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[Intervention Review]

Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection

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ABSTRACT

Background

Pneumocystis jiroveci pneumonia (PCP) remains the most common opportunistic infection in patients infected with the human immunodeficiency virus (HIV). Among patients with HIV infection and PCP the mortality rate is 10% to 20% during the initial infection and this increases substantially with the need for mechanical ventilation. It has been suggested that corticosteroids adjunctive to standard treatment for PCP could prevent the need for mechanical ventilation and decrease mortality in these patients.

Objectives

To assess the effects of adjunctive corticosteroids on overall mortality and the need for mechanical ventilation in HIV-infected patients with PCP and substantial hypoxaemia (arterial oxygen partial pressure < 70 mmHg or alveolar-arterial gradient > 35 mmHg on room air).

Search methods

For the original review we searched *The Cochrane Library* (2004, Issue 4), MEDLINE (January 1980 to December 2004) and EMBASE (January 1985 to December 2004) without language restrictions. We further reviewed the reference lists from previously published overviews, searched UptoDate version 2005 and Clinical Evidence Concise (Issue 12, 2004), contacted experts in the field and searched the reference lists of identified publications for citations of additional relevant articles.

In this update of our review, we searched the above-mentioned databases in September 2010 and April 2014 for trials published since our original review. We also searched for ongoing trials in ClinicalTrials.gov and the World Health Organization International Clinical Trial Registry Platform (ICTRP). We searched for conference abstracts via AEGIS.

Selection criteria

Randomised controlled trials that compared corticosteroids to placebo or usual care in HIV-infected patients with PCP in addition to baseline treatment with trimethoprim-sulfamethoxazole, pentamidine or dapsone-trimethoprim, and reported mortality data. We excluded trials in patients with no or mild hypoxaemia (arterial oxygen partial pressure > 70 mmHg or an alveolar-arterial gradient < 35 mmHg on room air) and trials with a follow-up of less than 30 days.

Data collection and analysis

Two teams of review authors independently evaluated the methodology and extracted data from each primary study. We pooled treatment effects across studies and calculated a weighted average risk ratio of overall mortality in the treatment and control groups using a random-effects model.

In this update of our review, we used the GRADE methodology to assess evidence quality.

Main results

Of 2029 screened records, we included seven studies in the review and six in the meta-analysis. Risk of bias varied: the randomisation and allocation process was often not clearly described, five of seven studies were double-blind and there was almost no missing data. The quality of the evidence for mortality was high. Risk ratios for overall mortality for adjunctive corticosteroids were 0.56 (95% confidence interval (CI) 0.32 to 0.98) at one month and 0.59 (95% CI 0.41 to 0.85) at three to four months of follow-up. In adults, to prevent one death, numbers needed to treat are nine patients in a setting without highly active antiretroviral therapy (HAART) available, and 23 patients with HAART available. The three largest trials provided moderate quality data on the need for mechanical ventilation, with a risk ratio of 0.38 (95% CI 0.20 to 0.73) in favour of adjunctive corticosteroids. One study was conducted in infants, suggesting a risk ratio for death in hospital of 0.81 (95% CI 0.51 to 1.29; moderate quality evidence).

Authors' conclusions

The number and size of trials investigating adjunctive corticosteroids for HIV-infected patients with PCP is small, but the evidence from this review suggests a beneficial effect for adult patients with substantial hypoxaemia. There is insufficient evidence on the effect of adjunctive corticosteroids on survival in infants.

PLAIN LANGUAGE SUMMARY

Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV infection

Pneumocystis jiroveci pneumonia (PCP), formerly called *Pneumocystis carinii* pneumonia, is the most common opportunistic infection among patients infected with HIV. In 1990, based on evidence from five randomised controlled trials, an expert panel recommended the use of corticosteroids for HIV-infected patients with PCP and substantial hypoxaemia (low levels of oxygen in the blood).

The objective of this systematic review was to assess the effects of adjunctive (additional) corticosteroids on mortality and the need for mechanical ventilation in patients co-infected with HIV and PCP. We searched for eligible studies up to April 2014. We included seven studies in this review and six in the meta-analysis (combining of study data).

The number and size of the trials investigating adjunctive corticosteroids for HIV-infected patients co-infected with PCP is small (the six trials included in the meta-analysis comprised 242 individuals in the intervention groups and 247 individuals in the control groups; the trial on infants comprised 47 individuals in the intervention group and 53 in the control group). Follow-up ranged from three to 14 months. The evidence from this review was of high quality for mortality and of moderate quality for need for mechanical ventilation and suggests a beneficial effect for adult patients with substantial hypoxaemia. For infants (18 months or younger) with HIV and suspected PCP there is insufficient evidence on whether the effect of adjunctive corticosteroids could improve survival (the confidence interval for the estimate of effect is wide, includes both clinically relevant benefit and harm and is of moderate quality).

Summary of findings for the main comparison. Adjunctive corticosteroids versus no such treatment for *Pneumocystis jiroveci* pneumonia in patients with HIV infection

Adjunctive corticosteroids versus no such treatment for *Pneumocystis jiroveci* pneumonia in patients with HIV infection

Patient or population: patients with *Pneumocystis jiroveci* pneumonia and HIV infection
Settings: hospital
Intervention: adjunctive corticosteroids

Comparison: no adjunctive corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Without adjunctive corticosteroids	With adjunctive corticosteroids				
Death at 1 month (adults)	**Study population[1]**		**RR 0.56** (0.32 to 0.98)	489 (6 studies)	⊕⊕⊕⊕ **high** [2,3,4]	
	247 per 1000	**138 per 1000** (79 to 242)				
	Low[1]					
	100 per 1000	**56 per 1000** (32 to 98)				
	High[1]					
	250 per 1000	**140 per 1000** (80 to 245)				
Death at 3 to 4 months (adults)	**Study population[1]**		**RR 0.59** (0.41 to 0.85)	448 (5 studies)	⊕⊕⊕⊕ **high** [2]	
	258 per 1000	**152 per 1000** (106 to 219)				
	Low[1]					
	100 per 1000	**59 per 1000**				

		(41 to 85)			
	High[1]				
	250 per 1000	**147 per 1000** (102 to 213)			
Death in hospital; children	**472 per 1000**	**382 per 1000** (241 to 608)	**RR 0.81** (0.51 to 1.29)	100 (1 study)	⊕⊕⊕⊖ **moderate** [5]
Need for mechanical ventilation at 1 month	**164 per 1000**	**62 per 1000** (33 to 120)	**RR 0.38** (0.2 to 0.73)	388 (3 studies)	⊕⊕⊕⊖ **moderate** [6]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]In Western countries where HAART is widely available the mortality rate is 10%; in developing countries where HAART is often not available the mortality rate is 25%.
[2]Lack of blinding was judged as less relevant to the outcome of mortality.
[3]Inconsistency among trials could be explained by the difference in the initiation of corticosteroids - all trials report starting corticosteroids within 3 days, but in Clement 1989 the majority of patients started corticosteroids after 2 days.
[4]The confidence interval of the summary estimate from all trials has an upper boundary close to 1 (no effect); however, if Clement 1989 (the trial introducing heterogeneity and initiating steroids later than other trials) is excluded in a sensitivity analysis, the upper boundary of the summary estimate changes to 0.7, i.e. all plausible effects are clinically relevant.
[5]Quality of evidence downgraded from high to moderate as there was only a single trial with a wide confidence interval of treatment effect including clinically relevant benefit and clinically relevant harm.
[6]Quality of evidence downgraded from high to moderate because lack of blinding could influence the decision of a caregiver to initiate mechanical ventilation.

BACKGROUND

Description of the condition

With the introduction of highly active antiretroviral therapy (HAART) more than two decades ago, the incidence of *Pneumocystis jiroveci* pneumonia (Stringer 2002) has decreased significantly in the Western hemisphere. However, PCP (the acronym stands for pneumocystis pneumonia) still remains one of the most common opportunistic infections in patients infected with the human immunodeficiency virus (HIV) (Kaplan 2000). Among patients with HIV infection and PCP the mortality rate is 10% to 20% during the initial infection and this increases substantially with the need for mechanical ventilation (Randall 2000).

Description of the intervention

Two to three days after starting anti-PCP therapy, the respiratory situation of PCP patients often worsens because of increased inflammation in the lungs as a reaction to pneumocystis particles from killed organisms. Corticosteroids given in conjunction with anti-PCP therapy may help to better control the inflammatory process. Therefore the corticosteroid treatment should be started as early as possible but within 72 hours after starting the PCP-specific therapy. So far, there is no evidence about an optimal dose or duration of adjunctive corticosteroids. The following 21-day oral regimen with prednisone has been recommended: 40 mg orally twice daily for days one to five, 40 mg once daily for days six to 10, and 20 mg once daily for days 11 to 21 (Benson 2004; EACS 2013). If parenteral administration is necessary, it is recommended to use methylprednisolone at 75% of the respective prednisone dose (CDC 2013). In children with severe PCP, it is recommended to start the corticosteroid treatment as early as possible but within 72 hours after diagnosis. The recommended dose of prednisone for children is 1 mg/kg of body weight twice daily for days one to five, 0.5 mg/kg once daily for days six to 10, and 0.5 mg/kg once daily for days 11 to 21 (NIH 2013). The alternative regimen with methylprednisolone (intravenous) is 1 mg/kg/dose every six hours for days one to seven, 1 mg/kg/dose once daily for days eight to nine, 0.5 mg/kg/dose twice daily for days 10 to 11, and 1 mg/kg/dose once daily for days 12 to 16 (NIH 2013).

How the intervention might work

Within two to three days of the initiation of anti-PCP therapy, the health status of patients often worsens. It is presumed that the patient's alveolar-arterial oxygen gradient and the inflammatory processes in the lungs increase as organisms are killed (Sax 2012). Adjunctive corticosteroids administered with initiation of anti-PCP therapy may reduce the inflammatory process and prevent this clinical worsening.

Why it is important to do this review

In 1990, an expert panel recommended the use of corticosteroids for HIV-infected patients with PCP and substantial hypoxaemia (initial arterial oxygen partial pressure of < 70 mmHg or alveolar-arterial gradient > 35 mmHg on room air) based on the evidence from five randomised controlled trials (Consensus 1990). The studies used for the consensus statement still represent the basis for the current guidelines for the treatment of adults (CDC 2013) and children (NIH 2013). However, at the time of the first consensus statement, one trial was not yet completed (Nielsen 1992), two trials had been stopped prematurely (Gagnon 1990; Montaner 1990), and one trial was not published in full (Clement 1989). In 1992, a systematic review qualitatively summarised the same incomplete data (Sistek 1992).

OBJECTIVES

To assess the effects of adjunctive corticosteroids on overall mortality and the need for mechanical ventilation in HIV-infected patients with PCP and substantial hypoxaemia (arterial oxygen partial pressure < 70 mmHg or alveolar-arterial gradient > 35 mmHg on room air).

METHODS

Criteria for considering studies for this review

Types of studies

We considered trials eligible for this review if they used random allocation of participants into parallel groups and reported mortality data. We excluded trials with a follow-up of less than 30 days.

Types of participants

All HIV-infected patients with moderate-severe PCP, defined as PCP with substantial hypoxaemia. We excluded patients with no or mild hypoxaemia (arterial oxygen partial pressure > 70 mmHg or an alveolar-arterial gradient < 35 mmHg on room air).

Types of interventions

We included studies if they compared corticosteroids to placebo or usual care in HIV-infected patients with PCP in addition to baseline treatment with trimethoprim-sulfamethoxazole, pentamidine or dapsone-trimethoprim.

Types of outcome measures

The main outcome measure of interest was overall mortality at one and three to four months of follow-up.

A secondary outcome measure was the need for mechanical ventilation.

Search methods for identification of studies

Electronic searches

We searched *The Cochrane Library* (2004, Issue 4), MEDLINE (January 1985 to December 2004) and EMBASE (January 1985 to December 2004) without language restrictions to identify randomised controlled trials that compared adjunctive corticosteroids to control in HIV-infected patients with PCP. We used the terms steroid*, corticosteroid*, glucocorticoid*, *Pneumocystis*, PCP, **carinii* and **jiroveci* as text words and Glucocorticoids, Adrenal Cortex Hormones, Steroids, *Pneumocystis* Infections, *Pneumocystis jiroveci* and Pneumonia, *Pneumocystis* as Medical Subject Headings. We restricted the search to articles indexed as randomised controlled trials (publication type) or drug therapy (subject heading) or those that included the words random* or placebo in their titles or abstracts. In this review update, we searched the above-mentioned databases in September 2010 and April 2014 for trials published since our original review. A detailed search strategy is presented in Appendix 1.

Searching other resources

We further reviewed the reference lists from previously published overviews (Consensus 1990; Sistek 1992), searched UptoDate version 2005 and Clinical Evidence Concise (Issue 12, 2004), contacted experts in the field and searched the reference lists of identified publications for citations of additional relevant articles. In this update of our review, we searched for ongoing trials in ClinicalTrials.gov and the World Health Organization International Clinical Trial Registry Platform (ICTRP). We searched for conference abstracts via AEGIS.

Data collection and analysis

Selection of studies

Two teams of investigators (MB/HCB and RB/HF) independently assessed study eligibility and quality and resolved any disagreement by consensus. We abstracted data from eligible trials in duplicate. HR and MB assessed trials identified during the update in 2010; HE and MB assessed potentially eligible trials identified in 2014.

Assessment of risk of bias in included studies

We assessed the risk of bias of the included trials with respect to random sequence generation; concealment of treatment allocation; blinding of patients, caregivers or assessors of clinical outcomes; completeness of follow-up; performance of a sample size calculation; and whether the trial was stopped early for benefit (Juni 1999; Montori 2005). HR and MB assessed trials identified during the update in 2010; HE and MB assessed potentially eligible trials identified in 2014.

Assessment of heterogeneity

We tested for heterogeneity with the Cochrane Q test and measured inconsistency of treatment effects across studies using the I^2 statistic (the percentage of total variance across studies that is due to heterogeneity rather than chance) (Higgins 2002; Higgins 2003).

Assessment of reporting biases

We investigated the presence of publication bias by means of funnel plots (Sterne 2001).

Data synthesis

We performed all analyses according to the intention-to-treat principle, i.e. we analysed patients in the groups to which they were randomised. In our main analysis we assumed that patients lost to follow-up did not have an event. In a sensitivity analysis we assumed that patients lost to follow-up experienced an event. We pooled treatment effects across studies and calculated a weighted average risk ratio of overall mortality in the treatment and control groups using a random-effects model. We performed statistical analyses using Review Manager 5.3 (RevMan 2014). We calculated numbers needed to treat to prevent one death by multiplying the mean relative risk reduction with an initial mean baseline risk (Marx 2003).

Sensitivity analysis

We carried out sensitivity analyses to examine treatment effects according to quality components of trials, whether the publication was a peer-reviewed article or just in abstract form, and whether trials were stopped early for benefit versus not.

'Summary of findings' table

In this update of our review, we used the GRADE methodology to assess the quality of the evidence (Guyatt 2008). We have presented the quality of the evidence for the following outcomes in a 'Summary of findings' table:

1. death at one month (adults);
2. death at three to four months (adults);
3. death in hospital (children).
4. need for mechanical ventilation

RESULTS

Description of studies

In our original search, we screened 1591 titles and abstracts. We excluded 1583 records and assessed eight in full text. Of these, two trials did not meet our inclusion criteria and we excluded them. One trial investigated only patients with mild hypoxaemia and had a short follow-up of only three days (Jeantils 1993), and another trial, Montaner 1993, was a subgroup analysis of a larger included trial (Montaner 1990). The remaining six trials investigated adults with HIV and moderate-severe PCP; one was only published in abstract form (Clement 1989), two were stopped prematurely due to apparent benefits in the treatment groups with adjunctive glucocorticoid therapy (Gagnon 1990; Montaner 1990), and one was stopped early due to published evidence from other studies in favour of adjunctive corticosteroids (Nielsen 1992). Only three studies were completed and published in full versions (Bozzette 1990; Nielsen 1992; Walmsley 1995).

The update search in 2010 yielded 335 records. We excluded 334 on the basis of the title and abstract. We assessed one study in full text and subsequently included it (Terblanche 2008). This study investigated adjunctive corticosteroid treatment in HIV-exposed infants less than 18 months old.

For the update search in 2014, we screened 103 records as titles and abstracts, which did not yield any further eligible studies. Overall, we screened 2029 titles and abstracts, excluded 2020, screened nine in full text and included seven of these in our systematic review. Details of the included and excluded trials are provided in the Characteristics of included studies and Characteristics of excluded studies tables, respectively.

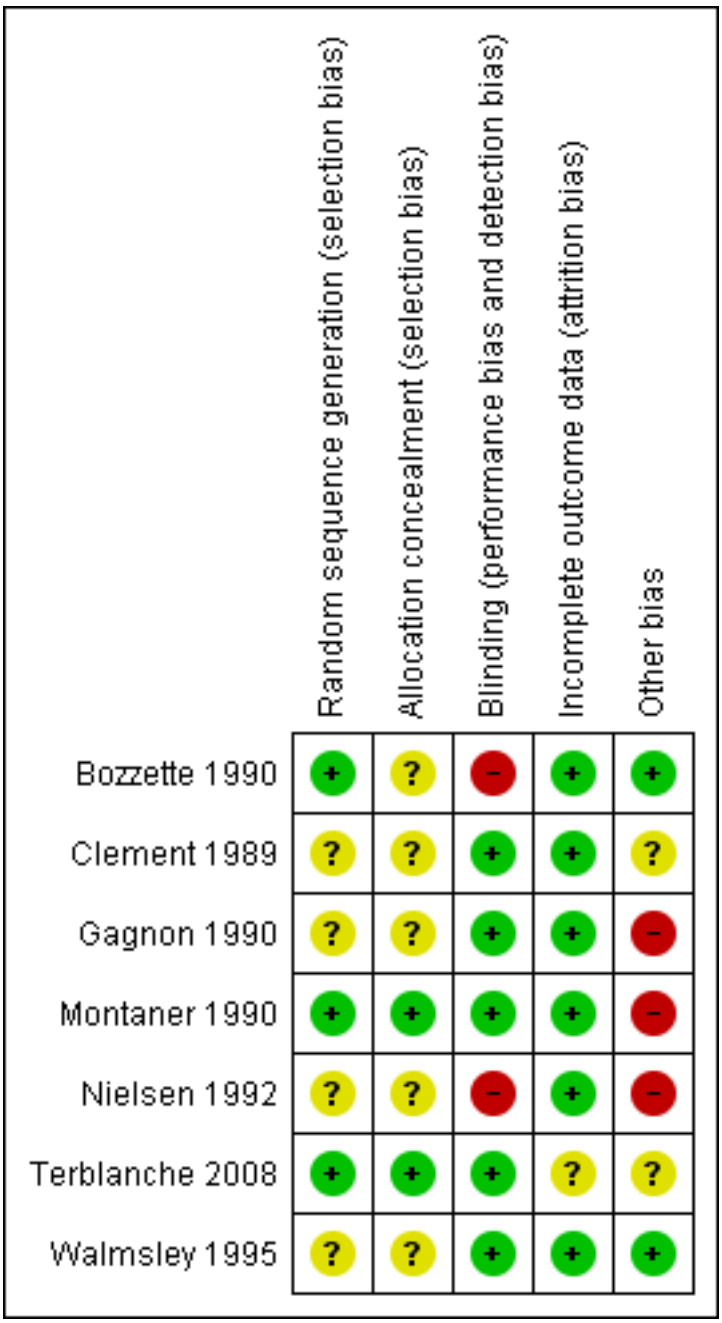
Risk of bias in included studies

The quality assessment for each study is shown in the 'Risk of bias' tables in Characteristics of included studies.

Overall, the risk of bias of the six studies included in the meta-analysis varied. Details of random sequence generation were reported in three of seven studies. Patient follow-up was almost complete for all included studies due to short follow-up periods (the total number of patients lost to follow-up was four). In the six studies conducted in adults, concealed allocation of participants was reported in three studies (Bozzette 1990; Montaner 1990; Walmsley 1995). Four trials reported double-blinding without specifying who was blinded (Clement 1989; Gagnon 1990; Montaner 1990; Walmsley 1995). Three trials were single-centre (Clement 1989; Gagnon 1990: Montaner 1990), and three were multi-centre (Bozzette 1990; Nielsen 1992; Walmsley 1995). Four trials reported the performance of a sample size calculation (Bozzette

1990; Gagnon 1990; Montaner 1990; Walmsley 1995). Two trials were stopped prematurely due to apparent treatment benefits of adjunctive corticosteroids (Gagnon 1990; Montaner 1990), and one was stopped due to external evidence of the benefits of corticosteroids (Nielsen 1992). The stopping early of clinical trials for benefit may lead to an overestimation of treatment effects due to catching the apparent benefit of treatment at a "random high" (Montori 2005). The overall risk of bias of the study conducted in infants was low (Terblanche 2008). Figure 1 gives an overview of the 'Risk of bias' assessment.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



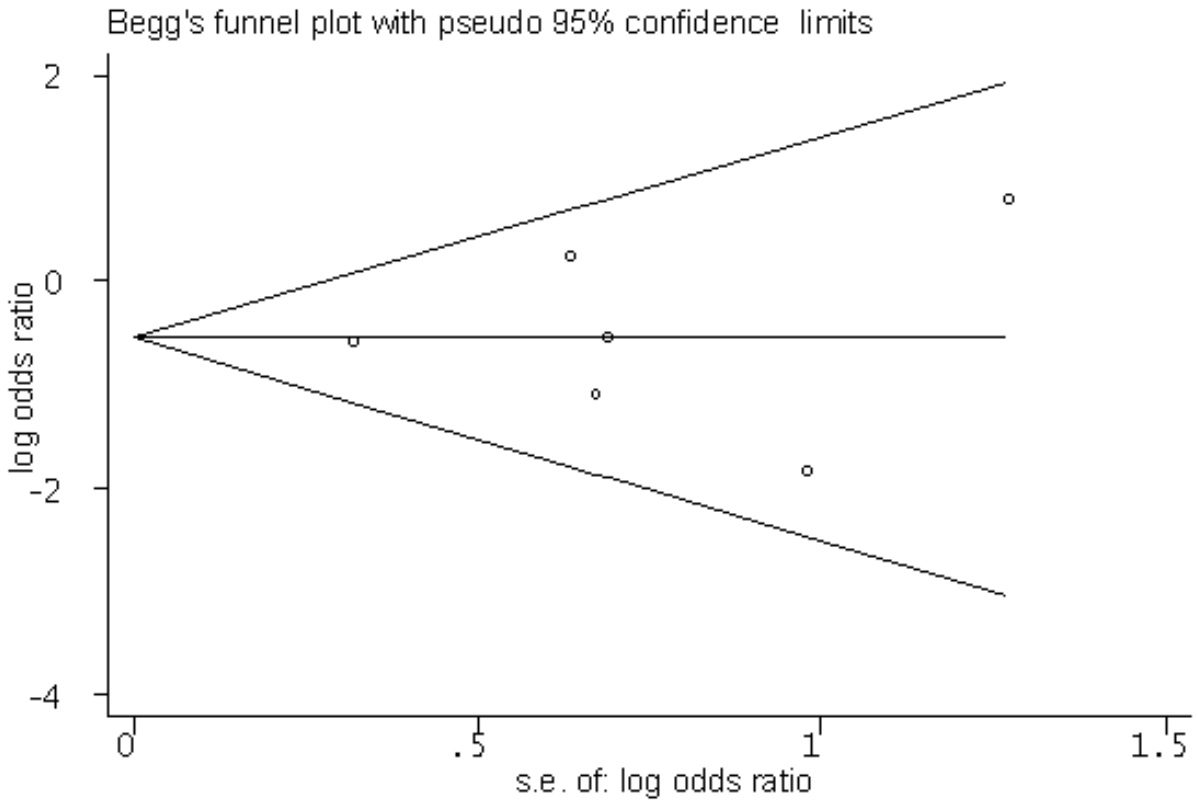
Effects of interventions

See: **Summary of findings for the main comparison** Adjunctive corticosteroids versus no such treatment for *Pneumocystis jiroveci* pneumonia in patients with HIV infection

We included seven trials in this systematic review. The six trials included in the meta-analysis comprised a total of 242 individuals in the intervention groups and 247 individuals in the control groups, with a follow-up ranging between three and 14 months. Figure 2 (funnel plot) indicates no evidence of publication bias. The trial in infants comprised 47 individuals in the intervention group and 53 in the control group, who were followed up until hospital discharge. Summary of findings for the main comparison gives an overview of

the intervention effects, with a GRADE analysis of evidence quality for each outcome.

Figure 2. Funnel plot to evaluate the presence of publication bias in trials investigating adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in HIV-infected patients. The funnel graph plots the log of the treatment odds ratio against the standard error (SE) of the log odds ratio (an indicator of sample size). Open circles represent trials included in the meta-analysis. The line in the centre indicates the summary log odds ratio. In the absence of publication bias, the log odds ratio estimates from smaller trials are expected to be scattered above and below the summary estimate, producing a symmetric triangular or funnel shape. When smaller trials with larger log odds ratios are missing, the funnel plot appears asymmetric and may indicate the presence of publication bias. In our systematic review the funnel plot looks symmetric. The Egger test for publication bias was not statistically significant (P value = 0.91).



Adjunctive corticosteroids versus placebo or usual care

Overall mortality

Risk ratios for overall mortality were significantly reduced for adjunctive corticosteroids in adult patients with HIV at one month (RR 0.56; 95% CI 0.32 to 0.98) (Analysis 1.1; Figure 3) and at three to four months of follow-up (RR 0.59; 95% CI 0.41 to 0.85) (Analysis 1.2; Figure 4). We found some evidence of heterogeneity among trials at one month (test of heterogeneity P value = 0.12; I^2 = 43%), whereas at three to four months treatment effects looked more homogenous (P value = 0.78; I^2 = 0%). We judged the quality of the evidence for these outcomes to be high as the influence of blinding is not of significant importance for the outcome mortality.

Figure 3. Forest plot of comparison: 1 Adjunctive corticosteroids versus no such treatment, outcome: 1.1 Death at 1 month; adults.

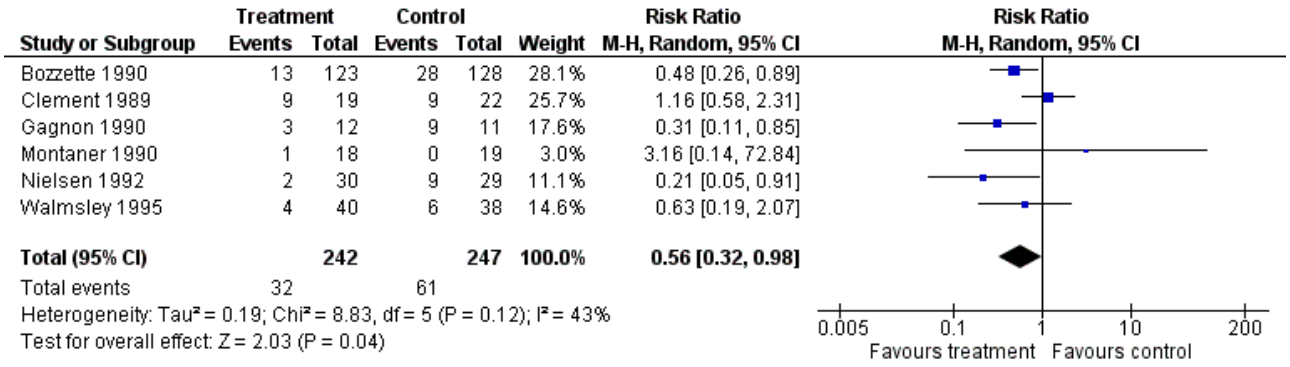
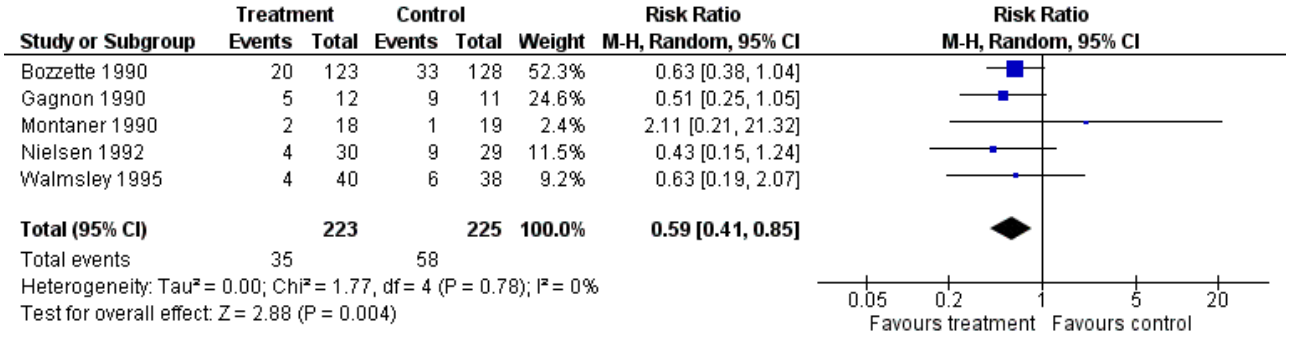


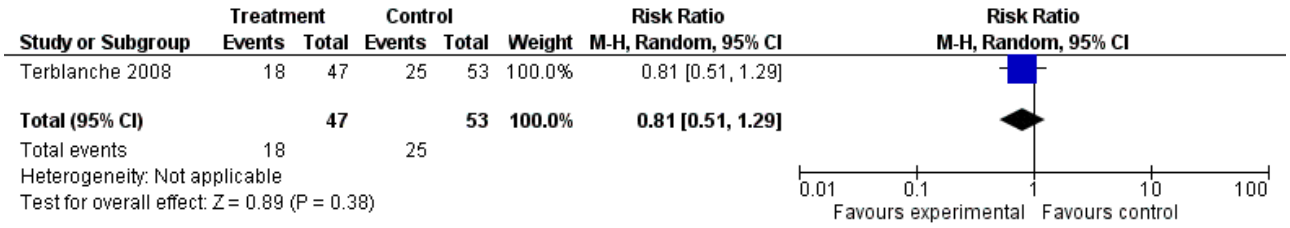
Figure 4. Forest plot of comparison: 1 Adjunctive corticosteroids versus no such treatment, outcome: 1.2 Death at 3 to 4 months; adults.



We explored inconsistencies among studies in sensitivity analyses. Heterogeneity was considerably reduced when the analysis was limited to trials reporting early adjunctive corticosteroids (within three days) that were published in full, i.e. excluding Clement 1989 (summary risk ratio for mortality at one month 0.44; 95% CI 0.28 to 0.69, heterogeneity P value = 0.49; I^2 = 0%) (Analysis 1.6). We carried out further sensitivity analyses for the mortality endpoint at one month. In trials that reported concealed allocation (Bozzette 1990; Montaner 1990; Walmsley 1995), the summary risk ratio was 0.54 (95% CI 0.32 to 0.92, heterogeneity P value = 0.49; I^2 = 0%) (Analysis 1.7). In trials reporting blinding of patients and caregivers (Clement 1989; Gagnon 1990; Montaner 1990; Walmsley 1995), the summary risk ratio was 0.71 (95% CI 0.33 to 1.55, heterogeneity P value = 0.14; I^2 = 44%) (Analysis 1.8). In trials not prematurely halted (Bozzette 1990; Clement 1989; Walmsley 1995), the summary risk ratio was 0.71 (95% CI 0.39 to 1.31, heterogeneity P value = 0.16; I^2 = 45%) (Analysis 1.9). The assumption that patients lost to follow-up at one month died gives a summary risk ratio of 0.56 (95% CI 0.32 to 0.97, heterogeneity P value = 0.11; I^2 = 44%) (Analysis 1.5).

The risk ratio for in-hospital mortality in infants receiving adjunctive corticosteroids was 0.81 (95% CI 0.51 to 1.29) (Terblanche 2008) (Analysis 1.3; Figure 5). We downgraded the quality of the evidence for this outcome from high to moderate as there was only one trial available, with a wide confidence interval including clinically relevant benefit and harm.

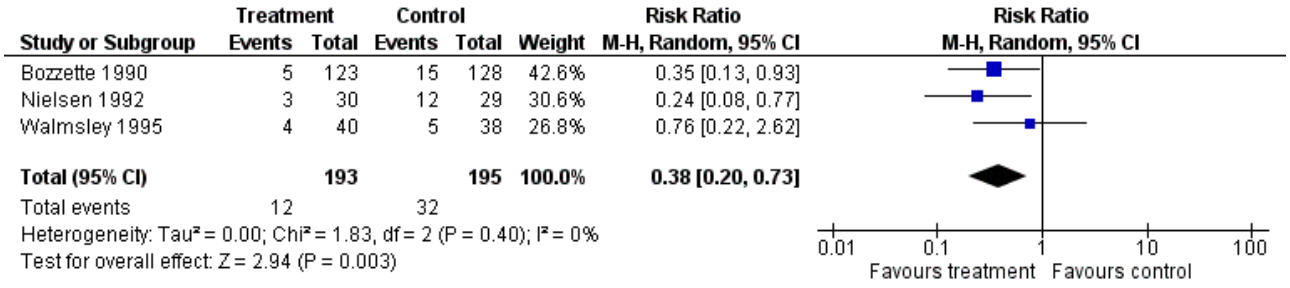
Figure 5. Forest plot of comparison: 1 Adjunctive corticosteroids versus no such treatment, outcome: 1.3 Death in hospital; children.



Need for mechanical ventilation

Reliable data on the need for mechanical ventilation were only available for the three largest trials (Bozzette 1990; Nielsen 1992; Walmsley 1995). Again, the risk ratio for this endpoint was largely reduced in the group with early adjunctive corticosteroids (0.38; 95% CI 0.20 to 0.73; P value = 0.40; I^2 = 0%) (Analysis 1.4; Figure 6). We downgraded the quality of the evidence for this outcome from high to moderate because lack of blinding could influence the decision of a caregiver to initiate mechanical ventilation.

Figure 6. Forest plot of comparison: 1 Adjunctive corticosteroids versus no such treatment, outcome: 1.4 Need for mechanical ventilation at 1 month; adults.



DISCUSSION

The meta-analysis of six randomised controlled trials in HIV-infected adults with *Pneumocystis jiroveci* pneumonia (PCP) and substantial hypoxaemia found a significant reduction in the relative risk of death with adjunctive corticosteroids of 44% at one month and 41% at three to four months. The average weighted mean mortality in the control groups of these trials at one month was 25%. This initial mortality rate of 25% can be assumed in settings where highly active antiretroviral therapy (HAART) is not available, which is still the case for most developing countries (Fisk 2003). In this situation we estimated that nine (95% confidence interval (CI) 6 to 200) HIV-infected adults with PCP have to be treated early with adjunctive corticosteroids to prevent one death during the first month after PCP diagnosis. In Western countries, where HAART is widely available, we estimated the respective number needed to treat to be 23 patients (95% CI 15 to 500), assuming an initial mortality rate of 10% (Sepkowitz 2002). With regard to the need for mechanical ventilation, the risk reduction with adjunctive corticosteroids was even greater in the investigated patient population, but the number of trials was small (n = 3).

Only one trial reported overall mortality during the hospitalisation of infants under 18 months of age diagnosed with PCP. There was insufficient evidence to be certain that adjunctive corticosteroids had an effect on mortality (confidence intervals were wide, including both clinically relevant benefit and harm). Due to limited resources, the authors of that trial fixed the number of participating infants at 100 (Terblanche 2008).

This review has several strengths and limitations. We conducted an extensive literature search and updates to retrieve all eligible trials. However, formal testing for publication bias was not powerful because of the small number of included trials. Even with a symmetric funnel plot (Figure 2), such bias cannot be ruled out. Moreover, with a small number of included trials the uncertainty interval for the inconsistency among trials may not be very informative (Higgins 2003). We focused mainly on mortality data, which may be less prone to ascertainment bias, and we analysed the data according to the intention-to-treat principle to get more conservative estimates. Finally, the trials included in this meta-analysis used different corticosteroid regimens. So far, neither the dosing nor the length and tapering schedule of corticosteroids has been adequately addressed in randomised trials. In former and current recommendations for adults (Benson 2004; CDC 2013), the corticosteroid schedule of the largest trial was adapted (Bozzette 1990). The former (Frieden 2009) and current guidelines (NIH 2013) for children have taken the trials in adults into account as well as three comparative observational studies in children (Bye 1994; McLaughlin 1995; Sleasman 1993).

There has been some concern among physicians treating patients with AIDS that further immunosuppression due to corticosteroid therapy could accelerate the onset of other HIV-related opportunistic complications (Lambertus 1990; Nelson 1993). However, with the exception of an increase in muco-cutaneous herpes simplex infection episodes (Bozzette 1990), adjunctive corticosteroids were not associated with an increase in opportunistic complications in any of the included trials. A large cohort study that used a standard 21-day tapering course of adjunctive corticosteroids found no difference in the risk of AIDS-related complications apart from an increase in oesophageal candidiasis (Gallant 1998).

It is possible that adjunctive corticosteroids are also beneficial for HIV-infected patients with mild hypoxaemia due to PCP (Jeantils 1993). However, in this situation the short-term mortality is low and possible unfavourable effects of corticosteroids might outweigh the benefits. Evidence from randomised controlled trials for non-HIV-infected patients with severe PCP is still lacking. Retrospective observational studies have shown conflicting results: while Pareja 1998 found that corticosteroids might be beneficial, Delclaux 1999 and Moon 2011 did not find an improvement of outcomes in non-HIV-infected patients with severe PCP.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review has confirmed and quantified the benefit of adjunctive corticosteroid therapy in HIV-infected adults with moderate-severe *Pneumocystis jiroveci* pneumonia (PCP). We estimated a relative risk reduction for overall mortality of 44% at one month and 41% at three to four months. We calculated

that nine patients must be treated with adjunctive corticosteroids in order to prevent one death in a setting where highly active antiretroviral therapy (HAART) is not available, and that 23 patients must be treated with adjunctive corticosteroids to prevent one death in a setting where HAART is available. The results corroborate the conclusions of the 1990 consensus statement (Consensus 1990), and support current recommendations for the management of PCP in HIV-infected adults (CDC 2013). In adults, it is recommended to start the corticosteroid treatment as early as possible but within 72 hours after starting the PCP-specific therapy. The recommended dose for prednisone is 40 mg orally twice daily for days one to five, 40 mg once daily for days six to 10, and 20 mg once daily for days 11 to 21 (Benson 2004; EACS 2013). If parenteral administration is necessary, it is recommended to use methylprednisolone at 75% of the respective prednisone dose (CDC 2013). In children with severe PCP, it is recommended to start the corticosteroid treatment as early as possible but within 72 hours after diagnosis. The recommended dose of prednisone is 1 mg/kg of body weight twice daily for days one to five, 0.5 mg/kg once daily for days six to 10, and 0.5 mg/kg once daily for days 11 to 21 (NIH 2013). The alternative regimen with methylprednisolone (intravenous) is 1 mg/kg/dose every six hours for days one to seven, 1 mg/kg/dose once daily for days eight to nine, 0.5 mg/kg/dose twice daily for days 10 to 11, and 1 mg/kg/dose once daily for days 12 to 16 (NIH 2013).

Implications for research

This systematic review has confirmed and quantified the benefit of adjunctive corticosteroid therapy in HIV-infected adults with moderate-severe PCP. The results underline the conclusions of the 1990 consensus statement (Consensus 1990), and support current recommendations for the management of PCP in HIV-infected patients (CDC 2013; NIH 2013). More research regarding adjunctive corticosteroids in HIV-infected infants is warranted.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bozzette 1990

Methods	Prospective, randomised, parallel-group, unblinded trial Max. follow-up: 84 days Sample size calculation performed Trial completed as planned
Participants	251 patients with AIDS and confirmed or presumed PCP and hypoxaemia ratio (partial pressure of arterial oxygen divided by fraction of inspired oxygen) > 75 Diagnosis of PCP: 75% bronchoalveolar lavage, 15% sputum, 10% clinically presumed Baseline treatment for PCP: 80% trimethoprim-sulfamethoxazole (15 to 20 mg trimethoprim per kg body weight per day oral or parenteral), 18% pentamidine (3 to 4 mg per kg per day parenteral), 2% dapsone (100 mg per day oral) Recruitment: June 1987 to June 1989 Study centres: 6 Country: USA Setting: tertiary care % male: 97 Mean age: 36 years Baseline characteristics similar for each group: yes
Interventions	Adjunctive prednisone (oral), 40 mg twice daily for 5 days, followed by 40 mg daily for 5 days, followed by 20 mg daily for the duration of anti-pneumocystis therapy. Patients unable to take oral medication received parenteral methylprednisolone (75% of respective prednisone doses) Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: 36 hours Control: no additional treatment. Patients with respiratory failure could be prescribed corticosteroids at the discretion of the primary physician (41% of patients (7 of 17) with respiratory failure in the corticosteroid group; 60% of patients (15 of 25) with respiratory failure in the control group)
Outcomes	1. Occurrence of respiratory failure (hypoxaemia ratio (partial pressure of arterial oxygen divided by fraction of inspired oxygen) < 75), intubation or death 2. Death 3. Dose-limiting toxicity of the initial standard therapy
Notes	Funding: California University-Wide AIDS Research Program Registration: not reported

Bozzette 1990 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was prepared centrally
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomization was prepared centrally, with blocks of four patients per stratum and a 1:1 proportion; it was carried out by means of sealed envelopes at the study sites."
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up in the corticosteroid group was 1 patient (1%) and in the control group 3 patients (2%)
Other bias	Low risk	Sample size calculation performed. Trial completed as planned

Clement 1989

Methods	Prospective, randomised, parallel-group trial with "double-blinding" Max. follow-up: 56 days Sample size calculation not reported
Participants	41 patients with confirmed PCP and an arterial partial pressure of oxygen below 50 mmHg on room air. Diagnosis of PCP: bronchoalveolar lavage or sputum Baseline treatment for PCP: 88% trimethoprim-sulfamethoxazole, 12% pentamidine Recruitment period not reported Study centres: 1 Country: USA Setting: tertiary care % male: not reported Age: not reported Methylprednisolone group: PaO2 = 280 mmHg, LDH = 600; placebo group: PaO2 = 290 mmHg, LDH = 718 (difference not significant); no other baseline characteristics reported
Interventions	Adjunctive methylprednisolone (intravenous), 60 mg every 6 hours for 2 days, then every 12 hours for 2 days, then once 60 mg, then 40 mg, then 20 mg, then 10 mg for 1 day each Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: not explicitly stated (29/41 patients received steroids/placebo ≥ 48 hours) Control: placebo
Outcomes	Survival at 56 days
Notes	The study was only published in abstract form Funding: not reported Registration: not reported

Risk of bias

Clement 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Patients were randomized to receive placebo (P) or intravenous methylprednisolone (MP) as adjunctive therapy the assignment being double-blinded." Who was blinded is not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "We prospectively enrolled 41 consecutive, consenting adults with documented PCP (by sputum induction or broncho-alveolar lavage)." At the end of follow-up (56 days) survival status was reported for all 41 patients
Other bias	Unclear risk	Inadequate information available

Gagnon 1990

Methods	Prospective, randomised, parallel-group, "double-blind, placebo-controlled" trial Max. follow-up: 14 months Sample size calculation performed (80 patients) Trial stopped prematurely for benefit at interim analysis (enrolment of 23 patients)
Participants	23 patients with HIV infection, engaged in behaviour placing them at risk of HIV infection, or with oral candidiasis at entry into the study and severe PCP, defined by a respiratory rate above 30 breaths per minute at rest, an alveolar-arterial oxygen difference above 30 mmHg while the patient breathed room air, and an arterial partial pressure of oxygen below 75 mmHg while the patient breathed 35% oxygen through a face mask but above 60 mmHg while the patient breathed 100% oxygen through a face mask. Intubated patients were excluded as well as patients with a history of hypersensitivity to both trimethoprim-sulfamethoxazole and pentamidine, a serum creatinine level > 3 times the upper limit of normal, an absolute neutrophil count below 1 x 10^9 cells per litre, and treatment with corticosteroids within a period of 2 weeks before study entry Diagnosis of PCP: histology from bronchoalveolar lavage, biopsy or sputum Baseline treatment for PCP: 100% trimethoprim-sulfamethoxazole at 15 mg/kg/day trimethoprim for 21 days. Modification of the treatment in the case of toxicity according to the protocol by Sattler et al (Sattler 1988) Recruitment: June 1989 to May 1990 Study centres: 1 Country: USA Setting: tertiary care % male: 83 Mean age (range): 38 (23 to 66) years Baseline characteristics similar for each group: yes
Interventions	Adjunctive methylprednisolone (intravenous), 40 mg every 6 hours for 7 days, followed by a tapering dose for 3 days in patients with a clinical relapse Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroids: < 72 hours Control: placebo
Outcomes	1. Survival until hospital discharge

Gagnon 1990 *(Continued)*

	2. Development of respiratory failure (defined as an arterial oxygen pressure > 60 mmHg while the patient breathed ≥ 60% oxygen through a face mask or rising partial pressure of carbon dioxide, in addition to need for intubation) and the completion of antibiotic therapy
Notes	Funding: Alliance Against AIDS, Miami Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation in blocks of 10 but how the randomisation was actually performed is not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind" placebo-controlled study but who was blinded is not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. No changes from intervention group to placebo group or vice versa
Other bias	High risk	Trial stopped early for benefit

Montaner 1990

Methods	Prospective, randomised, parallel-group, "double blind, placebo-controlled" trial Max. follow-up: 90 days Sample size calculation performed (70 patients; sequential analysis with triangular test) Trial stopped prematurely for benefit (enrolment of 37 patients)
Participants	37 patients > 18 years with known HIV and first episode of confirmed PCP, and oxygen saturation by pulse oximetry of 85% or more and less than 90% at rest or a 5-percentage-point decrease in oxygen saturation with exercise while breathing room air. Exclusion criteria: current treatment with systemic corticosteroids or prior treatment within 30 days, active pulmonary pathology other than PCP, cytomegalovirus disease, need for mechanical ventilation prior to randomisation, contraindication to corticosteroids (for example, uncontrolled hypertension, psychosis, active peptic ulcer or mycobacterial disease) Diagnosis of PCP: 100% bronchoalveolar lavage Baseline treatment for PCP: trimethoprim-sulfamethoxazole (20 mg/kg and 100 mg/kg per day oral or intravenous qid), pentamidine (4 mg/kg per day, intravenous), dapsone-trimethoprim (100 mg oral od and 20 mg/kg per day oral qid) for at least 14 days Recruitment: ? to April 1989 Study centres: 1 Country: Canada Setting: tertiary care % male: 95 Median age: not reported Baseline characteristics similar for each group: only CD4 cell count reported
Interventions	Adjunctive prednisone (Deltasone, oral), 60 mg daily for 7 days, followed by 50 mg, then 40 mg, 30 mg, 20 mg, 15 mg, 10 mg, 5 mg daily (each for 2 days)

Montaner 1990 *(Continued)*

	Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: 48 hours Control: placebo
Outcomes	Early deterioration defined by a 10% decrease in baseline oxygen saturation at rest occurring not before day 3
Notes	Funding: National Health Research Development Programme (NHRDP), Department of Health and Welfare, Canada Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out by the hospital pharmacy according to a computer-generated table
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was carried out in blocks of ten patients by the hospital pharmacy according to a computer-generated table of random numbers. Individual presealed envelopes were used to keep each patient's code."
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind placebo-controlled trial". Who was blinded was not described. Low risk of detection bias for mortality. For all 8 placebo patients with early deterioration the seal was broken and treatment with corticosteroids initiated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Other bias	High risk	Trial stopped early for benefit

Nielsen 1992

Methods	Prospective, randomised, parallel-group, unblinded trial Max. follow-up: 90 days Sample size calculation not reported Trial stopped prematurely due to external evidence in favour of adjunctive corticosteroids
Participants	59 patients with HIV and a first episode of confirmed PCP, and an arterial partial pressure of oxygen below 67.5 mmHg and/or an arterial partial pressure of CO2 below 30 mmHg on room air. Exclusion criteria: unconfirmed PCP within 72 hours after anti-PCP treatment, treatment with cotrimoxazole or corticosteroids in the preceding 14 days, concomitant (myco-)bacterial pulmonary infection diagnosed by microscopy of the bronchoalveolar lavage, uncontrolled diabetes mellitus, pregnancy or age < 18 years Diagnosis of PCP: histology of bronchoalveolar lavage or biopsy Baseline treatment for PCP: 100% trimethoprim-sulfamethoxazole (15 mg trimethoprim/75 mg sulfamethoxazole per kg per day) in 4 divided doses for at least 14 days. The medication was given intravenous on day 1 to 10 and then oral administration was allowed. Patients with intolerance 2% (1 patient) or lack of clinical response to cotrimoxazole 14% (8 patients) changed to pentamidine (4 mg per kg intravenous per day) Recruitment: October 1988 to May 1990 Study centres: 3 Country: Denmark, Netherlands Setting: tertiary care % male: 95

Nielsen 1992 *(Continued)*

	Median age (range): 37 (26 to 68) Baseline characteristics similar for each group: yes
Interventions	Adjunctive methylprednisolone (intravenous), 2 mg/kg body weight every 6 hours for 10 days Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: < 24 hours Control: no additional treatment
Outcomes	1. Survival to discharge from hospital 2. Survival at day 90 3. Need for mechanical ventilation during the initial episode
Notes	Funding: not reported Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation but no further details given
Allocation concealment (selection bias)	Unclear risk	Not reported (see above)
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label trial; low risk of detection bias for the outcome mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. No changes from treatment to control group or vice-versa
Other bias	High risk	Sample size calculation not reported. Trial stopped prematurely due to external evidence in favour of adjunctive corticosteroids

Terblanche 2008

Methods	Prospective, randomised, placebo-controlled trial. Trial is "double-blind" but who was blinded was not reported Follow-up until hospital discharge Sample size calculation: not reported. Number restricted to 100 participants due to time and financial constraints Trial completed as planned
Participants	100 infants who had been exposed to HIV with severe pneumonia, which was confirmed or clinically suspected to be caused by *Pneumocystis jiroveci* Oxygenation: no entry criteria reported. Mean oxygen saturation in a) prednisone group: 69% (SD 15.8), b) placebo 72% (SD 13.8). Clinical diagnosis of PCP: patients with "atypical" pneumonia with the following features: a) hypoxia out of proportion to the clinical findings on auscultation; b) C-reactive protein (CRP) count < 10 mg/l or low; c) lactate dehydrogenase (LDH) level > 500 IU/l; d) bilateral perihilar interstitial infiltrates on chest

Terblanche 2008 *(Continued)*

	radiograph (CXR) compatible with a diagnosis of PCP; and e) positive HIV enzyme-linked immunosorbent assay (ELISA) Patients who were still hospitalised on day 7 had induced sputum and nasopharyngeal aspirates collected For the results of the virological testing see: Table 1 Baseline treatment for PCP: "Standard antibiotic regimen including co-trimoxazole" Recruitment: February 2005 to 31 March 2006 Study centres: 3 Country: South Africa Setting: university hospitals % male: 52 Mean age in months (SD): prednisone group: 3.4 (2), placebo group: 3.2 (1.4) Baseline characteristics similar for each group: yes
Interventions	Adjunctive prednisone 2 mg/kg/day for 7 days Control: placebo 36% (17/47 patients) in the intervention group and 42% (22/53 patients) in the placebo group received additional prednisone at 48 hours due to clinical deterioration or an independent indication for steroid therapy
Outcomes	1. In-hospital survival (intention-to-treat and per-protocol analysis both unadjusted and adjusted for age and hospital) 2. Independence of oxygen (intention-to-treat and per-protocol analysis both unadjusted and adjusted for age and hospital) 3. Subgroup analysis for clinically less ill patients
Notes	Funding: not reported Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of random number generator
Allocation concealment (selection bias)	Low risk	Quote: "A random number generator was used to determine the allocation to steroid or placebo treatment, which were provided in a double-blind fashion by the hospital pharmacists according to study number."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind, placebo-controlled trial", but who was blinded is not explained
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Survival documented for all included patients. The fact that additional steroids could be given could lead to an underestimation of the treatment effect in the analysis following the intention-to-treat principle

Terblanche 2008 *(Continued)*

Other bias	Unclear risk	Sample size calculation: not reported. Number restricted to 100 participants due to time and financial constraints. Trial completed as planned

Walmsley 1995

Methods	Prospective, randomised, parallel-group, "double-blind", placebo-controlled trial Max. follow-up for clinical outcomes: 6 months Sample size calculation performed (70 patients) Trial completed as planned
Participants	78 patients with known or suspected HIV infection and confirmed first or recurrent episode of PCP, and an arterial partial pressure of oxygen below 70 mmHg while the patient breathed room air or an alveolar-arterial oxygen gradient above 40 mmHg if arterial blood gases could not be assessed on room air. Exclusion criteria: < 18 years, contraindication to corticosteroids (active gastrointestinal bleeding in the previous 3 months, ocular herpes simplex infection, poorly controlled diabetes mellitus), more than 1 significant pathogen found on direct examination of the initial pulmonary specimen (i.e. acid-fast bacilli), extensive Kaposi's sarcoma of the respiratory tract seen at bronchoscopy, or treatment with systemic corticosteroids for any reason in the 3 months prior to randomisation Diagnosis of PCP: bronchoalveolar lavage, biopsy, sputum Baseline treatment for PCP: 82% trimethoprim-sulfamethoxazole (15 to 20 mg trimethoprim per kg per day intravenous or oral), 17% pentamidine (3 to 4 mg per kg per day oral), 1% dapsone (100 mg per day) plus trimethoprim (15 to 20 mg per kg per day) for 21 days. Patients intolerant or failing to respond to their initial PCP therapy could be switched to another form of either standard or salvage treatment (eflornithine, 4% (3 patients)) Recruitment: August 1986 to January 1991 Study centres: 3 Country: Canada Setting: tertiary care % male: 99 Mean age: 37 Baseline characteristics similar for each group: yes
Interventions	Adjunctive methylprednisolone (intravenous), 40 mg every 12 hours for 10 days Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: < 24 hours Control: placebo Patients could receive steroids outside the study protocol based on the clinical judgement of the treating physician; the seal was not broken in those cases. 16 patients received corticosteroids outside the study protocol: 6 patients in the intervention group and 10 patients in the placebo group
Outcomes	1. Composite of death before hospital discharge, requirement for mechanical ventilation for 6 or more days, failure to achieve an arterial partial pressure of oxygen > 70 mmHg on room air by day 10 of therapy 2. Adverse drug reactions resulting in discontinuation of the antimicrobial medication 3. Time to defervescence 4. Time to improvement of chest radiographs 5. Superinfections during acute therapy 6. Opportunistic infections or malignancies in the 6 months after treatment 7. Potential adverse reactions to corticosteroids, including hypertension, hyperglycaemia, gastrointestinal bleeding and neuropsychiatric disturbances

Walmsley 1995 *(Continued)*

Notes	There was no statistically significant difference in the primary endpoint between randomised groups The study was published 4 years after its completion Funding: grants from the National Health Research and Development Program (NHRDP), Grant 6606-3373-AIDS, and the Sunnybrook Health Sciences Center Foundation for Research Registration: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details described
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was performed by the random numbers method in a 1:1 ration by the TGH pharmacy department, and blocks of randomization codes were forwarded to participating centers."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind placebo-controlled trial", but who was blinded is not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up but 10 patients in the placebo group received the intervention: might cause bias and lead to an underestimate of the true treatment effect
Other bias	Low risk	Sample size calculation performed (70 patients). Trial completed as planned

LDH: lactate dehydrogenase
PCP: *Pneumocystis jiroveci* pneumonia
SD: standard deviation

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

Study	Reason for exclusion
Jeantils 1993	Small pilot study on 10 patients with no or mild hypoxaemia (arterial partial pressure of oxygen above 70 mmHg) and a follow-up of only 3 days; no mortality
Montaner 1993	Study on a subgroup of patients from the already included study Montaner 1990

DATA AND ANALYSES

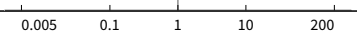
Comparison 1. Adjunctive corticosteroids versus no such treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 1 month; adults	6	489	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.32, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Death at 3 to 4 months; adults	5	448	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.41, 0.85]
3 Death in hospital; children	1	100	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.51, 1.29]
4 Need for mechanical ventilation at 1 month; adults	3	388	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.20, 0.73]
5 Sensitivity analysis: Death at 1 month; adults; loss to follow-up = dead	6	489	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.32, 0.97]
6 Sensitivity analysis: Death at 1 month; adults; without Clement 1989	5	448	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.28, 0.69]
7 Sensitivity analysis: Death at 1 month; adults; concealed allocation only	3	366	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.32, 0.92]
8 Sensitivity analysis: Death at 1 month; adults; blinding of patients and caregivers	4	179	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.33, 1.55]
9 Sensitivity analysis: Death at 1 month; adults; trials not prematurely halted	3	370	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.39, 1.31]

Analysis 1.1. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 1 Death at 1 month; adults.

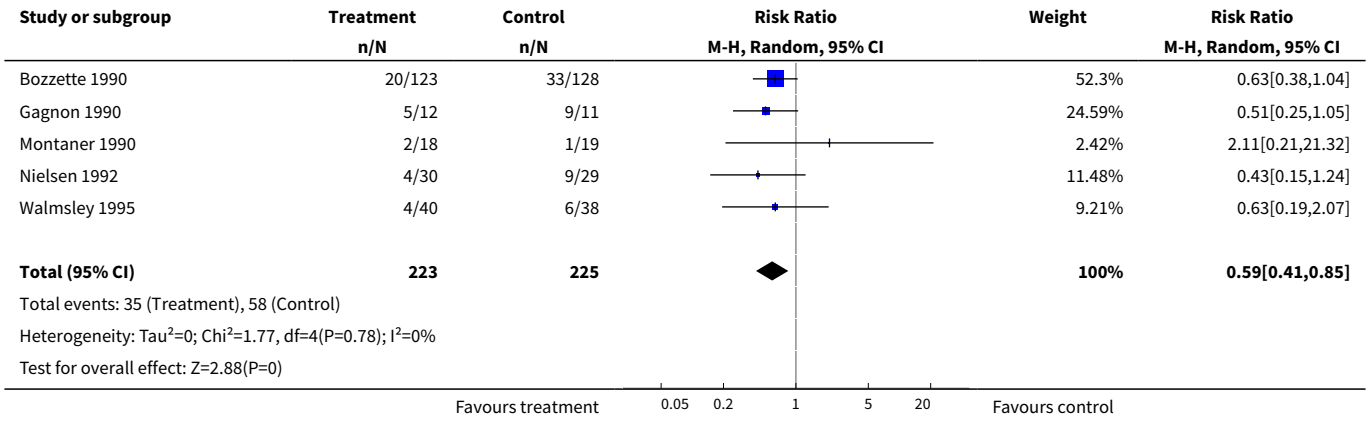
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bozzette 1990	13/123	28/128		28.11%	0.48[0.26,0.89]
Clement 1989	9/19	9/22		25.68%	1.16[0.58,2.31]
Gagnon 1990	3/12	9/11		17.59%	0.31[0.11,0.85]
Montaner 1990	1/18	0/19		2.96%	3.16[0.14,72.84]
Nielsen 1992	2/30	9/29		11.07%	0.21[0.05,0.91]
Walmsley 1995	4/40	6/38		14.59%	0.63[0.19,2.07]
Total (95% CI)	**242**	**247**		**100%**	**0.56[0.32,0.98]**
Total events: 32 (Treatment), 61 (Control)					
Heterogeneity: Tau^2=0.19; Chi^2=8.83, df=5(P=0.12); I^2=43.37%					
Test for overall effect: Z=2.03(P=0.04)					



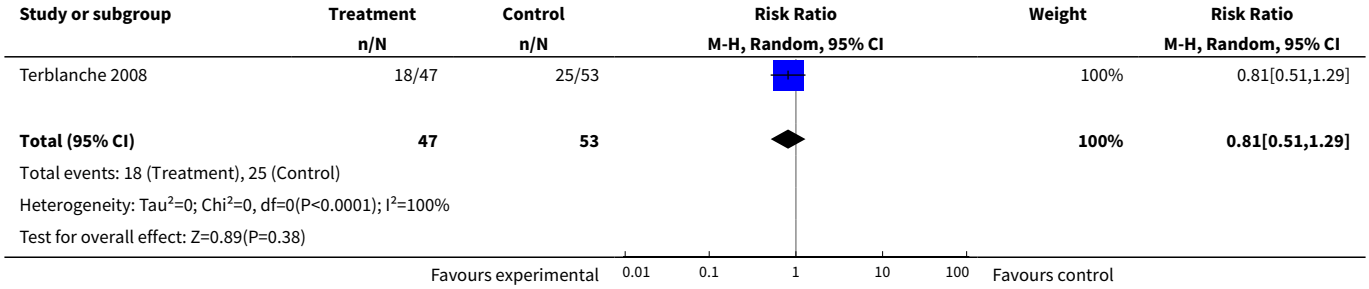
Favours treatment

Favours control

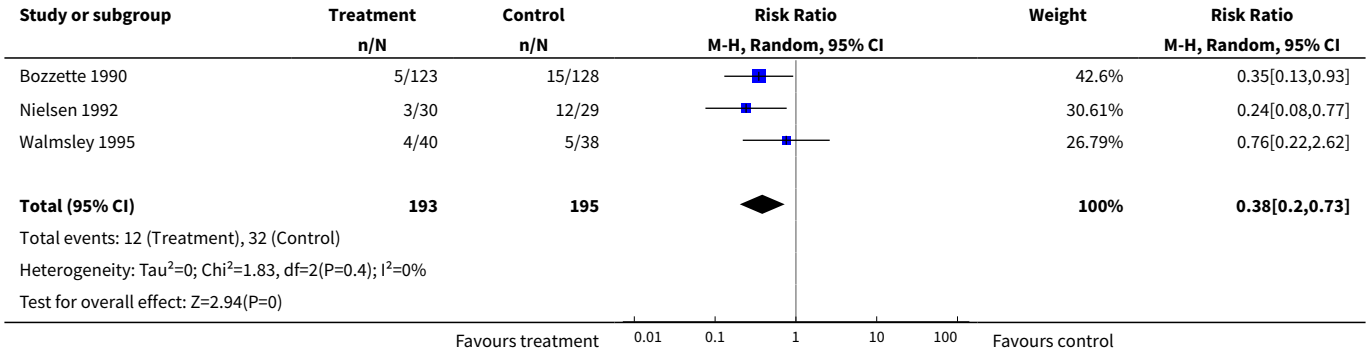
Analysis 1.2. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 2 Death at 3 to 4 months; adults.



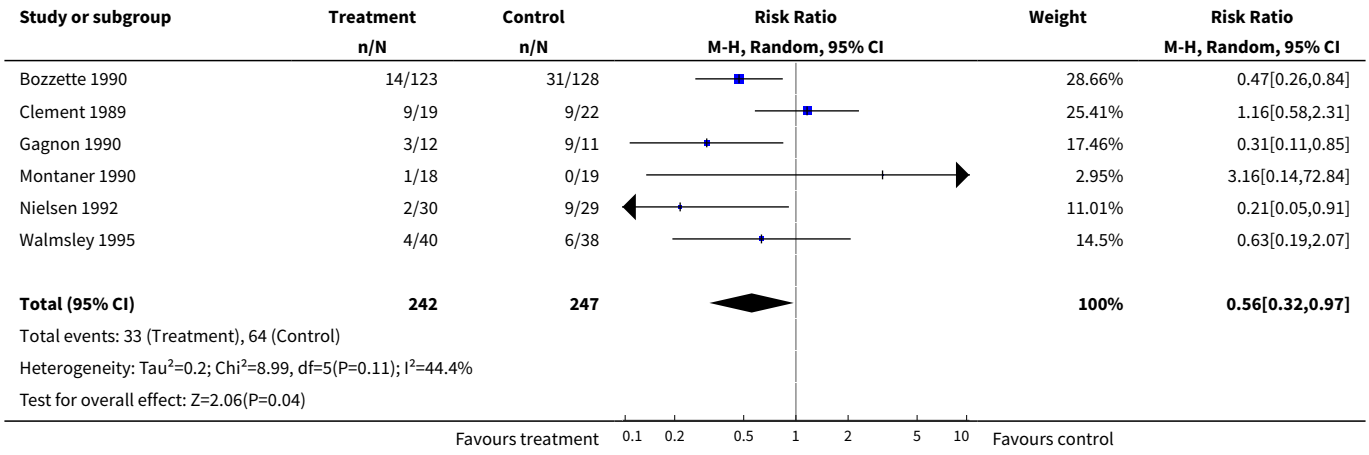
Analysis 1.3. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 3 Death in hospital; children.



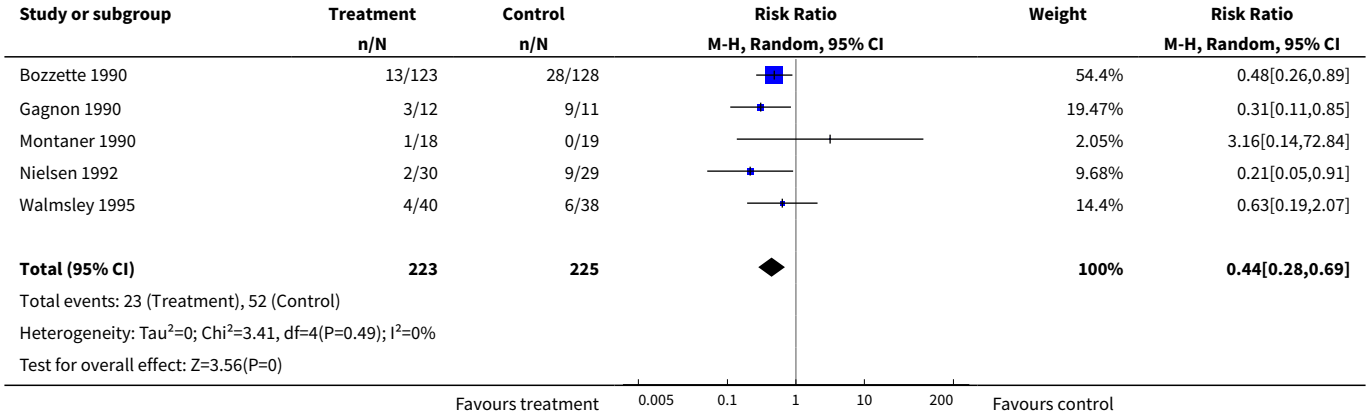
Analysis 1.4. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 4 Need for mechanical ventilation at 1 month; adults.



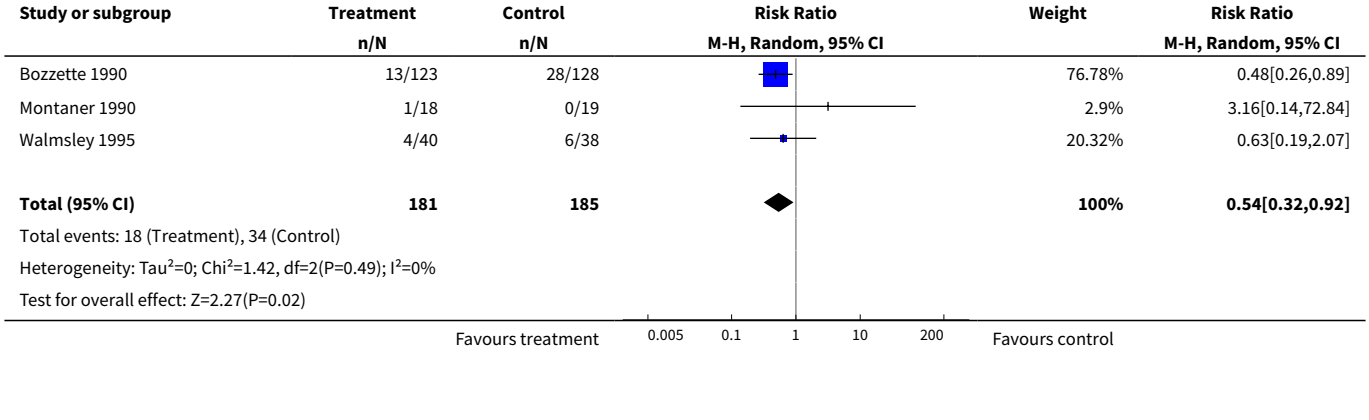
Analysis 1.5. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 5 Sensitivity analysis: Death at 1 month; adults; loss to follow-up = dead.



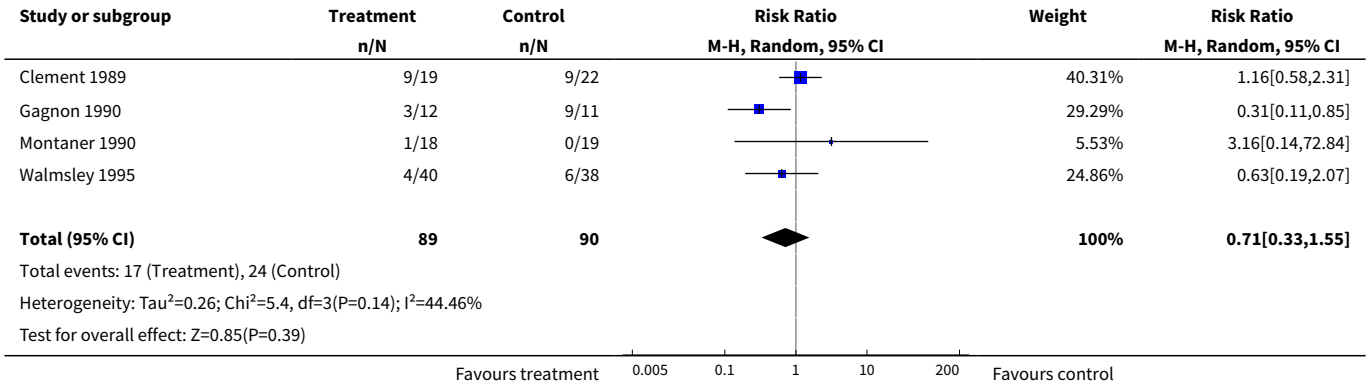
Analysis 1.6. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 6 Sensitivity analysis: Death at 1 month; adults; without Clement 1989.



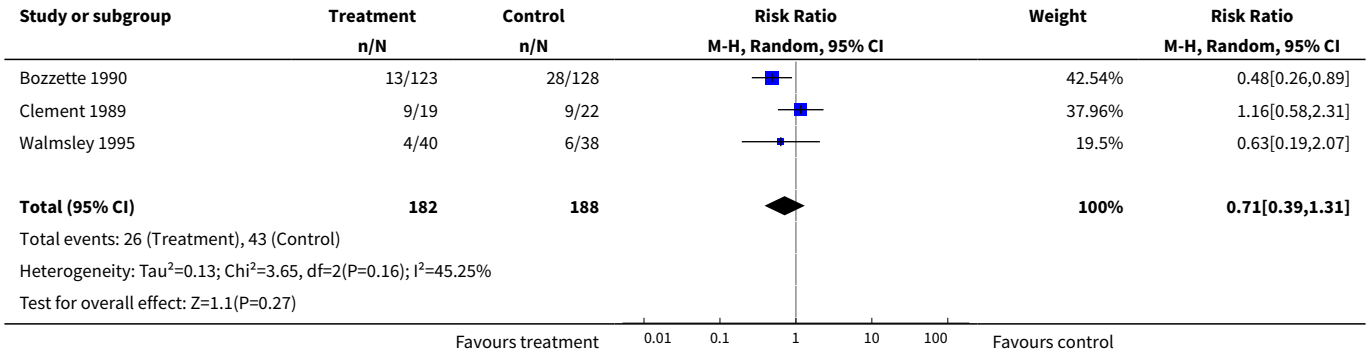
Analysis 1.7. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 7 Sensitivity analysis: Death at 1 month; adults; concealed allocation only.



Analysis 1.8. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 8 Sensitivity analysis: Death at 1 month; adults; blinding of patients and caregivers.



Analysis 1.9. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 9 Sensitivity analysis: Death at 1 month; adults; trials not prematurely halted.



ADDITIONAL TABLES

Table 1. Results of virological testing in Terblanche 2008

Treatment group	PCP PCR in sputum	PCP IF	Nasopharyngeal aspirate for respiratory viruses
Prednisone group	5/9	3/39	RSV: 1/41 CMV: 1/41
Placebo group	3/6	5/46	RSV: 7/47 Adenovirus: 1/47 Influenza A: 2/47 Parainfluenza 3: 1/47

PCP: *Pneumocystis jiroveci* pneumonia

APPENDICES

Appendix 1. PubMed search strategy

Search	Most recent queries
#5	Search #1 AND #2 AND #3 AND #4 Limits: Publication Date from 2004/12/01 to 2010/08/30
#4	Search steroids[mh:noexp] OR adrenal cortex hormones[mh:noexp] OR steroid*[tiab] OR adrenal cortex hormones[tiab] OR glucocorticoids[mh] OR glucocorticoid*[tiab] OR corticosteroid*[tiab] OR Pneumonia, Pneumocystis/drug therapy[mh]
#3	Search PCP OR pneumonia, pneumocystis[mh] OR pneumocystis[tiab] OR pneumocystis jiroveci-i[mh] OR jiroveci[tiab] OR jirovecii[tiab] OR pneumocystis infections[mh] OR pneumocystis carini-i[mh] OR carinii[tiab] OR carinus[tiab] OR carini[tiab]
#2	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]

WHAT'S NEW

Date	Event	Description
7 January 2015	New citation required but conclusions have not changed	No new studies identified. This review will not be updated again.
7 January 2015	New search has been performed	Complete update of the review.

HISTORY

Review first published: Issue 3, 2006

Date	Event	Description
11 April 2014	New search has been performed	Literature searches updated: - 11 Ap ril 2014: EMBASE, PubMed, CENTRAL, Clinical Trials.gov, WHO ICTRP, AEGIS

Date	Event	Description
8 September 2010	New search has been performed	Literature searches updated: - 8 September 2010: EMBASE - 9 September 2010: CENTRAL, WHO ICTRP, ClinicalTrials.gov - 17 September 2010: PubMed, AEGIS
29 October 2008	Amended	Converted to new review format.
24 May 2006	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

MB and HCB conceived the study and performed the first literature search. HR, MB, HE, HCB, RB and HF checked the eligibility and quality of trials, and extracted the necessary data. HR, HE and MB performed the statistical analyses and drafted the manuscript with the help of HCB, RB and HF. All authors read and approved the final version.

DECLARATIONS OF INTEREST

The authors declare that they have no competing interests.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pneumocystis carinii; AIDS-Related Opportunistic Infections [*drug therapy]; Adrenal Cortex Hormones [*therapeutic use]; Chemotherapy, Adjuvant; Hypoxia [etiology] [therapy]; Pneumonia, Pneumocystis [*drug therapy]; Randomized Controlled Trials as Topic; Respiration, Artificial

MeSH check words

Adult; Humans