ray (pleural thickening and pleural adhesions) after the disease has resolved (*low certainty evidence*). There was not enough information about lung function to be sure whether or not corticosteroids reduce the risk of lung function impairment after TB pleurisy (*very low certainty evidence*).

Corticosteroids may increase the risk of adverse events leading to discontinuation of the trial drug (*low certainty evidence*). From one trial in people living with HIV, there was no detectable increase in HIV-related conditions with corticosteroids, although cases of Kaposi's sarcoma were only seen in the corticosteroid group and numbers of participants and events were too small to rule out an effect of corticosteroids (*very low certainty evidence*).

As the risk of disability and long-term illness after TB pleurisy is unclear, research looking at the association between TB pleurisy and lung function impairment would be useful to inform future research into corticosteroids for TB pleurisy.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Steroids compared with placebo for pleural TB

Patient or population: adults and adolescents with pleural TB
Settings: hospital care and community follow-up
Intervention: corticosteroids
Comparison: placebo

Outcomes	Illustrative comparative risks[1] (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Corticosteroids			
Residual pleural fluid on chest X-ray at 8 weeks	**62 per 100**	**33 per 100** (23 to 48)	**RR** 0.54 (0.37 to 0.78)	237 (2 trials)	⊕⊕◯◯[1,2,3,4] **low**
Residual pleural fluid on chest X-ray at 24 weeks	**29 per 100**	**10 per 100** (5 to 19)	**RR** 0.35 (0.18 to 0.66)	237 (2 trials)	⊕⊕◯◯[1,2,3,4] **low**
Pleural changes at the end of follow-up (pleural adhesions or pleural thickening on chest X-ray; follow-up 6 to 24 months)	**50 per 100**	**36 per 100** (29 to 46)	**RR** 0.72 (0.57 to 0.92)	393 (5 trials)	⊕⊕◯◯[5,6,7] **low**
Long-term functional respiratory impairment (> 6 months)	-	-	Average percentage predicted FVC similar in corticosteroid and control groups	187 (2 trials)	⊕◯◯◯[8] **very low**
Adverse events leading to treatment discontinuation (follow-up 6 to 24 months)	**1 per 100**	**3 per 100** (1 to 7)	**RR** 2.78 (1.11 to 6.94)	590 (6 trials)	⊕⊕◯◯[9,10] **low**

HIV-related infections (cryptococcal meningitis)	**5 per 100**	**3 per 100** (1 to 12)	**RR** 0.59 (0.15 to 2.42)	103 (1 trial)	⊕◯◯◯[11,12] **very low**
HIV-related cancer (Kaposi's sarcoma)	**14 per 1000**[13]	**180 per 1000** (1 to 316)	**RR** 12.87 (0.73 to 225.40)	103 (1 trial)	⊕◯◯◯[14,15] **very low**

[1]The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RR: risk ratio; TB: tuberculosis; FVC: forced vital capacity

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]Downgraded by one for risk of bias: of the four trials that reported this outcome, we excluded two trials from the final analysis due to high risk of selection bias, after a subgroup analysis suggested the pooled estimate including these studies could be misleading (Bang 1997; Lee 1999). We judged this to be our best estimate of effect. However because we excluded trials from this analysis this generates uncertainty, so we have downgraded the quality of the evidence.

[2]Not downgraded for inconsistency: heterogeneity in the original meta-analysis was likely due to differences in study quality. A subgroup analysis showed that statistical heterogeneity disappeared when we excluded trials that were at high risk of selection bias.

[3]Downgraded by one for imprecision: the CI around the summary effect estimate is wide due to the small number of participants and events in each included trial.

[4]Not downgraded for indirectness: the included trials were performed in different settings and time periods and used widely available drugs and diagnostic techniques. Although the trials did not include children, we did not downgrade as pleural TB is less common in children than in adults. One trial included HIV-positive people, Elliott 2004, and this trial contributed most of the participants in the meta-analysis. When making recommendations relating to the use of corticosteroids for pleural TB in children or in HIV-negative adults, guideline panels may wish to consider downgrading for indirectness.

[5]Downgraded by one for serious risk of bias: we assessed two trials as at high risk of bias for randomization method (Bang 1997; Lee 1999), and the other three trials were at unclear risk of bias (Galarza 1995; Lee 1988; Wyser 1996). Only Wyser 1996 reported that outcome assessors were blinded to the treatment allocation.

[6]Downgraded by one for serious imprecision: the CI around the summary effect estimate is wide, ranging from a maximum risk reduction with steroids of 43% to a minimum risk reduction of 7%, which may not be clinically significant when weighed against possible harms of steroids.

[7]Not downgraded for indirectness: the trials were performed in a variety of settings, and all used drugs and diagnostic techniques that are widely available. We did not include any HIV-positive people in this meta-analysis, so when making recommendations regarding the use of corticosteroids in HIV-positive people with TB pleurisy, guideline panels may wish to consider downgrading for indirectness. Only one trial included children aged over 11 years of age (Galarza 1995), but we did not downgrade as pleural TB is not common in children.

[8]Two of the six trials reported pulmonary function tests at the end of treatment (Galarza 1995; Wyser 1996), but data were insufficient to combine these outcomes in a meta-analysis. The data are in Table 7, and suggest that in these trials there was little or no difference in mean percentage predicted FVC at the end of treatment. The number of participants in each group with pulmonary function tests suggestive of a functional respiratory impairment are not reported.

[9]Downgraded by one for risk of bias: there were concerns about randomization method and allocation concealment. Additionally, reporting of adverse events varied significantly across the trials, and some trials only reported on adverse events in the steroid group, and it is likely that some trials did not detect or report all adverse events.

[10]Downgraded by one for serious imprecision: the CI around the summary effect estimate is wide, with a maximum increased risk of adverse effects leading to study drug discontinuation of nearly 700% and a minimum increased risk of 12%, which may not be clinically significant when weighed against possible benefits of steroids.

[11]Downgraded by two for serious imprecision: the CI around the summary effect estimate is very wide, and possible effects range from large benefits to significant harms.

[12]Downgraded by one for indirectness: only one trial included HIV-positive people and assessed HIV-related adverse events (Elliott 2004). Participants in this trial were not treated with antiretroviral therapy, which is known to prevent cryptococcal meningitis in HIV-positive people; therefore this estimate may not be applicable to HIV-positive people on antiretroviral therapy. This trial did not include any children.

[13]Prevalence of Kaposi's sarcoma of 1.4% in HIV-positive adults on clinic enrolment taken from Semeere 2016, a multi-centre prospective cohort study performed in Uganda and Kenya.

[14]Downgraded by two for serious imprecision: the CI around the summary effect estimate is very wide, and possible effects range from large benefits to significant harms.

[15]Downgraded by one for indirectness: only one trial included HIV-positive people and assessed HIV-related adverse events (Elliott 2004). Participants in this trial were not treated with antiretroviral therapy, which is known to treat and prevent Kaposi's sarcoma in HIV-positive people, therefore this estimate may not be applicable to HIV-positive people on antiretroviral therapy. This trial did not include any children.

BACKGROUND

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* complex, and is a major cause of illness and death worldwide. In 2014 approximately 9.6 million people newly developed the disease and there were 1.5 million deaths globally (WHO 2015). TB infects the lungs, and is transmitted by droplet spread from coughing people with active pulmonary TB, but it can also spread to other body sites and cause extrapulmonary TB (EPTB).

Description of the condition

Pleural TB is one of the most common forms of EPTB, with an incidence of 3% to 25% of people with TB (Light 2010; Sharma 2004). The incidence is higher in high TB prevalence settings (Jeon 2014). Immune compromise is an important risk factor for all forms of TB, and evidence suggests that pleural TB is more common in people living with HIV (Batungwanayo 1993; Frye 1997; Pozniak 1995; Saks 1992). Pleural TB can be a manifestation of TB disease post-primary infection, or due to reactivation of latent TB (Light 2010).

Clinically, pleural TB presents as an acute illness consisting of cough, fever, chest pain, and shortness of breath (Morehead 1998), and usually a pleural effusion is demonstrated on chest X-ray. Pleural TB usually resolves without treatment of any kind, but untreated patients may experience longer duration of the acute symptoms and risk recurrence of active TB at a later point in time (Light 2010). Pleural TB can be complicated by massive effusion leading to respiratory compromise in the short term, and pleural thickening, fibrosis, and pleural adhesions causing impaired respiratory function in the medium- to long-term.

Pleural TB is thought to be caused by a delayed type (type IV) hypersensitivity reaction following release of mycobacterial antigens into the pleural space (Rossi 1987), as a result of rupture of a subpleural focus of TB infection in the lung (Stead 1955). This explains the tendency towards resolution of the effusion and associated symptoms with or without treatment of the TB infection, and the fact that culture of pleural fluid is nearly always negative for *M. tuberculosis*. There appears to be a spectrum of disease in pleural TB in terms of the extent of the underlying lung infection, which could be important in terms of patient outcomes and the potential for corticosteroids to be effective (Table 1). A systematic review that includes 18 trials and 3816 participants suggests that corticosteroids probably do not improve mortality rates, sputum smear or culture conversion in people with pulmonary TB (Critchley 2014). One cohort study of people with pleural TB in Spain reported evidence of pulmonary TB infection on chest X-ray in 20% of 254 participants (Valdés 1998). Pulmonary involvement rose to 86% in another cohort where computed tomography (CT) scanning was used (Kim 2006). Shu 2011 demonstrated that pulmonary involvement (as defined by positive sputum culture and/or chest X-ray appearances) was an important predictor of mortality in hospitalised pleural TB patients in Korea, and was associated with a longer hospital stay.

Diagnosis of pleural TB can be challenging with traditional microscopy and culture methods being relatively insensitive when used on pleural fluid, and newer modalities such as Xpert® MTB/RIF have similar limitations (Denkinger 2014). Histopathological examination and mycobacterial culture performed on pleural biopsy samples are regarded as more reliable tests, and yielded a diagnosis in 227/248 patients (91%) in one cohort study (Valdés 1998).

Description of the intervention

Corticosteroids are hormones produced by the adrenal cortex which have a variety of physiological functions, including carbohydrate metabolism, protein catabolism, regulation of electrolytes, the stress response and control of inflammation. Corticosteroids induce their anti-inflammatory effect through the regulation of gene expression in cells, leading to increased expression of genes which inhibit inflammatory pathways, and repression of genes encoding pro-inflammatory proteins (Barnes 2006). Multiple synthetic forms of these hormones have been produced and are used in the treatment of a wide variety of inflammatory conditions. Prednisolone is a synthetic corticosteroid derived from cortisol, and prednisone is a pro-drug that is converted into the active form prednisolone by the liver. Several formulations of each drug are used for different conditions and diseases; in TB pleurisy patients are usually offered them in tablet form.

Corticosteroids have been used in medicine for many decades, and have well-characterised adverse effect profiles. Adverse effects for medium to long-term use include hyperglycaemia, hypertension, increased risk of infection, osteoporosis, gastric ulceration and gastrointestinal bleeding, thinning of the skin, proximal myopathy, psychiatric symptoms, and development of moon face, striae and acne (Cushing's syndrome). The use of synthetic corticosteroids can induce adrenocorticoid insufficiency, and so patients receiving more than one week's treatment must have the dose slowly reduced to avoid acute adrenal insufficiency causing hypotension and hypoglycaemia which can be life-threatening (BNF 2016).

How the intervention might work

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 delayed type hypersensitivity inflammatory response triggered by the release of tubercular antigens into the pleural space

which is believed to be responsible for tuberculous pleurisy. One corticosteroid is prednisone, which is converted in the liver into the active drug, prednisolone. 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).

Corticosteroids have anti-inflammatory properties, produced mainly via suppression of pro-inflammatory gene expression and activation of anti-inflammatory genes (Barnes 2006). While the inflammatory response is necessary to control the infection, excessive inflammation can lead to tissue damage and fibrosis, which could cause long-term morbidity. Suppression of the inflammatory response in pleural TB could reduce the symptoms and signs associated with the inflammatory process: fever, progression of the pleural effusion, malaise. Corticosteroids could therefore reduce the duration or severity of symptoms in the short term, and also reduce the risk of tissue damage leading to lung impairment in the long term.

Why it is important to do this review

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. The previous version of this Cochrane review (Engel 2007), which included six trials and 633 participants, concluded that data were insufficient to support the use of corticosteroids in pleural TB.

In addition to the uncertainty about benefits of corticosteroid therapy, there is concern about potential risks. In immunocompromised 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's sarcoma, a vascular tumour accompanied by numerous unconnected lesions of the skin and 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 TB (Anonymous 1983). Other adverse effects associated with corticosteroids include high blood pressure, high blood glucose or exacerbation of existing diabetes mellitus, weight gain, increased susceptibility to infection, gastrointestinal bleeding and in long-term use osteoporosis and changes to the skin and face.

We updated this review with the aim of adding any new evidence that may have been published since the previous search in 2007. For this version, we revised the protocol, and in particular altered the outcomes of interest. This was informed by discussions with expert clinicians which took place during the development of a new guideline on extrapulmonary TB in India, the INDEX-TB guidelines (INDEX-TB 2016).

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 controlled trials (RCTs) and quasi-RCTs.

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; staining and microscopy for acid-fast bacilli, or culture of sputum, or both; pleural fluid; or pleural biopsy.

Types of interventions

Intervention

Any corticosteroid at any dose.

Control

Placebo or no adjunctive treatment.

Both treatment groups should receive the same antituberculous drug regimen.

Types of outcome measures

Short term (under six months)

- Time to resolution of clinical symptoms (as defined by the authors, including fever and pain)
- Time to resolution of pleural effusion

Long term (six months or more)

- Pleural changes at the end of treatment (pleural thickening and pleural adhesions)
- Change in respiratory function
- Disability (as defined by authors)
- Deaths from any cause

We will also report on other outcomes of resolution as defined by the author.

Adverse effects

- Corticosteroid-associated adverse effects
- HIV-associated adverse effects

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).

Electronic searches

We searched the following databases using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register (18 November 2016); the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (18 November 2016); MEDLINE (1966 to 18 November 2016); Embase (1974 to 18 November 2016); and LILACS (1982 to 18 November 2016). We also searched Current Controlled Trials (18 November 2016) using 'tuberculosis' and 'pleur*' as search terms.

Searching other resources

We performed hand searches of the reference lists of all studies identified with the above methods.

Data collection and analysis

Selection of studies

The review authors 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-text article before we made a decision on study eligibility, and we contacted the study authors where necessary. We consulted translators when abstracts were unavailable in English. We assessed the full-text articles of potentially relevant studies and included trials that met the inclusion criteria. We listed studies that did not meet our inclusion criteria and stated the reason for exclusion in a 'Characteristics of excluded studies' table. We constructed a PRISMA diagram to illustrate the study selection process.

Data extraction and management

Two review authors (PD and HR) independently extracted data from the included trials on participant characteristics, diagnostic criteria, HIV status, antituberculous drug regimen, corticosteroid regimen, and outcome measures using a pre-piloted data extraction form. One review author (JY) extracted data from Bang 1997 and Lee 1999 as both trial reports were in Korean. We resolved disagreements through discussion and contacted the corresponding trial author in the case of unclear or missing data.
For dichotomous outcomes, we recorded the number of participants that experienced the event and the number of participants in each treatment group. For continuous outcomes, we extracted the arithmetic means and standard deviations for each treatment group together with the numbers of participants in each group.

Assessment of risk of bias in included studies

Two review authors (PD and HR, or JY and HR) independently assessed the risk of bias for each included trial using the Cochrane 'Risk of bias' tool (Higgins 2011). We resolved any differences of opinion through discussion with reference to the trial reports, and through discussion with the Cochrane Infectious Diseases Group Co-ordinating Editor, Paul Garner. We followed the guidance to assess whether adequate steps had been taken to reduce the risk of bias across six domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessors
- Incomplete outcome data
- Selective reporting
- Other bias

When assessing risk of bias related to blinding (performance bias or detection bias), we planned to consider the implications of blinding separately for each outcome, as appropriate.
For assessment of bias related to incomplete outcome data (attrition bias), we used the following criteria to assess risk of bias.

- Low risk: less than 5% of participants were lost to follow-up
- Unclear risk: between 5 and 10% of participants were lost to follow-up

- High risk: more than 10% of participants were lost to follow-up

For selective reporting (reporting bias), we used the following criteria to determine the risk of bias.

- Low risk: the trial authors stated in the introduction or method sections the outcomes they would look at, and they reported all of them in the results section
- Unclear risk: the trial authors did not state in the introduction or method sections the outcomes they would look at
- High risk: the trial authors stated the outcomes they would look at but they did not report all of them in the results section

We categorized these judgments as either at low, high, or unclear risk of bias. We attempted to contact the trial authors for clarification if any details were unclear; where our judgement is recorded as 'unclear' we were unable to amend our judgement after we contacted the trial authors. The results of the 'Risk of bias' assessment are displayed in the 'Characteristics of included studies' tables.

Measures of treatment effect

For dichotomous outcomes, we used relative risk as the measure of treatment effect for analysis. For continuous outcomes we planned to use mean difference, but this was not necessary in the final review draft.

Unit of analysis issues

There were no cluster-RCTs amongst the included trials, so individual participants were the unit of analysis.

Dealing with missing data

The primary analysis was an intention-to-treat analysis where all participants randomized to treatment were included in the denominator, where possible. This analysis assumes that all losses to follow-up have good outcomes. We planned to explore the effect of losses to follow-up on the overall effect estimates by performing sensitivity analyses.

Assessment of heterogeneity

We assessed heterogeneity by visually inspecting the forest plots to determine closeness of point estimates with each other and overlap of confidence intervals (CIs). We used the Chi² test with a P value of 0.10 to indicate statistical significance, and the I^2 statistic to assess heterogeneity with a value of 50% taken to indicate statistical heterogeneity. We planned to investigate heterogeneity through the following subgroup analyses: corticosteroid dose, HIV status, and methodological quality.

Assessment of reporting biases

We planned to look for publication bias by constructing a funnel plot, but there were too few studies to do this.

Data synthesis

We analysed the data using Review Manager 5 (RevMan 5) (Review Manager 5). For outcomes where it was possible to combine data and clinical heterogeneity was low, we decided to perform a meta-analysis. We used risk ratios (RR) with 95% CIs and the fixed-effect model. For outcomes where it was not possible to combine data, we described the results in tables. We summarized the adverse event data in tables and performed meta-analysis for adverse events leading to discontinuation of the trial drug, and HIV-associated adverse events.

Subgroup analysis and investigation of heterogeneity

Where there was substantial unexplained statistical heterogeneity, we carried out subgroup analyses to investigate possible causes.

Sensitivity analysis

To explore the possible effect of losses to follow-up, we planned to conduct a worst case scenario analysis and compare it with an available-case analysis for the outcome pleural changes at the end of treatment. There were few losses to follow-up in the included trials, and the two trials with the highest number of losses to follow-up did not state which treatment groups these participants were randomized to. Therefore we did not conduct the sensitivity analysis as planned.

Quality of the evidence

We assessed the quality of the evidence using the GRADE approach (Jüni 2001). We used GRADEpro Guideline Development Tool (GDT) software to construct a 'Summary of findings' table (GRADEpro GDT 2014).

RESULTS

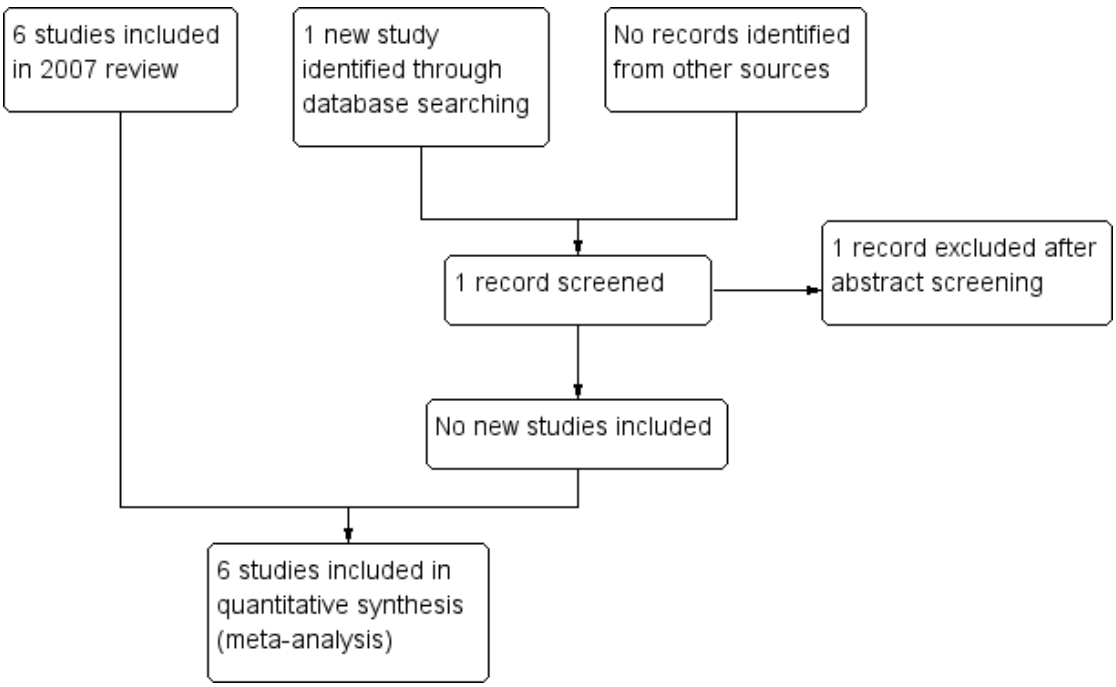
Description of studies

Results of the search

In the 2007 version of this Cochrane Review, we screened 48 studies, of which we identified 27 published trials for possible inclusion into the review. Six trials met the inclusion criteria (Engel 2007). In this review update, the search returned one new study, which we excluded. Figure 1 shows the study selection process.

We have described the characteristics of the included studies in the 'Characteristics of included studies' tables and summarized the results in Table 2.

Figure 1. Study flow diagram.



Included studies

Settings

The six trials included 633 participants, with a range of 45 to 197 per trial, and were conducted in a various countries: Taiwan (Lee 1988), Spain (Galarza 1995), South Africa (Wyser 1996), Korea (Bang 1997; Lee 1999), and Uganda (Elliott 2004). All trials were single centre trials based in large tertiary care hospitals.

Participants

All participants were adults except in one trial, Galarza 1995, which included people aged 11 years and older. All trials included participants of both sexes; overall 59% were male, with a range of 51% to 64% across trials.

One trial included only HIV-positive participants (Elliott 2004), two trials excluded HIV-positive participants (Galarza 1995; Wyser 1996), while the other included trials did not mention the HIV status of the participants.

All but one trial, Galarza 1995, specified the exclusion of participants with co-morbidities that may be exacerbated by the use of corticosteroids, particularly hypertension, diabetes mellitus, and peptic ulcer disease. Elliott 2004 also specified the exclusion of participants with another major HIV-related disease.

We have described the diagnostic tests performed in each included trial in Table 3. Diagnosis of pleural TB was made on the basis of either characteristic histopathological features on pleural biopsy or positive culture or acid-fast bacilli (AFB) on smear microscopy staining from pleural fluid, biopsy or sputum in three trials (Elliott 2004; Lee 1999; Wyser 1996). Galarza 1995 also included participants with a diagnosis of tuberculous pleurisy based on a combination of at least two of: reactive Mantoux test, lymphocytic pleural fluid, and raised adenosine deaminase activity in pleural fluid. Bang 1997 only included participants who had positive microscopy for AFB from sputum, pleural fluid, or pleural biopsy.

Lee 1988 included participants with pleural biopsy "reported as pleural tuberculosis or chronic granulomatous inflammation".

Interventions

We have summarized the antituberculous therapy (ATT) regimens used in the included trials in Table 2, and the corticosteroid regimens used in Table 4.

Four trials compared either prednisone or prednisolone with placebo as an adjunct to an established antituberculous regimen containing at least isoniazid and rifampicin (Elliott 2004; Galarza 1995; Lee 1988; Wyser 1996). Bang 1997 and Lee 1999 did not use any comparative treatment in the control group.

Four trials used weight-based dosing of corticosteroids; Bang 1997 started at 1.0 mg/kg twice daily, Galarza 1995 started at 1.0 mg/kg/day, and Lee 1988 and Wyser 1996 started at 0.75 mg/kg/day. Elliott 2004 started at 50 mg/day for all participants, and Lee 1999 started at 30 mg four times daily. Lee 1988 and Wyser 1996 tapered the dose of corticosteroid according to the participant's clinical progress; the other included trials either had fixed tapering regimens or did not describe the tapering regimen.

All included trials described performing diagnostic pleural aspiration (thoracocentesis) as part of eligibility screening and diagnosis of pleural TB. Two trials also performed therapeutic thoracocentesis (Galarza 1995; Wyser 1996). In Galarza 1995, pleural fluid was drained in all participants before discharge "until a third of the hemithorax was observed to be occupied in a standard chest radiograph". In Wyser 1996, thoracoscopy and bronchoscopy were performed in all participants under general anaesthesia at admission, and chest drains were left in situ for 48 hours following the procedure to drain remaining pleural fluid.

Outcomes

Follow-up varied from six months to 24 months. Two trials did not clearly state the length of follow-up (Bang 1997; Lee 1999).

None of the included trials reported all the outcome measures chosen for this review.

Five trials reported on resolution or improvement of clinical symptoms in some way. Bang 1997 and Wyser 1996 both used self-reported questionnaires to assess the time until symptom improvement and resolution in all participants; Wyser 1996 asked participants to grade the severity of a range of symptoms on a visual analogue scale. Lee 1988 reported the time to resolution of symptoms "including fever, chest pain and dyspnoea" for all participants, but did not specify how this was assessed. Elliott 2004 reported on improvement of anorexia, weight loss, and cough, but data for other symptoms was not reported. Galarza 1995 reported on time to resolution of fever.

Five trials reported on time to resolution of pleural effusion (Bang 1997; Elliott 2004; Galarza 1995; Lee 1988; Lee 1999). Four trials reported the number of participants with residual pleural effusion at various time points during treatment (Bang 1997; Elliott 2004; Lee 1988; Lee 1999). Bang 1997 and Lee 1988 also reported the mean number of days to resolution of pleural effusion. Galarza 1995 reported the mean reabsorption index for all participants over time. The trial authors calculated the reabsorption index as follows: (length of affected hemithorax/length of healthy hemithorax) x 100. Wyser 1996 reported recurrence of pleural effusion, rather than time to resolution, as all participants had therapeutic thoracocentesis at the start of treatment.

Five trials reported on pleural changes at various time points throughout treatment and at the end of follow-up (Bang 1997; Galarza 1995; Lee 1988; Lee 1999; Wyser 1996). Galarza 1995 and Wyser 1996 described the diagnostic criteria for pleural thickening on chest X-ray (Wyser 1996 also used high-resolution computed tomography). Three trials did not describe the criteria for classifying participants as having pleural adhesions or pleural thickening (Bang 1997; Lee 1988; Lee 1999).

Two trials reported on respiratory function (Galarza 1995; Wyser 1996). In Wyser 1996, spirometry and body plethysmography were performed at admission and at various points during follow-up. In Galarza 1995, spirometry was performed at the start and end of treatment. Neither trial reported the complete data for this outcome.

Disability was not reported in any of the included trials. Only one trial reported any deaths (Elliott 2004).

Elliott 2004 reported on CD4+ cell count at enrolment to the trial and at 1, 2, 6, and 18 months after start of treatment. A subset of participants (N = 40) also had blood and pleural fluid specimens analysed for HIV viral load.

All trials reported adverse events, although there was variation in the level of detail. Elliott 2004 reported on HIV-related disease as well as corticosteroid-related adverse events.

Excluded studies

We have listed the reasons for excluding 22 studies in the 'Characteristics of excluded studies' section.

Risk of bias in included studies

See the 'Characteristics of included studies' tables for details of individual included trials. The results of the 'Risk of bias' assessment are summarized in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included trials.

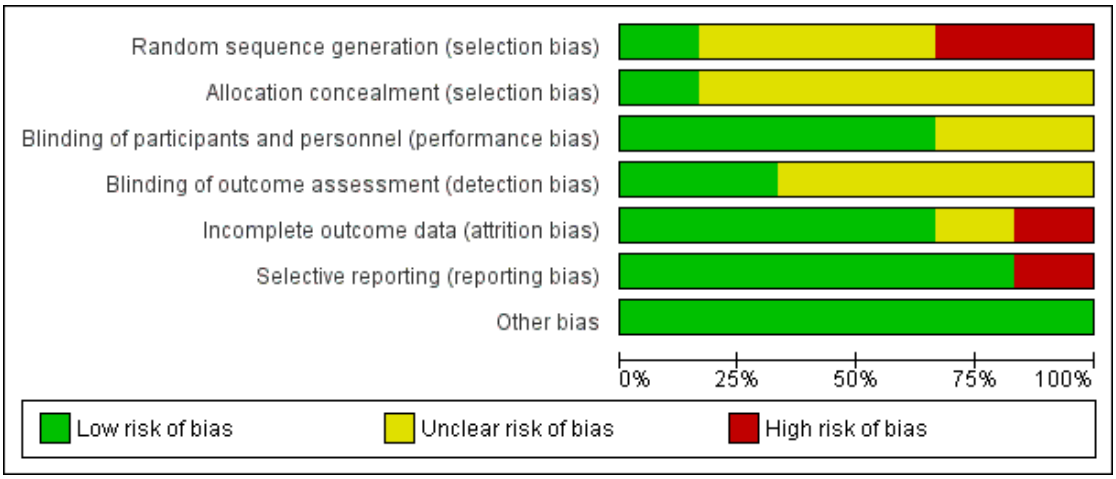
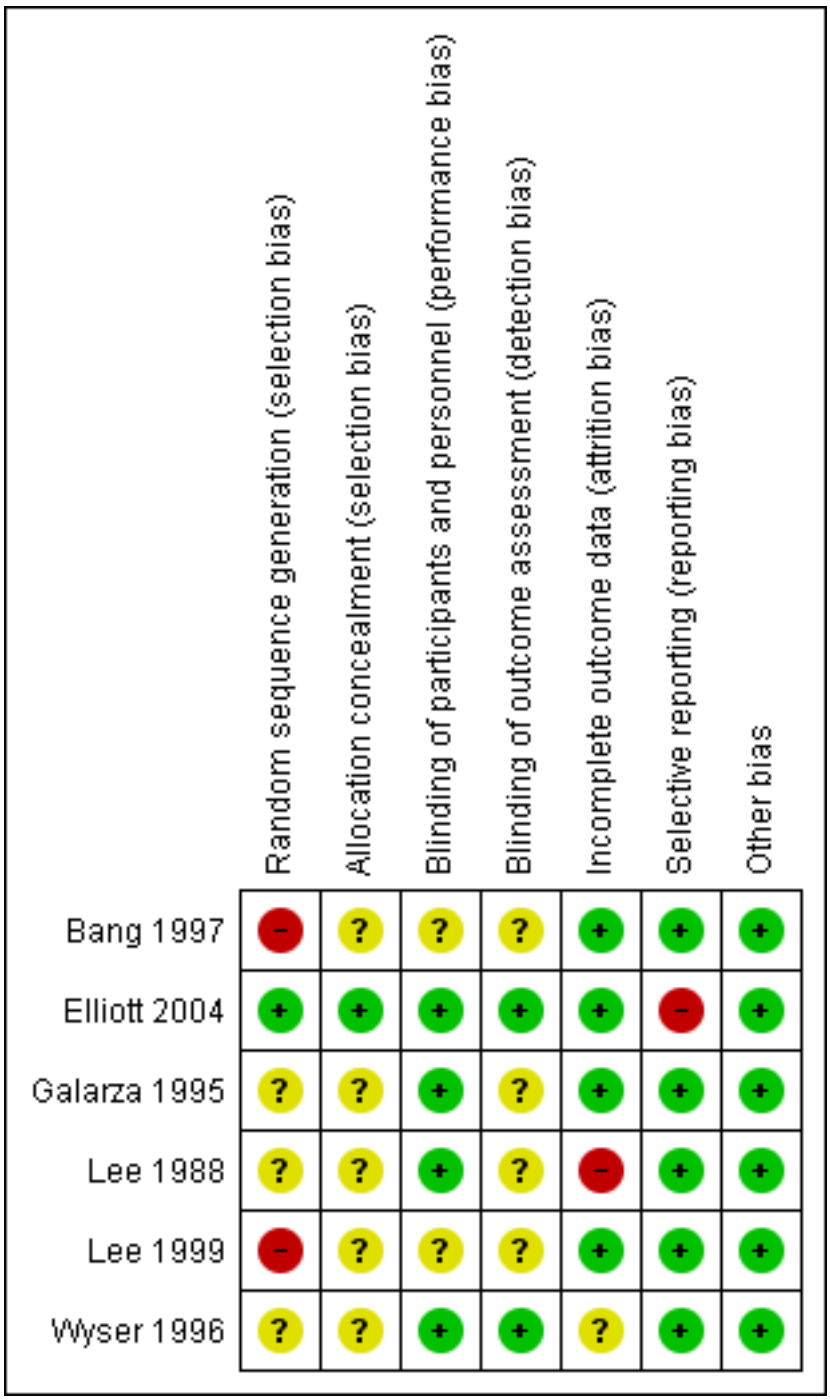


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial.



Allocation

All included trials were reported as randomized. Elliott 2004 explicitly stated that random numbers were computer-generated, which we considered to be low risk of bias. The other included trials did not indicate how the sequence was generated, and we assessed them as at unclear risk of bias.

One trial gave a detailed description of the method of allocation concealment and we assessed it as at low risk of bias; 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 describe the method of allocation concealment, and so we classified them as at unclear risk of bias.

Blinding

Four trials described blinding of participants and personnel and we assessed them as at low risk of bias (Elliott 2004; Galarza 1995; Lee 1988; Wyser 1996). Bang 1997 and Lee 1999 did not mention blinding, and therefore we classified them as at unclear risk of bias. Two trials specified blinding of outcome assessors and we assessed them as being at low risk of bias (Elliott 2004; Wyser 1996). None of the other trials reported whether or not outcome assessors were blinded to treatment allocation, and so we assessed them as at unclear risk of bias.

Incomplete outcome data

Three trials did not report any losses to follow-up (Bang 1997; Galarza 1995; Lee 1999). Bang 1997 excluded one participant in the corticosteroid group from the analysis as the trial drug had to be stopped due to epigastric pain. Elliott 2004 reported 3/197 (1.5%) participants lost to follow-up; one from the placebo group and two from the corticosteroid group. We categorised these trials as at low risk for attrition bias.

Wyser 1996 excluded 4/74 (5.4%) from the analysis; three due to noncompliance with treatment and one due to a diagnosis of oesophageal cancer during treatment. The authors do not report which groups the excluded participants were allocated to. We categorised this trial as at unclear risk of attrition bias.

Lee 1988 excluded 5/45 (11.1%) from the analysis; one due to a diagnosis of renal cell carcinoma during treatment, and four were lost to follow-up. We classified this trial as at high risk of attrition bias.

Selective reporting

Trial protocols were unavailable for all of the included trials. Five trials stated the outcomes clearly in the introduction and methods sections of the study reports, and reported all stated outcomes (Bang 1997; Galarza 1995; Lee 1988; Lee 1999; Wyser 1996). Elliott 2004 reported that the hypothesis of the trial was that prednisolone would improve long-term survival, and decrease HIV viral replication, but did not list the planned outcomes. We assessed this trial as at high risk of reporting bias because in the results section it implied that data on resolution of symptoms that did not demonstrate a statistically significant positive effect of prednisolone was not reported, whereas data were reported for the outcomes of anorexia, weight, and cough where a statistically significant positive effect was found.

Other potential sources of bias

We did not find enough trials that met the inclusion criteria for us to conduct a funnel plot to look for possible publication bias.

Effects of interventions

See: **Summary of findings for the main comparison**

Time to resolution of clinical symptoms

Due to the different units of measurement used in the trials, and insufficient reported data, it was not possible to combine the effects in a meta-analysis for this outcome. We have presented the results from the included trials in Table 5. Qualitatively, corticosteroids appear to be associated with more rapid resolution of symptoms, but we were unable to assess the relative effect of corticosteroids statistically.

Time to resolution of pleural effusion

Five trials reported on time to resolution of pleural effusion (Bang 1997; Elliott 2004; Galarza 1995; Lee 1988; Lee 1999). We combined data for the number of participants with a residual pleural effusion on chest X-ray in each treatment group from four trials. Bang 1997, Elliott 2004, and Lee 1988 reported data across three time points (4 weeks, 8 weeks, and 24 weeks), and Lee 1999 reported data for two time points (8 weeks and 24 weeks). Galarza 1995 presented the mean reabsorption index for each treatment group at four weeks, and so we could not use data from this trial in the meta-analysis. We have presented the results from each trial in Table 6. Wyser 1996 reported on recurrence of pleural effusion, as all participants had drainage of their pleural effusions at admission to the trial, and reported no recurrences of pleural effusion in either group.

The initial meta-analysis, which includes data from Bang 1997, Elliott 2004, Lee 1988, and Lee 1999, found substantial statistical

heterogeneity at all three time points, and we conducted a subgroup analysis to explore this (Analysis 2.1; Analysis 2.2). When we excluded trials that were at high risk of bias for selection bias (randomization and allocation concealment) from the meta-analysis, the statistical heterogeneity resolved. In these two trials it is possible that the trial investigators allocated a greater proportion of participants with more severe pleural effusions to the corticosteroid group, believing that corticosteroids would be of benefit to them (Bang 1997; Lee 1999). This would lead to bias towards the null, and a misleading summary effects estimate. For this reason, we excluded the trials that were at high risk of selection bias from the meta-analysis.

The results showed a reduction in the risk of having residual pleural fluid on chest X-ray at all three time points in participants treated with corticosteroids: by 36% at four weeks (RR 0.64, 95% CI 0.49 to 0.84; 237 participants, 2 trials), 45% at eight weeks (RR 0.54, 95% CI 0.37 to 0.78; 237 participants, 2 trials), and 65% at 24 weeks (RR 0.35, 95% CI 0.18 to 0.66; 237 participants, 2 trials).

Pleural changes on chest X-ray at the end of treatment

Five trials reported on chest X-ray changes to the pleura at the end of treatment (Bang 1997; Galarza 1995; Lee 1988; Lee 1999; Wyser 1996). The terms 'pleural thickening' and 'pleural adhesions' were used to describe these changes, and in some cases seemed to be used interchangeably. We found that corticosteroids may reduce the risk of having pleural changes on chest X-ray after at least six months by 28% (RR 0.72, 95% CI 0.57 to 0.92; 393 participants, 5 trials, *low certainty evidence*; Analysis 1.2).

One trial, Galarza 1995, attempted to quantify the degree of pleural thickening by measuring the maximal pleural thickening in millimetres at 1, 6, and 12 months after enrolment, and reported the mean maximal pleural thickness for each treatment group. The prednisolone group had a mean maximal pleural thickness of 1.77 mm (range 0 to 40 mm), and for the placebo group 2.23 mm (0 to 15 mm), with a P value of more than 0.05.

Wyser 1996 also performed high resolution CT scan of the chest in most participants, and found 17/32 participants in the prednisolone group and 21/35 participants in the placebo group had pleural thickening at the end of treatment using this test (P = 0.52).

None of the included trials looked at the extent of pleural changes on chest X-ray in terms of area of pleural change.

Change in respiratory function

Two trials with 191 participants measured improvement in respiratory function and found no difference between the groups (Galarza 1995; Wyser 1996). We have summarized the results in Table 7.

In Galarza 1995, mean forced vital capacity (FVC) was 95% in both the treatment and control groups at the end of treatment; in Wyser 1996 it was 85% in the corticosteroids group and 80% in the placebo group (P = 0.65). We could not perform a meta-analysis due to insufficient reported data.

Disability

None of the included trials looked at disability or functional impairment after treatment for TB pleurisy.

Death from any cause

Only Elliott 2004 reported any deaths, with 36/99 deaths in the prednisolone group, and 39/98 deaths in the placebo group, meaning the relative risk of death in the prednisolone group was 0.91 (95% CI 0.64 to 1.31; 197 participants, 1 trial; Analysis 1.3), which indicated that prednisolone did not confer a survival benefit. The trial authors commented that mortality rates were higher in participants with low CD4+ cell counts on enrolment to the trial.

Adverse effects of treatment

More participants in the corticosteroid group had adverse events leading to discontinuation of the study drug (RR 2.78, 95% CI 1.11 to 6.94; 590 participants, 6 trials, *low certainty evidence*; Analysis 1.4). We have summarized the results in Table 8.

There was variation in the level of detail reported across the different trials, and assessment of participants to detect adverse effects of treatment also varied.

Bang 1997 reported one participant from the corticosteroid group was withdrawn from the study due to aggravation of epigastric pain.

Lee 1988 reported one participant from the corticosteroid group developed moon-shaped face, epigastric pain, and lower limb oedema which resolved on tapering the study drug.

Wyser 1996 reported that the only adverse effect observed was epigastric pain, which affected 4/34 participants in the corticosteroid group and 3/36 participants in the placebo group.

Elliott 2004 reported 9/99 participants in the corticosteroid group stopped the trial drug due to hyperglycaemia (two participants), hypertension (three participants), herpes zoster (three participants), or oesophageal candidiasis (one participant). In the placebo group 2/98 participants stopped the trial drug; one participant due to hyperglycaemia and one participant due to hypertension.

Galarza 1995 reported no adverse events in either treatment group, and Lee 1999 reported no significant adverse events in the participants treated with steroids.

HIV-associated adverse events

Only Elliott 2004 included HIV-positive participants. The trial reported adverse events related to HIV, including candidiasis, herpes simplex and herpes zoster, cryptococcal meningitis, gastroenteritis, and Kaposi's sarcoma (summarized in Table 9). For most of these adverse events there was no difference between the corticosteroid and placebo groups. For Kaposi's sarcoma, there was a statistically non-significant trend towards increased risk with corticosteroids: 6/99 in the corticosteroid group developed Kaposi's sarcoma compared with 0/98 in the placebo group (RR 12.87, 95% CI 0.73 to 225.40; 197 participants, 1 trial, *very low certainty evidence*).

DISCUSSION

Summary of main results

See 'Summary of findings' table 1 (Summary of findings for the main comparison).

Six trials met the inclusion criteria; we have not included any new trials since the 2007 version of this Cochrane Review (Engel 2007), and we did not find any trials in progress that address this question.

There was a trend towards faster resolution of symptoms, such as fever and chest pain, with corticosteroids across all included trials, but the trials reported insufficient data to produce a meta-analysis addressing time to resolution of symptoms, and there were variations across studies in terms of which symptoms were reported and who the participants were monitored and assessed.

Corticosteroids probably reduce the time to resolution of pleural effusion.

Corticosteroids may reduce risk of pleural changes on chest X-ray at the end of treatment by 28% (RR 0.72, 95% CI 0.57 to 0.92; 393 participants, 5 trials, *low certainty evidence*). On average, half the participants in the control group had pleural changes at the end of at least six months, giving an estimated absolute risk reduction of 14% with corticosteroids.

There was insufficient data to draw conclusions about the effect of corticosteroids on respiratory function after treatment, and none of the included trials reported on disability after treatment. Only one trial reported on death (Elliott 2004), and the trial authors' analysis suggests that death was related to low CD4+ cell counts, which implied that death was related to severity of HIV disease. Corticosteroids had no effect on all-cause mortality in this trial (RR 0.91, 95% CI 0.64 to 1.31; 197 participants, 1 trial).

Corticosteroids may increase risk of adverse events leading to discontinuation of the study drug (RR 2.78, 95% CI 1.11 to 6.94; 587 participants, 6 trials, *low certainty evidence*). Commonly reported adverse effects included epigastric pain, hypertension, and hyperglycaemia.

Only one trial included HIV-positive people and reported on HIV-associated adverse events (Elliott 2004). While there was no significant difference between the corticosteroid and placebo groups for any of the conditions observed, Kaposi's sarcoma was only observed in the group receiving steroids: 6/99 in the corticosteroid group developed Kaposi's sarcoma compared with 0/98 in the placebo group (RR 12.87, 95% CI 0.73 to 225.40; 197 participants, 1 trial, *very low certainty evidence*).

Overall completeness and applicability of evidence

The six trials included male and female participants, who were mostly HIV-negative adults. One trial included children over the age of 11 years (Galarza 1995), and one trial included only HIV-positive adults (Elliott 2004). The trials reflected the fact that pleural TB is more common in adults, but HIV-positive people are under-represented in this review, and the results of the pooled estimates may be less applicable to HIV-positive people. The included trials were all conducted in tertiary hospital settings, in a countries varying from low to high TB burden and HIV prevalence.

The method of diagnosis of pleural TB varied between the included trials (see Table 3), but were representative of diagnostic tests commonly available in high- and middle-income settings. Culture and histopathology are less accessible in low-income settings, where diagnosis may be based on clinical presentation and X-ray findings alone.

The antituberculous treatment (ATT) that participants received varied across the included trials, and in some trials the treatment given was significantly different from widely recommended first-line treatment for drug-sensitive TB (see Table 2). Most notably, the older trials included either two drugs (Lee 1988), or three drugs (Galarza 1995; Wyser 1996), in their regimens rather than all four currently recommended first-line drugs in the intensive phase of treatment. Participants were given at least six months of ATT in all trials. This variation in ATT was not associated with statistically significant heterogeneity in any of our analyses. As the more recent trials used regimens that are the same or very similar to currently recommended regimens for drug-sensitive TB, it is unlikely that the variation in ATT regimens between the trials limits the applicability of the evidence.

For some outcomes, such as respiratory function and time to resolution of symptoms, incomplete reporting of data and differences in units meant that we could not combine data to generate a summary effects estimate.

Quality of the evidence

We assessed the quality of the evidence using the GRADE approach (Jüni 2001), and reported the outcomes in a 'Summary of findings' table (Summary of findings for the main comparison).

For time to resolution of pleural effusion, we combined data on residual pleural fluid on chest X-ray from four trials. As described in the results section, after exploring high unexplained statistical heterogeneity for this outcome, we chose to exclude the two trials that were at high risk of selection bias from the final analysis to avoid a misleading summary estimate of effect. The exclusion of studies from the meta analysis generates uncertainty, and therefore we chose to downgrade by one because of this. We also downgraded for imprecision; the number of participants and events is small, the meta analysis is probably underpowered.

We graded the summary effects estimate for pleural changes at the end of treatment as low certainty evidence, and downgraded due to concerns about risk of bias relating to randomization and allocation methods, and for imprecision relating to the relatively small number of events and participants.

For long-term functional respiratory impairment, we graded the quality of the evidence as very low. Meta-analysis was not possible for this outcome due to insufficient reporting of data, and we reported the available data in Table 7. Although two trials reported the mean percentage predicted forced vital capacity (FVC) at the end of treatment (Galarza 1995, Wyser 1996), neither the results per participant nor the variance were reported.

For adverse events leading to discontinuation of the trial drug, we assessed the quality of the evidence as low. We downgraded for risk of bias relating to randomization and allocation concealment, and also reporting as some trials did not report on adverse events in detail. Also a few only referred to adverse effects associated with steroids in the steroid group, which raised the concern that adverse events in the control group were not detected or reported.

For adverse events relating to HIV, we graded the estimates of effect relating to two serious, life-threatening HIV-related diseases - cryptococcal meningitis and Kaposi's sarcoma - and judged the quality of the evidence to be very low. We downgraded by two for imprecision caused by the small number of events and participants, and also by one for indirectness as the participants were all from one single-centre trial and none were on antiretroviral therapy. These estimates of effect may not be applicable to HIV-positive people in other settings or those taking antiretroviral therapy.

Potential biases in the review process

We attempted to limit bias in the review process. Vittoria Lutje, the Cochrane Infectious Diseases Group Information Specialist, conducted the literature searches, and it is unlikely that these searches missed any major trials; however, we cannot rule out the possibility that we missed some small unpublished trials. The funnel plot did not assist with this because there were too few included trials. To limit bias in the trial selection process and data extraction, we independently examined the search results, determined study selection, and extracted data.

Agreements and disagreements with other studies or reviews

There are relatively few studies and reviews on this topic in the literature. We could find no other systematic reviews that address this question. Chapman 2004, a narrative review of the diagnosis and management of pleural space infection, comments that the role of steroids is uncertain as study findings are conflicting, and do not provide information about the effect of steroids on long-term lung function and mortality. Another narrative review, Ferreiro 2014, drew similar conclusions, and noted that the conflicting results between studies and the possibility raised by Elliott 2004 that use of corticosteroids in HIV-positive patients with TB pleurisy may lead to increased risk of Kaposi's sarcoma. Kadhiravan 2010 commented on the previous version of this review (Engel 2007), and noted that while there appears to be an effect of corticosteroids on pleural thickening, the available evidence does not show an effect on lung function.

AUTHORS' CONCLUSIONS

Implications for practice

The included trials in this review do not provide substantive evidence on patient-important outcomes to guide recommendations on the use of corticosteroids in people with TB pleurisy. The efficacy of corticosteroids in reducing the time to resolution of pleural effusion or symptoms is uncertain, although the included trials that were at low risk of bias did demonstrate more rapid resolution of pleural effusion on chest X-ray in participants treated with corticosteroids. There may be a decreased risk of pleural changes such as pleural thickening and pleural adhesions on chest X-ray at the end of treatment with corticosteroids, but it is unclear how this relates to patient-important outcomes such as disability, lung function, and mortality. The concerns raised regarding adverse events in both HIV-negative and HIV-positive people with pleural TB need to be taken into account when deciding whether or not to use corticosteroids.

Current guidelines for TB treatment do not recommend the use of corticosteroids in pleural TB (INDEX-TB 2016; NICE 2016; WHO 2010).

Implications for research

The literature search performed for this update revealed no new trials that compared corticosteroids to placebo in people with pleural TB, and no trials are ongoing at the time of publication of this

Cochrane Review. We prepared a rapid update of this review as part of the development process of guidelines on extrapulmonary TB in India, the INDEX-TB Guidelines (INDEX-TB 2016). During discussions regarding the use of corticosteroids for pleural TB, the guideline panel noted that, as pleural TB is generally associated with low mortality, the priority outcome for consideration is lung function. The panel felt that the main outcomes in the available studies are at best proxy measures for lung function, and, given the evidence for adverse effects of corticosteroids, made a conditional recommendation against their use in pleural TB.

It is notable that the two trials included in this review that do report on lung function suggest that, while there was no qualitative difference between the two treatment groups, many people who have been successfully treated for pleural TB have poorer than expected lung function. There are still questions to be answered regarding lung function, disability, and mortality after pleural TB.

A systematic review of studies that investigated the prevalence of chronic lung disease in general populations concluded that pulmonary TB is strongly associated with chronic lung disease, including chronic obstructive pulmonary disease (COPD) and bronchiectasis (Byrne 2015). Two studies included in the review showed a stronger association between pulmonary TB and chronic lung disease in non-smokers than in smokers, which suggested that the relationship is not due to confounding risk factors alone. Indeed, the association between pulmonary TB and chronic lung disease has been recognized for many decades. More recently the interconnected causal relationships between TB, HIV, smoking, and chronic lung disease have been further elucidated, although many questions regarding pathophysiology remain unanswered (van Zyl Smit 2010). There is less evidence regarding the association between pleural TB and chronic lung disease or respiratory impairment. Candela 2003 reported on functional sequelae in terms of pulmonary function testing in a cohort of 81 Spanish adults with pleural TB with a median follow-up time of 23 months after diagnosis. Investigators found that 8/81 (10%) of the participants had a restrictive ventilatory deficit (one or both of FVC and TLC < 80% of predicted, with a FEV_1/FVC ratio > 80% of predicted) at the end of follow-up, which they describe as mild to moderate in all but two cases who were both smokers with a pre-existing diagnosis of COPD. They found no statistically significant association between residual pleural thickening on chest X-ray and functional sequelae at end of follow-up, although the sample was too small to rule out an association. They also found that the pleural fluid profile of participants that went on to have a restrictive ventilatory deficit demonstrated lower levels of lactate dehydrogenase and higher lymphocyte count, suggesting a difference in the inflammatory response in the pleural space. Their results provide context to the results of this review: if there is poor correlation between pleural thickening on chest X-ray and functional sequelae, we cannot conclude that if corticosteroids reduce pleural thickening they are likely to be of benefit in terms reducing rates of lung function impairment.

Given the uncertainties that exist, further research is warranted to explore the relevance of discriminating between people presenting with isolated pleural TB and pleuro-pulmonary TB, using different imaging modalities such as computed tomography and ultrasound. Cohort studies are needed in people who have pleural TB of either type to assess the incidence of functional sequelae, as measured using spirometry and also disability metrics validated for disability related to impaired lung function. The utility of further randomized controlled trials for corticosteroids in pleural TB would be informed by the results of such research.

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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	**Setting:** Inha University Hospital, South Korea **Date:** recruitment from June 1991 to September 1994 **Trial design:** prospective randomized study **Follow-up:** duration not clearly reported, 8 to 9 months. Chest X-rays were performed weekly while participants were hospitalized, then monthly after discharge. Participants were asked to complete a questionnaire detailing their symptoms every day until resolution of all symptoms
Participants	**Number of participants:** 84 adults (83 included in analysis, 1 participant was excluded because they experienced increased epigastric pain after commencing steroids and so study drug was stopped); 49 male (59%), 34 female (41%) **Age:** mean 34 years, range 18 to 50 years **Inclusion criteria:** patients who were admitted to the hospital and diagnosed with tuberculous pleurisy. All participants had pleural biopsy and diagnostic pleurocentesis performed on the 1st or 2nd day of admission. Diagnosis of tuberculosis (TB) pleurisy was based upon the following: histological findings corresponding to TB on pleural biopsy, acid-fast bacilli (AFB) positive on smear microscopy or culture positive from sputum, pleural fluid, or pleural biopsy **Exclusion criteria** • People with pleural effusion caused by congestive heart failure, pneumonia, or malignancy • People with diabetes, hypertension, and peptic ulcer disease who could not be treated with corticosteroids **HIV status:** all participants were HIV-negative. The trial took place during a period when HIV infection was very uncommon in South Korea
Interventions	**Intervention:** ATT plus prednisolone 1 mg/kg twice daily, tapered by 10 mg each week until complete cessation **Control:** ATT alone ATT: isoniazid (400 mg/day), rifampicin (600 mg/day; 450 mg if weight 50 kg or less), pyrazinamide (1500 mg/day), ethambutol (800 mg/day) for 2 months followed by same regimen minus pyrazinamide for 7 months
Outcomes	• Mean duration to relief from symptoms, as assessed by a self-reporting questionnaire asking about presence or absence of sensation of fever, chest pain, cough, sputum production, shortness of breath, night sweats, weight loss, and fatigue • Rate of reabsorption of pleural fluid • Pleural adhesions and thickening
Notes	

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**

Bang 1997 (*Continued*)

Random sequence generation (selection bias)	High risk	The trial authors did not state the method of randomization, and the number of participants in each group appears imbalanced (steroid group N = 34, control group N = 50) "Patients deemed eligible for this study were randomized to the steroid group and the non-steroid group."
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report this information.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial authors did not report this information.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial authors did not report this information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported.
Selective reporting (reporting bias)	Low risk	The trial protocol was unavailable, but the trial authors reported all outcomes specified in the introduction in the results
Other bias	Low risk	We did not identify any other sources of bias.

Elliott 2004

Methods	**Setting:** National TB Treatment centre, Mulago Hospital, Kampala, Uganda **Date:** recruitment from November 1998 to January 2002 **Trial design:** randomized, doubled-blind, placebo-controlled trial **Follow-up:** all participants were followed up until July 2002; median follow-up time was 1.48 years in the steroid group, and 1.65 years in the placebo group. Participants were managed in hospital or as daily ward attenders for the first week of treatment, and after that were discharged home and visited regularly to monitor treatment for 8 weeks. Participants then attended clinic monthly until the end of ATT, and then 3-monthly after ATT completion
Participants	**Number of participants (% female):** 197, 83 (42%) female. 98 received placebo and 99 received prednisolone. Three participants were lost to follow-up and excluded from the analysis (1 from placebo group, 2 from prednisolone group) **Age:** mean 34 years **Inclusion criteria:** participants were eligible for screening if they were > 18 years old with clinical features consistent with pleural TB and a pleural effusion occupying at least 1/3 of 1 hemithorax on chest X-ray. Screening procedures consisted of medical examination;

Elliott 2004 (*Continued*)

	blood samples including glucose, HIV, and cryptococcal antigen tests; urine sample for dipstick; diagnostic pleural aspiration, and pleural biopsy if possible. Pleural TB was considered to be confirmed if a patient had a positive culture for *M. tuberculosis* from pleural biopsy, pleural fluid, or sputum or if histopathological analysis of pleural tissue was consistent with tuberculous pleurisy **Exclusion criteria:** people recently treated with glucocorticoids, pregnant, or breast-feeding women, and people not resident in Kampala were excluded from screening. The trial excluded people after screening if they failed to completed the screening procedures, pleural fluid could not be obtained, they had empyema, they had a second major HIV-related disease, they had risk factors for serious steroid-related adverse events (history of diabetes or finding of glycosuria, history or finding of hypertension, history of peptic ulcer disease, or mental illness), they could not receive standard doses of antituberculous treatment (ATT) (for example, concurrent liver disease), they were HIV-negative **HIV status:** the trial excluded HIV-negative people
Interventions	**Intervention:** ATT plus prednisolone 50 mg daily for 2 weeks, then 40 mg daily for 2 weeks, then 25 mg daily for 2 weeks, then 15 mg daily for 2 weeks, then stopped **Control:** ATT plus placebo. ATT: daily rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months, followed by daily rifampicin and isoniazid for 4 months; doses adjusted for weight using standard criteria
Outcomes	• All-cause mortality • Time to resolution of anorexia, cough, and pleural effusion • Weight • CD4 count and viral load • Adverse events related to steroid use • Adverse events related to HIV
Notes	The trial authors did not mention antiretroviral therapy in this trial. We contacted the trial authors to check whether any of the participants were given antiretroviral therapy, and they reported that to the best of their knowledge none of the participants were taking antiretroviral therapy at any time during the trial

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was generated by a statistician who was not involved in the care of the patients, by use of STATA (version 5; Stata Corporation). Randomization was done in blocks of 20."
Allocation concealment (selection bias)	Low risk	"Prednisolone and matching placebo tablets were packaged in identical plastic bags, which were labeled with randomization code numbers by two people who were not involved in the study. Medical staff gave participants the next number

Elliott 2004 (*Continued*)

		in the sequence in the order in which they were enrolled."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All participants and medical, laboratory, and statistical staff remained blinded to the treatment allocation until all data collection had been completed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All participants and medical, laboratory, and statistical staff remained blinded to the treatment allocation until all data collection had been completed."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Nine participants were lost to follow-up, 6/98 in the steroid group and 3/99 in the placebo group, representing 5% of the total participants
Selective reporting (reporting bias)	High risk	The study protocol was not available. The primary outcome was all-cause mortality and this is clearly stated, but the other outcomes are not specified in the introduction or methods section "The use of prednisolone was associated with more-rapid improvement in all of the principal symptoms and signs of pleural tuberculosis. This effect was statistically significant, particularly during the first few weeks of treatment, for anorexia, weight loss, and cough (figure 3A-C)." Only data related to the statistically significant outcomes for symptomatic improvement are reported
Other bias	Low risk	We did not identify any other potential sources of bias.

Galarza 1995

Methods	**Location:** Hospital Universitari de Bellvitge, Barcelona, Spain **Date:** January 1985 and December 1992 **Trial design:** prospective, randomized, double blind, placebo controlled study **Follow-up:** 6 months
Participants	**Number of participants (% female):** 117, 58 (48%) female. 60 received placebo, 57 received prednisone. No losses to follow-up reported **Age:** 11 to 53 years **Inclusion criteria:** diagnosis of tuberculous pleurisy was made if patients met at least one of the following criteria

Galarza 1995 (*Continued*)

	• Pleural exudate with positive culture for *M. tuberculosis* • Pleural biopsy culture positive for *M. tuberculosis* • Caseating granulomas with Langhans giant cells, epithelioid cells, and lymphocytes • Compatible clinico-radiological picture plus 2 or more of the following: Mantoux test reaction of >6 mm or conversion using 5 units of tuberculin PPD-S, lymphocytic pleural fluid (> 70% lymphocytes), pleural fluid levels of adenosine deaminase activity (ADA) > 60 U/mL (reported in Cañete 1994) **Diagnostic algorithm:** thoracocentesis with analysis of pleural biopsy and pleural fluid **Exclusion criteria:** diagnostic investigations not consistent with the inclusion criteria, HIV seropositive **HIV status:** the trial excluded HIV-positive people
Interventions	**Intervention:** prednisone plus standard regimen **Control:** placebo plus standard regimen Prednisone: single oral dose of 1 mg/kg/day for 15 days tapering off over the next 15 days 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
Outcomes	• Time to resolution of fever • Lung function assessed by forced vital capacity (FVC) at end of treatment • Pleural thickening at baseline and at 1, 6, and 12 months after start of treatment • Rate of reabsorption of pleural fluid on chest x-ray at baseline and at 1, 6, and 12 months after start of treatment • Adverse effects
Notes	A definite microbiological or pathological diagnosis was confirmed in 63% of participants Before discharge, pleural fluid was drained until 1/3 of hemithorax was occupied on standard chest X-ray in all participants

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe the method of randomization
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomly assigned to receive, in a double blind fashion, either prednisolone or placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial authors did not mention the blinding of outcome assessors

Galarza 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial authors did not report any losses to follow-up; there were no unexplained defaulters
Selective reporting (reporting bias)	Low risk	No protocol available, but the trial authors reported on the 2 main outcomes specified in the introduction
Other bias	Low risk	We did not identify any other source of bias.

Lee 1988

Methods	**Location:** Chang Gung Memorial Hospital, Taipei, Taiwan **Date:** October 1983 with recruitment until June 1987 **Trial design:** double-blind, placebo-controlled, randomized study **Follow-up:** up to 24 months
Participants	**Number of participants (% female):** 45 recruited to study, 16/40 (40%) female. 40 participants included in analysis, 21 in steroid group, 19 in placebo group. Five participants were excluded from the analysis, 1 due to a diagnosis of renal cell carcinoma and 4 were lost to follow-up. The trial authors did not report which group the excluded participants were randomized to **Age:** mean age 28.7 years, range 18 to 45 years **Inclusion criteria:** under 45 years, new pleural effusion not previously treated, with pleural biopsy reported at TB or chronic granulomatous inflammation **Exclusion criteria:** history of pulmonary TB, diagnosis of alternative cause of pleural effusion such as heart failure, malignancy, pneumonia, history of other pulmonary disease or condition that contraindicated the use of steroids such as diabetes, peptic ulcer, hypertension **HIV status:** not reported
Interventions	**Intervention:** prednisolone plus standard regimen **Control:** 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 by 5 mg per week until discontinued 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	• Time to resolution of clinical symptoms • Rate of reabsorption of pleural fluid on chest x-ray • Pleural adhesions • Adverse effects
Notes	Diagnostic thoracocentesis (< 50 mL) performed on the first day for all participants; no participants reported as having therapeutic thoracocentesis Criteria for tapering prednisolone dose as follows

Lee 1988 (*Continued*)

	• Right-sided effusion with fluid level only one intercostal space higher than the left hemidiaphragm • Left-sided effusion with fluid level at the same height as the right hemidiaphragm • Complete resolution of the effusion

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Those who were eligible for the study were randomly assigned to treatment with either prednisolone plus antituberculosis drugs (steroid group) or placebo with antituberculosis drugs (placebo group."
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial authors described this as "double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial authors did not mention whether blinding of outcome assessors took place or not
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial excluded 5 participants excluded from the final analysis; 1 due to diagnosis of renal cell carcinoma and 4 due to loss to follow-up with no further information given. Therefore the trial authors included 89% of recruited participants in the final analysis. The trial authors did not report which groups the five excluded participants were randomized to
Selective reporting (reporting bias)	Low risk	There was no protocol available, but the trial authors reported all outcomes that they clearly stated in the methods
Other bias	Low risk	We did not identify any other sources of bias.

Lee 1999

Methods	**Setting:** Chung-Ang University Hospital, South Korea **Date:** February 1990 to February 1997 **Trial design:** prospective randomized study **Follow-up:** participants were followed up at 2 months and 6 months, and in a final visit to the out-patient department after treatment. Median follow-up was 9 months in the steroid group and 12 months in the control group
Participants	**Number of participants:** 82, 29 (35%) female; 32 participants in the steroid group and 50 in the control group. No losses to follow-up reported **Age:** mean 32 years, range 17 to 51 years **Inclusion criteria:** people admitted to hospital with a diagnosis of TB pleurisy based on TB on pleural biopsy, or pleural effusion with AFB stain positive on microscopy of sputum, pleural fluid, or pleural biopsy, or *M. tuberculosis* culture positive on sputum, pleural fluid, or pleural biopsy. Pleural biopsy and diagnostic pleurocentesis were performed on all patients on the 1st or 2nd day of admission **Exclusion criteria:** people with pleural effusion due to other causes (not specified by the trial authors). People with diabetes, hypertension, or peptic ulcer disease who could not receive corticosteroids. People who were "not cooperative" **HIV status:** not mentioned.
Interventions	**Intervention:** ATT plus prednisolone 30 mg once daily for 1 month and then tapered over the following month. **Control:** ATT alone. ATT regimen: isoniazid, rifampicin, pyrazinamide, and 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
Outcomes	• Time to resolution of pleural effusion • Development of pleural adhesions, defined as lack of resolution of pleural effusion on chest x-ray up to final visit
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The trial did not state the method of randomization, and the number of participants in each group appears imbalanced (steroid group N = 50, control group N = 32). "… patients were randomized to the steroid group and the non-steroid group"
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report on the method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial authors did not report on blinding of participants and personnel

Lee 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial did not report on blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	The trial protocol was unavailable, but the trial authors reported all outcomes specified in the introduction in the results
Other bias	Low risk	We did not identify any other sources of bias.

Wyser 1996

Methods	**Setting:** Tygerberg Hospital, Cape Town, South Africa **Date:** April 1994 with recruitment until January 1995 **Trial design:** double-blind, placebo-controlled, randomized study **Follow-up:** 6 months
Participants	**Number of participants (% female):** 74 participants randomized, 70 included in analysis, 36 in placebo group, 34 in prednisone group, 27/70 (36.5%) female. The trial authors excluded 4 participants from analysis, 3 due to non-compliance with treatment, 1 due to diagnosis of oesophageal cancer at follow-up. The trial authors did not report to which group the excluded participants were randomized to **Age:** mean age 33 years **Inclusion criteria:** pleural biopsy specimen proving TB pleurisy, based on presence of caseating granulomata with or without AFB on histological examination, or a positive culture for *M. tuberculosis*. **Diagnostic algorithm:** thoracoscopy followed by bronchoscopy under general anaesthesia, with biopsies of the parietal pleura taken for histological examination and culture **Exclusion criteria:** people with other causes of exudative effusion such as pneumonia or cancer. People with contraindications to corticosteroids such as diabetes mellitus, uncontrolled hypertension, peptic ulcer disease, and empyema. People with HIV **HIV status:** the trial authors excluded HIV-positive people.
Interventions	• Prednisone plus standard regimen • 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	• 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

Wyser 1996 (*Continued*)

	• Lung function at end of treatment as assessed by total lung capacity (TLC) and FVC • Recurrence of effusion • Residual pleural thickening at 24 weeks • Adverse effects
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"All eligible patients were randomly assigned in a double-blind fashion to treatment with either prednisone plus standard anti-TB therapy (prednisone group) or placebo plus standard anti-TB therapy (placebo group)."
Allocation concealment (selection bias)	Unclear risk	The trial described the placebo tablets as "identical". The trial authors did not clearly describe the method of concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial authors described the trial as "double blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessors were "blinded to the clinical history"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial authors excluded four participants from the analysis; 3 due to "non-compliance with the treatment"
Selective reporting (reporting bias)	Low risk	The protocol was unavailable, but the trial authors reported the outcomes described in the introduction
Other bias	Low risk	We did not identify any other source of bias.

Abbreviations: AFB: acid-fast bacilli; ATT: antituberculous treatment; FVC: forced vital capacity; HIV: human immunodeficiency virus; TB: tuberculosis.

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

Study	Reason for exclusion
Aspin 1958	No randomization
Bilaceroglu 1999	Participants did not have pleurisy - cases of pulmonary tuberculosis (TB)
Cherednikova 1973	Case series
Cisneros 1996	Review
Damany 1968	Numbers of participants in each trial arm not clearly stated
Filler 1963	No randomization
Fleishman 1960	Diagnosis of TB not confirmed
Grewal 1969	No randomization
Khomenko 1990	Participants did not have pleurisy - cases of pulmonary TB
Manresa 1997	Letter referring to included trial (Galarza 1995)
Mansour 2006	No randomization
Mathur 1960	No randomization
Mathur 1965	No randomization
Mayanja-Kizza 2005	Participants did not have pleurisy - cases of pulmonary TB
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 TB
Singh 1965	No randomization
Starostenko 1989	No randomization
Tani 1964	No randomization
Tanzj 1965	No randomization

Abbreviations: TB: tuberculosis.

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

ChiCTR-TRC-10000747

Trial name or title	A multi-center, randomized, double-blind, parallel placebo trial to evaluate the clinical efficacy of glucocorticosteroid for tuberculous pleurisy
Methods	Interventional randomized parallel control trial
Participants	Inclusion criteria • Male or female, aged between 18 to 65 years • Presented with typical clinical features and signs suggesting pleurisy • Willing to join the study and signs informed consent form • Consistent with the diagnosis criteria in patients with tuberculous pleurisy Exclusion criteria • Severe cardiac diseases,lung diseases, hematological diseases, malignant tumor, hypoimmunity diseases, mental diseases, diabetes • Digestive system diseases, such as peptic ulcer or alimentary tract haemorrhage • Abnormal of blood-fasting sugar or postprandial blood sugar (2 hours) • Chronic liver diseases,such as viral hepatitis type B or C • Chronic hepatic or renal inadequacy (ALT>1.5 upper limits of normal; Cr > upper limits of normal) • Alcohol or drug abuse • Package chest or pachynsis pleurae • Course of disease > 14 days • Antituberculous therapy > 30 days • Woman either pregnant or lactating • Have accepted glucocorticosteroid • Participate in other clinical trials within 3 weeks • Contraindication to glucocorticosteroid Target sample size: Group A: 500; Group B: 500; Total: 1000
Interventions	Group A: prednisone orally taken 30 mg once daily for 2 weeks, then reduce to 20 mg once daily for 3rd week; finally reduce to 10 mg for 4th week; Group B: placebo orally taken 30 mg once daily for 2 weeks, then reduce to 20 mg once daily for 3rd week; finally reduce to 10 mg for 4th week
Outcomes	Primary outcome • Rate of pleura thickening Secondary outcome • Time of pleural thickening; • Time of pleural effusion absorption
Starting date	Date of first enrolment: 1 January 2010 Last refreshed: 29 June 2014
Contact information	Huangzhong Shi, Department of Respiratory of Wuhan Union Hospital, No. 1277 Liberation Avenue, Wuhan 430022. Tel: +86 027 85726010. Email: xinjbwh@163.com JIianbo Xin, Department of Respiratory of Wuhan Union Hospital, No. 1277 Liberation Avenue, Wuhan 430022. Tel: +86 027 85726757. Email: xinjbwh@163.com

ChiCTR-TRC-10000747 (*Continued*)

Notes	Sponsors: Wuhan Union Hospital; National Science Fund for Distinguished Young Scholars, National Natural Science Foundation of China Trial is identical to ChiCTR-TRC-09000747 (www.chictr.org.cn/showproj.aspx?proj=8789) We contacted the trial authors for further information but did not receive a response to date

NCT00338793

Trial name or title	A Multicenter, Placebo-Controlled, Double-Blind, Randomized Clinical Trial to Evaluate the Efficacy and Safety of Corticosteroids for Treatment of Patients With Tuberculous Pleurisy
Methods	Interventional double-blinded randomized parallel safety/efficacy study
Participants	Inclusion criteria • Male or female, over 18 years of age • Signed written informed consent • Presented with clinical features suggesting pleural tuberculosis • Had not previously received treatment or prophylaxis for tuberculosis • Had not recently received treatment with glucocorticoids • Were not pregnant or breast-feeding Exclusion criteria • Failed to complete the screening procedures • Were seropositive for HIV • Tuberculous meningitis • Had risk factors for serious steroid-related adverse events (a history of diabetes or positive urine glucose, a history or clinical finding of hypertension, or a history of peptic ulcer disease or mental illness) • Standard doses of antituberculosis drugs could not be used (as in participants with concurrent liver disease) • Psychiatric illness • Alcoholism Target sample size: 1500
Interventions	Prednisolone versus placebo
Outcomes	Primary outcomes • Adverse drug effects • Death • Presence of pleural thickening • Pulmonary function at completion of treatment Secondary outcomes • Failure rate at the end of treatment • Improvement in clinical symptoms and signs (such as pleuritic chest pain, temperature) • Reabsorption of pleural effusion
Starting date	Date of registration: 19 June 2006 Date of first enrollment: July 2006

NCT00338793 (*Continued*)

Contact information	Xin Zhou, MD, Department of Respiratory Diseases, First Affiliated Hospital, Shanghai Jiaotong University, Shanghai, China Zhan-Cheng Gao, MD, PhD, Department of Respiratory Diseases, People's Hospital, Peking University, Beijing, China Huan-Zhong Shi, MD, PhD, Institute of Respiratory Diseases, First Affiliated Hospital, Guangxi Medical University, Nanning 530021, Guangxi, China
Notes	Sponsors: Guangxi Medical University; Bureau of Science and Technology of Guangxi Province, China; Ministry of Education, China; National Natural Science Foundation of China Recruitment completed. We contacted the trial authors but have not received a reply to date

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 Residual pleural effusion on chest X-ray	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 At 4 weeks	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.84]
1.2 At 8 weeks	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.37, 0.78]
1.3 At 24 weeks	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.18, 0.66]
2 Pleural changes at the end of treatment (pleural thickening and pleural adhesions)	5	393	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.92]
3 Death from any cause	1	197	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.64, 1.31]
4 Adverse events leading to study drug discontinuation	6	590	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [1.11, 6.94]
5 HIV-associated adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Cryptococcal meningitis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Oesophageal candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Oral candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Gastroenteritis	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.5 Herpes simplex	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.6 Herpes zoster	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.7 Kaposi sarcoma	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Effect of study quality on the outcome residual pleural fluid on chest X-ray

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Residual pleural fluid on chest X-ray - studies at high risk of selection bias excluded	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 At 4 weeks	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.84]
1.2 At 8 weeks	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.37, 0.78]
1.3 At 24 weeks	2	237	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.18, 0.66]
2 Residual pleural fluid on chest X-ray - studies at high risk of selection bias included	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 At 4 weeks	3	321	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.52, 1.07]
2.2 At 8 weeks	4	403	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.47, 1.12]
2.3 At 24 weeks	4	403	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.30, 0.98]

ADDITIONAL TABLES

Table 1. Theoretical framework describing differences between isolated tuberculous pleurisy and pulmonary TB with tuberculous pleurisy (pleuro-pulmonary TB)

Clinical Feature	Isolated pleural TB	Pleuro-pulmonary TB
Sputum microscopy/culture	Negative	Some positive
Pleural fluid	Usually demonstrates exudative effusion Usually negative for *M. tuberculosis* on smear and culture	Usually demonstrates exudative effusion Usually negative for *M. tuberculosis* on smear and culture
Chest X-ray	Discrete pleural effusion, or pleural thickening, or both	Pleural effusion with other changes such as consolidation, cavities, atelectasis, or hilar enlargement
Chest computed tomography (CT)	May demonstrate underlying lung infection	Demonstrates underlying lung infection
Pathogenesis	Predominantly driven by delayed type hypersensitivity reaction	Predominantly driven by TB infection of the lung
Prognosis	Most people will improve with no antituberculous treatment (ATT), but may experience a relapse of TB infection	People may deteriorate and die without ATT

Table 2. Summary of characteristics of included studies

Trial	Country	Year	Participants		Adults or children	HIV status	ATT regimen	Therapeutic thoracocentesis performed
			Steroid group	Control group				
Bang 1997	South Korea	1991 to 1994	34	50	Adults	Not reported	2RHZE/7RHE	No
Elliott 2004	Uganda	1998 to 2002	99	98	Adults	Positive	2RHZE/4RH	No
Galarza 1995	Spain	1985 to 1992	57	60	Both	Negative	6RH	Yes
Lee 1988	Taiwan	1983 to 1987	21	19	Adults	Not reported	3RHE/6-9RH	No
Lee 1999	South Korea	1990 to 1997	50	32	Adults	Not reported	6RHZE or 2RHZS/4RHZ	No

Table 2. Summary of characteristics of included studies (*Continued*)

Wyser 1996	South Africa	1994 to 1995	34	36	Adults	Negative	6RHZ	Yes

Abbreviations: ATT: antituberculous treatment; E: ethambutol; H: isoniazid; R: rifampicin; S: streptomycin; Z: pyrazinamide.

Table 3. Diagnostic testing in included trials

Trial	Diagnostic criteria for pleural TB	Other diagnostic tests
Bang 1997	Microscopy positive for AFB or culture positive from sputum, pleural fluid, or pleural biopsy	• Chest X-ray
Elliott 2004	Positive culture from pleural biopsy, pleural fluid, or sputum, or histopathologic analysis of pleural biopsy consistent with tuberculous pleurisy	• Chest X-ray • HIV test (rapid test and ELISA) • Serum cryptococcal antigen test • $CD4^+$ cell count • HIV viral load (plasma and pleural fluid) • Serum glucose
Galarza 1995	At least one of the following • Pleural exudate with positive culture • Pleural biopsy culture positive • Pleural biopsy with caseating granulomas with Langhans giant cells, • Epithelioid cells and lymphocytes • Compatible clinico-radiological picture plus 2 or more of the following: ○ age < 40 years, PPD > 6 mm or conversion using 5 units of tuberculin PPD-S, lymphocytic pleural fluid (> 70% lymphocytes), pleural fluid levels of adenosine deaminase activity (ADA) > 60 U/mL	• Chest X-ray • Simple spirometry (FVC and FEV_1) • Serum biochemistry • Full blood count • HIV test
Lee 1988	Pleural biopsy reported as pleural TB or chronic granulomatous inflammation	• Chest X-ray • Unspecified diagnostic tests to exclude heart failure, malignancy, pneumonia, diabetes mellitus • Chest ultrasound or CT scan in participants with persisting pleural effusion after 3 months
Lee 1999	TB on pleural biopsy, or pleural effusion *plus* AFB stain positive or culture positive from sputum, pleural fluid, or pleural biopsy	• Chest X-ray
Wyser 1996	Pleural biopsy with caseating granulomata with or without AFB on histological examination, or positive culture	• Chest X-ray • Unspecified tests to rule out pneumonia, empyema, malignancy, diabetes mellitus • HIV test • Thoracoscopy and bronchoscopy performed under

Table 3. Diagnostic testing in included trials (*Continued*)

		general anaesthesia • High-resolution CT chest at three levels to measure pleural thickness • Spirometry and body plethysmography

Abbreviations: ADA: adenosine deaminase activity; AFB: acid-fast bacilli; CT: computed tomography; ELISA: enzyme-linked immunosorbent assay; FEV_1: forced expiratory volume at one second; FVC: forced vital capacity; HIV: human immunodeficiency virus; PPD: purified protein derivative; PPD-S: purified protein derivative-standard; TB: tuberculosis

Table 4. Corticosteroid regimens in included studies

Trial	Steroid	Regimen
Bang 1997	Prednisolone	1 mg/kg twice daily, tapered by 10 mg each week until cessation
Elliott 2004	Prednisolone	50 mg daily for 2 weeks, 40 mg daily for 2 weeks, then 25 mg daily for 2 weeks, then 15 mg daily for 2 weeks, then stopped
Galarza 1995	Prednisone	1 mg/kg/day for 15 days, tapering over the next 15 days
Lee 1988	Prednisolone	0.75 mg/kg/day, tapered by 5 mg per week until discontinued once radiological improvement was seen
Lee 1999	Prednisolone	30 mg four times daily for 1 month and tapered over the following month
Wyser 1996	Prednisone	0.75 mg/kg/day for 2 to 4 weeks; dose tapered by 5 mg/day over 2 weeks after clinical and radiological improvement

Abbreviations: mg: milligrams

Table 5. Results: Time to resolution of symptoms

	Trial	Indicator	Units	Corticosteroids	Control
Mean values	Bang 1997	"Fever, pleuritic pain, malaise and breathlessness"	Mean days to resolution	3.8 (N = 34)	7.4[1] (N = 50)
	Galarza 1995	"Fever duration"	Mean days	3.32 (N = 57)	4.15 (N = 60)
	Lee 1988	"Fever, pleuritic pain, malaise and breathlessness"	Mean days to resolution	2.4 (N = 21)	5.6 (N = 19)

Table 5. Results: Time to resolution of symptoms (*Continued*)

Cut-offs (categorical)	Elliott 2004	"Anorexia"	Number of participants with anorexia at 4 weeks	3/99 (3%)	18/98 (18.4%)
		"Cough"	Number of participants with cough at 4 weeks	35/99 (35.4%)	57/98 (58.2%)
		"Weight"	Mean weight in kg at 4 weeks	57	52.5
	Wyser 1996	Symptoms resolved in all patients (VAS score)	Weeks	12	16

Abbreviations: kg: kilograms; VAS: visual analogue scale
[1]P < 0.05.

Table 6. Time to resolution of pleural effusion on chest X-ray

	Trial	Units	Corticosteroids	Control
Mean values	Bang 1997	Mean days to resolution	88 (N=34)	100 (N=50)
	Lee 1988	Mean days to resolution	54.5 (N=21)	123.2 (N=19)
	Galarza 1995	Reabsorption index[1] at 4 weeks	93%	89%[2]
Categorical values	Bang 1997	Number of participants with residual effusion at 4 weeks	26/34 (76.5%)	39/50 (78%)
		Number of participants with residual effusion at 8 weeks	19/34 (55.9%)	30/50 (60%)
		Number of participants with residual effusion at 24 weeks	2/34 (5.9%)	3/50 (6%)
	Elliott 2004	Number of participants with residual effusion at 4 weeks	38/99 (38.4%)	56/98 (57.1%)
		Number of participants with residual effusion at 8 weeks	25/99 (30.3%)	42/98 (56.1%)
		Number of participants with residual effusion at 24 weeks	10/99 (10.1%)	25/98 (25.5%)[3]
	Lee 1988	Number of participants with residual effusion at 4 weeks	9/21 (42.9%)	15/19 (78.9%)

Table 6. Time to resolution of pleural effusion on chest X-ray (*Continued*)

		Number of participants with residual effusion at 8 weeks	5/21 (23.8%)	12/19 (63.2%)
		Number of participants with residual effusion at 24 weeks	1/21 (4.8%)	6/19 (31.6%)
	Lee 1999	Number of participants with residual effusion at 8 weeks	29/32 (90.6%)	49/50 (98%)
		Number of participants with residual effusion at 24 weeks	20/32 (62.5%)	44/50 (88%)

Abbreviations: N: number of participants
[1]Reabsorption index = (length of affected hemithorax/length of healthy hemithorax) x 100.
[2]P = 0.01.
[3]Data at this time point extrapolated from graph. Data for 4 weeks and 8 weeks from the trial authors (unpublished data).

Table 7. Pulmonary function at the end of treatment

Trial	Indicator	Units	Corticosteroids	Control
Galarza 1995	Percentage predicted FVC	Mean percentage predicted FVC	95% (N = 57)	95% (N = 60)[1]
Wyser 1996	Percentage predicted FVC	Mean percentage predicted FVC	85% (N = 34)	80% (N = 36)[2]
	Lung function impairment	Number of participants with restrictive PFT results	11/34 (33.3%)	14/36 (39.4%)[3]

Abbreviations: FVC: forced vital capacity; N: number of participants; PFT: pulmonary function tests
[1]Range 65% to 130% in steroid group, 63% to 140% in placebo group.
[2]Read from graph, P = 0.65.
[3]P = 0.72. Results extrapolated from percentages.

Table 8. Adverse events leading to discontinuation of the trial drug

Trial	Corticosteroid	Control
Bang 1997	1/34 (2.9%)[1]	0/50
Elliott 2004	9/99 (9.1%)[2]	2/98 (2.0%)
Galarza 1995	0/57	NR
Lee 1988	1/21 (4.8%)[3]	NR

Table 8. Adverse events leading to discontinuation of the trial drug (*Continued*)

Lee 1999	NR	NR
Wyser 1996	4/34 (11.8%)	3/36 (8.3%)[4]

Abbreviations: NR: not reported
[1]Aggravation of epigastric pain in one patient, steroids stopped, and patient withdrawn from the trial.
[2]Trial drug discontinued for hyperglycaemia (two participants), hypertension (three participants), herpes zoster (three participants), oesophageal candidiasis (one participant) in the corticosteroid group; in the placebo group hyperglycaemia (one participant) and hypertension (one participant).
[3]One participant developed moon facies, epigastric pain, and lower limb oedema, all of which resolved on tapering the dosage.
[4]Epigastric pain was the only adverse effect noted, and affected four participants in the steroid group and three in the control group.

Table 9. Results: HIV-related adverse events

Trial	Indicator	Control (N/98)	Corticosteroid (N/99)
Elliott 2004	Kaposi's sarcoma	0	6 (6.1%)
	Cryptococcal meningitis	5 (5.1%)	3 (3.0%)
	Oesophageal candidiasis	23 (23.5%)	35 (35.4%)
	Oral candidiasis	31 (32.6%)	31 (31.3%)
	Herpes zoster	19 (19.4%)	22 (22.2%)
	Oral or genital herpes simplex	20 (20.4%)	22 (22.2%)
	Gastroenteritis	28 (28.6%)	34 (34.3%)

Abbreviations: N: number of participants

WHAT'S NEW

Last assessed as up-to-date: 18 November 2016.

Date	Event	Description
20 February 2017	New search has been performed	Complete new edition, with a new protocol, fresh data extraction, GRADE assessment of the certainty of evidence, and a new review author team

(*Continued*)

20 February 2017	New citation required but conclusions have not changed	We updated the review updated with a new review author team. We performed a new literature search; we did not include any new trials. We revised the Background section. Also, we amended the objective and selection criteria. The review authors performed data extraction and 'Risk of bias' assessments. We included a 'Summary of findings' table and performed GRADE assessments. Also we revised the Results and Discussion sections.

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 3, 1998

Date	Event	Description
10 September 2008	Amended	Converted to new review format with minor editing.
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 antituberculos 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

HR and PD refreshed the protocol and performed the selection of studies. HR, PD, and YJ extracted data and performed 'Risk of bias' assessments for the included trials. HR revised the Background, Methods, Results, and Discussion sections, with input from PD and YJ.

DECLARATIONS OF INTEREST

HR was employed by the Cochrane Infectious Diseases Group, which is funded by a grant from the UK Government DFID.

PD is employed by the National Institute for Research in Tuberculosis, Chennai, a permanent institute under the Indian Council of Medical Research, which is funded by the Government of India through the Ministry of Health and Family Welfare.

HR and PD conducted the preliminary work that contributed to the conception and design of this Cochrane Review as part of the evidence review process for the Indian Extra-Pulmonary TB (INDEX-TB) Guidelines, a guideline for extrapulmonary TB commissioned by the Ministry of Health and Family Welfare, Government of India. Global Health Advocates funded this guideline, and the All India Institute of Medical Sciences, New Delhi convened it.

SOURCES OF SUPPORT

Internal sources

- South African Medical Research Council, South Africa.
- University of Cape Town, South Africa.
- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated this review with the aim of adding any new evidence that may have been published since the previous search in 2007. For this version, we revised the protocol, and in particular altered the outcomes of interest. This was informed by discussions with expert clinicians which took place during the development of a new guideline on extrapulmonary TB in India, the INDEX-TB guidelines (INDEX-TB 2016).

NOTES

There is a discrepancy between the number of participants across all the trials in this update and the previous version (Engel 2007). This is because the data extraction was done again using a different data extraction tool.

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