Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection (Review)

Briel M, Bucher H, Boscacci R, Furrer H
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Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection (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 increases substantially with the need for mechanical ventilation. It was suggested that in these patients corticosteroids adjunctive to standard treatment for PCP could prevent the need for mechanical ventilation and decrease mortality.

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 hypoxemia (arterial oxygen partial pressure <70 mmHg or alveolar-arterial gradient >35 mmHg on room air).

Search methods

We searched Medline (January 1980-December 2004), EMBASE (January 1985-December 2004) and The Cochrane Library (Issue 4, 2004) without language restrictions to identify randomised controlled trials that compared adjunctive corticosteroids to control in HIV-infected patients with PCP. We further reviewed the reference lists from previously published overviews, we searched UptoDate version 2005 and Clinical Evidence Concise (Issue 12, 2004), contacted experts of the field, and searched reference lists of identified publications for citations of additional relevant articles.

Selection criteria

Trials were considered eligible for this review 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, used random allocation, and reported mortality data. We excluded trials in patients with no or mild hypoxemia (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 reviewers 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 by using a random effects model.
Main results

Six studies were included in the review and meta-analysis. Risk ratios for overall mortality for adjunctive corticosteroids were 0.56 (95% confidence interval [CI], 0.32-0.98) at 1 month and 0.68 (95% CI, 0.50-0.94) at 3-4 months of follow-up. To prevent 1 death, numbers needed to treat are 9 patients in a setting without highly active antiretroviral therapy (HAART) available, and 23 patients with HAART available. Only the 3 largest trials provided data on the need for mechanical ventilation with a risk ratio of 0.38 (95% CI, 0.20-0.73) in favour of adjunctive corticosteroids.

Authors’ conclusions

The number and size of trials investigating adjunctive corticosteroids for HIV-infected patients with PCP is small, but evidence from this review suggests a beneficial effect for patients with substantial hypoxemia.

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 randomized control trials, an expert panel recommended the use of corticosteroids for HIV-infected patients with PCP and substantial hypoxemia (low levels of oxygen in the blood). The objective of this systematic review was to assess the effects of adjunctive corticosteroids on mortality, and the need for mechanical ventilation in patients co-infected with HIV and PCP. Six studies were included in this review and meta-analysis. While the number and size of the trials investigating adjunctive corticosteroids for HIV-infected patients co-infected with PCP is small, evidence from this review suggests a beneficial effect for patients with substantial hypoxemia.

Background

With the introduction of highly active antiretroviral therapy (HAART) more than a decade ago, the incidence of Pneumocystis jiroveci pneumonia (PCP) (Stringer 2002) has decreased significantly in the Western hemisphere. However, PCP still remains the most common opportunistic infection 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 increases substantially with the need for mechanical ventilation (Randall 2000). In 1990, an expert panel recommended the use of corticosteroids for HIV-infected patients with PCP and substantial hypoxemia (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). This consensus statement still represents the basis of current treatment guidelines (Benson 2004). However, at the time this statement was made, one trial was not yet completed (Nielsen 1992), two trials were 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

The objectives of this systematic review and meta-analysis of randomised controlled trials were to assess the magnitude of effects of adjunctive corticosteroid therapy on overall mortality and the need for mechanical ventilation in HIV-related PCP. In addition, we provide numbers needed to prevent one death that may serve as estimates for the expected benefit of adjunctive corticosteroid therapy in the presence and absence of HAART.

Methods

Criteria for considering studies for this review

Types of studies

Trials were considered eligible for this review if they used random allocation of participants into parallel groups and reported mortality data. Trials with a follow-up of less than 30 days were excluded.
Types of participants
All HIV-infected patients with PCP and substantial hypoxemia. Patients without or mild hypoxemia (arterial oxygen partial pressure >70 mmHg or an alveolar-arterial gradient <35 mmHg on room air) were excluded.

Types of interventions
Studies were included 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 1 and 3–4 months of follow-up. A secondary outcome measure was the need for mechanical ventilation.

Search methods for identification of studies
We searched MEDLINE (January 1985–December 2004), EMBASE (January 1985–December 2004) and the Cochrane Library (Issue 4, 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, *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. 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 of the field, and searched reference lists of identified publications for citations of additional relevant articles.

Data collection and analysis
Two teams of investigators (MB/HCB and RB/HF) independently assessed study eligibility and quality and resolved any disagreement by consensus. Data of eligible trials were abstracted in duplicate. We assessed the quality of included trials with respect to concealment of treatment allocation; blinding of patients, care-givers or assessors of clinical outcomes; completeness of follow-up; performance of a sample size calculation; and if the trial was stopped early for benefit (Juni 1999; Montori 2005).

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
We identified 8 trials that met our inclusion criteria. We excluded one trial (Jeantils 1993) because it investigated only patients with mild hypoxemia and had a short follow-up of only 3 days, and another trial (Montaner 1993) which was a subgroup analysis of a larger included trial (Montaner 1990). Of the remaining six trials, 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 (Montaner 1990; Gagnon 1990), and one was stopped early due to published evidence from other studies in favor of adjunctive corticosteroids (Nielsen 1992). Only three studies were completed and published in full version (Bozzette 1990; Nielsen 1992; Walmsley 1995). Details of included trials are provided in the Table of Included Studies.

Risk of bias in included studies
The quality assessment for each study is listed in the Table of Included Studies.
Overall, the methodological quality of the six included studies was heterogeneous. An exception was patient follow-up which was complete for all included studies due to short follow-up periods. Concealed allocation of participants was reported for three studies (Montaner 1990; Bozzette 1990; Walmsley 1995). None of the studies reported to have assessed clinical outcomes in a blinded fashion, four trials reported blinding of care-givers and patients...
Montaner 1990; Clement 1989; Gagnon 1990; Walmsley 1995), three were single-center (Clement 1989; Montaner 1990; Gagnon 1990) and three multi-center studies (Bozzette 1990; Nielsen 1992; Walmsley 1995), four trials reported the performance of a sample size calculation (Montaner 1990; Bozzette 1990; Gagnon 1990; Walmsley 1995), and two trials were stopped prematurely due to apparent treatment benefits of adjunctive corticosteroids (Montaner 1990; Gagnon 1990). 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).

**Effects of interventions**

There were six trials included in the systematic review and meta-analysis with a total of 242 individuals in the intervention groups and 247 individuals in the control groups. The Figure 1 indicated no evidence of a publication bias.

![funnel plot](funnel-plot.png)

**Figure 1. funnel plot.** Funnel plot to evaluate the presence of a 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 (s.e.) 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 a 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 a publication bias. In our systematic review the funnel plot looks symmetric.

The Egger test for publication bias was not statistically significant ($P = 0.91$).

**Overall mortality**

Risk ratios for overall mortality were significantly reduced for adjunctive corticosteroids at 1 month (0.56; 95% CI, 0.32-0.98) and at 3-4 months (0.68; 95% CI, 0.50-0.94) of follow-up. We found some evidence of heterogeneity among trials at 1 month (test of
heterogeneity, P=0.12; I2=43% [95% uncertainty interval [UI], 0%-78%]) whereas at 3-4 months treatment effects looked more homogenous (P=0.46; I2=0% [95% UI, 0%-75%]).

In a sensitivity analysis heterogeneity was considerably reduced when the analysis was limited to trials with 13624350early136243500MRMarina Rifkind136243500What does this mean? (<3 days) adjunctive corticosteroids that were published in full, i.e. excluding Clement et al. (Clement 1989) (summary risk ratio for mortality at 1 month: 0.45 [95% CI, 0.29-0.70], heterogeneity P=0.49; I2=0% [95% UI, 0%-79%]). In further sensitivity analyses for the mortality endpoint at 1 month summary risk ratios were 0.55 (95% CI, 0.32-0.93) in trials that reported concealed allocation (Montaner 1990; Bozzette 1990; Walsley 1995), 0.74(95% CI, 0.45-1.21) in trials reporting blinding of patients and care-givers (Gagnon 1990; Montaner 1990; Clement 1989; Walsley 1995), and 0.64 (95% CI, 0.42-0.98) in trials not prematurely halted (Clement 1989; Bozzette 1990; Walsley 1995).

Need for mechanical ventilation

Reliable data on the need for mechanical ventilation was only available for the 3 largest trials (Nielsen 1992; Bozzette 1990; Walsley 1995). Again, the risk ratio for this endpoint was largely reduced in the group with 13624350early136243501MRMarina Rifkind136243501Same comment as above adjunctive corticosteroids (0.38;95% CI, 0.20-0.73; P=0.40; I2=0% [95% UI, 0%-90%]).

**DISCUSSION**

This systematic review of 6 randomised controlled trials in HIV-infected patients with PCP and substantial hypoxemia found a significant reduction in the relative risk of death for adjunctive corticosteroids of 44% at 1 month and of 32% at 3-4 months. The average-weighted mean mortality in control groups of included trials at one month was 25%. This initial mortality-rate of 25% can be assumed in settings where HAART is not available which is still the case for most developing countries (Fisk 2003). In this situation we estimated that 9 (95% CI, 6-200) HIV-infected patients with PCP have that be treated early with adjunctive corticosteroids to prevent 1 death during the first month after PCP diagnosis. In Western countries, where HAART is widely available, the respective number to treat was estimated to be 23 (95% CI, 15-500) patients assuming an initial mortality rate of 10% (Sepkowitz 2002). With regard to the need for mechanical ventilation the risk reduction for adjunctive corticosteroids was even greater in the investigated patient population, but the number of trials was small (n=3).

This review has several strengths and limitations. We conducted an extensive literature search 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 Figure 1, 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 that may be less prone to ascertainment bias, and we analysed the data according to the intent-to-treat principle to get more conservative estimates. Finally, the trials included in this meta-analysis used different corticosteroid regimen. So far, neither the dosing nor the length and tapering schedule of corticosteroids has been adequately addressed in randomised trials. In current recommendations (Benson 2004) the corticosteroid schedule of the largest trial (Bozzette 1990) was adapted.

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 (Lamberts 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 which 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 esophageal candidiasis (Gallant 1998).

It is possible that adjunctive corticosteroids are also beneficial for HIV-infected patients with mild hypoxemia 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. Moreover, while corticosteroids might also be beneficial for non-HIV-infected patients with severe PCP (Pareja 1998), evidence from randomised controlled trials is still lacking.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

This systematic review confirmed and quantified the benefit of adjunctive corticosteroid therapy in HIV-infected patients with moderate-severe PCP. We estimated a relative risk reduction for overall mortality of 44% at 1 month and 32% at 3-4 months. We calculated that 9 patients must be treated with adjunctive corticosteroid in order to prevent one death in a setting where HAART is not available, and that 23 patients must be treated with adjunctive corticosteroid to prevent 1 death in a setting where HAART available.. The results underline the conclusions of the early released consensus statement (Consensus 1990), and support current recommendations for the management of PCP in HIV-infected patients (Benson 2004).

**Implications for research**

This systematic review confirmed and quantified the benefit of
adjunctive corticosteroid therapy in HIV-infected patients with moderate-severe PCP. The results underline the conclusions of the early released consensus statement (Consensus 1990), and support current recommendations for the management of PCP in HIV-infected patients (Benson 2004).

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Bozzette 1990 [published data only]

Clement 1989 [published data only]

Gagnon 1990 [published data only]

Montaner 1990 [published data only]

Nielsen 1992 [published data only]

Walmsley 1995 [published data only]

References to studies excluded from this review

Jeantils 1993 [published data only]

Montaner 1993 [published data only]

Additional references

Benson 2004

Consensus 1990

Fisk 2003

Gallant 1998

Grant 1997
Profound immunosuppression across the spectrum of opportunistic disease among hospitalized HIV-infected adults in Abidjan, Cote d'Ivoire. AIDS 1997.

Higgins 2002

Higgins 2003

Juni 1999

Kaplan 2000

Lambertus 1990

Marx 2003
Marx A, Bucher HC. Numbers needed to treat derived from meta-analysis: a word of caution. ACP J Club 2003;138:A11–A12.

Montori 2005

Nelson 1993

Pareja 1998

Randall 2000

Sepkowitz 2002

Sistek 1992

Sterne 2001

Stringer 2002

* Indicates the major publication for the study
### Characteristics of included studies  
*ordered by study ID*

**Bozzette 1990**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Prospective, randomized, parallel group, unblinded trial. Max. follow-up 84 days. Sample size calculation performed. Trial completed as planned.</th>
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<tbody>
<tr>
<td>Participants</td>
<td>251 patients with AIDS and confirmed or presumed PCP and hypoxemia ratio [partial pressure of arterial oxygen divided by fraction of inspired oxygen] &gt;75. Diagnosis of PCP: 75% bronchoalveolar lavage, 15% sputum, 10% clinically presumed. Baseline treatment for PCP: 80% trimethoprim-sulfamethoxazole, 18% Pentamidine, 2% Dapsone. Recruitment: June 1987 - June 1989 Study centers: 6 Country: USA Setting: Tertiary care % male: 98 Median age: 36 Baseline characteristics similar for each group: Yes</td>
</tr>
<tr>
<td>Interventions</td>
<td>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 antipneumocystis therapy. Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: 36 hours. Control: No additional treatment.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>1. Occurrence of respiratory failure (hypoxemia ratio [partial pressure of arterial oxygen divided by fraction of inspired oxygen] &lt;75, intubation, or death. 2. death 3. dose-limiting toxicity of the initial standard therapy.</td>
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#### Risk of bias

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<td>A - Adequate</td>
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**Clement 1989**

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<tr>
<th>Methods</th>
<th>Prospective, randomized, parallel group trial with blinding of patients and care-givers. No blinded outcome assessment. Max. follow-up 56 days. Sample size calculation not reported.</th>
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<tr>
<td>Participants</td>
<td>41 patients with confirmed PCP and an arterial partial pressure of oxygen below 50 mmHg on room air. Diagnosis of PCP: Bronchoalveolar lavage, sputum. Baseline treatment for PCP: 88% trimethoprim-sulfamethoxazole, 12% Pentamidine.</td>
</tr>
</tbody>
</table>
**Clement 1989 (Continued)**

| Recruitment period | Study centers: 1  
|---|---  
| Country: USA  
| Setting: Tertiary care  
| % male: not reported  
| Age: not reported  
| Baseline characteristics not reported.  

**Interventions**

Adjunctive methylprednisolon (i.v.), 60 mg every 6 hours for 2 days, then every 12 hours for 2 days, then once daily for 2 days, followed by 40, then 20, then 10 mg daily.  
Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: Unlimited  
Control: Placebo.

**Outcomes**

Survival at 56 days

**Notes**

The study was only published in abstract form.

**Risk of bias**

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**Gagnon 1990**

**Methods**

Prospective, randomized, parallel group trial with blinding of patients and care-givers. No blinded outcome assessment. Max. follow-up 120 days.  
Sample size calculation performed (80 patients).  
Trial stopped prematurely for benefit at interim analysis (enrolment of 23 patients)

**Participants**

23 patients with AIDS and PCP, and 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.  
Diagnosis of PCP: bronchoalveolar lavage, biopsy, sputum.  
Baseline treatment for PCP: 100% trimethoprim-sulfamethoxazole for 21 days.  
Recruitment: June 1989 - May 1990  
Study centers: 1  
Country: USA  
Setting: Tertiary care  
% male: 83  
Mean age (range): 38 (23-66)  
Baseline characteristics similar for each group: Yes
### Gagnon 1990 (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Adjunctive methylprednisolon (i.v.), 40 mg every 6 hours for 7 days, followed by a tapering dose for 3 days if needed. 40 mg daily for 5 days, followed by a tapering dose for 3 days. Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: 72 hours. Control: Placebo.</th>
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### Montaner 1990

<table>
<thead>
<tr>
<th>Methods</th>
<th>Prospective, randomized, parallel group trial with blinding of patients and care-givers. No blinded outcome assessment. Max. follow-up 30 days. Sample size calculation performed (70 patients; sequential analysis with triangular test), Trial stopped prematurely for benefit (enrolment of 37 patients)</th>
</tr>
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<tr>
<td>Participants</td>
<td>37 patients with 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. Diagnosis of PCP: 100% bronchoalveolar lavage. Baseline treatment for PCP: Trimethoprim-sulfamethoxazole, Pentamidine, Dapsone. Recruitment: ? - April 1989 Study centers: 1 Country: Canada Setting: Tertiary care % male: 95 Median age: not reported Baseline characteristics similar for each group: Only CD4 cell count reported</td>
</tr>
<tr>
<td>Interventions</td>
<td>Adjunctive prednisone (oral), 60 mg daily for 7 days, followed by 50, then 40, 30, 20, 15, 10, 5 mg daily (each for 2 days). Maximal interval between initiation of baseline treatment for PCP and initiation of corticosteroid: 48 hours. Control: Placebo</td>
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<tr>
<td>Outcomes</td>
<td>10% decrease in baseline oxygen saturation at rest occurring not before day 3</td>
</tr>
<tr>
<td>Notes</td>
<td>10% decrease in baseline oxygen saturation at rest occurring not before day 3</td>
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### Montaner 1990 (Continued)

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<td>Allocation concealment?</td>
<td>Yes</td>
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### Nielsen 1992

**Methods**
- Prospective, randomized, parallel group, unblinded trial. Max. follow-up 90 days.
- Sample size calculation not reported.
- Trial stopped prematurely due to external evidence in favor 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 or an arterial partial pressure of CO2 below 30 mmHg on room air.
- Diagnosis of PCP: bronchoalveolar lavage, biopsy.
- Baseline treatment for PCP: 100% trimethoprim-sulfamethoxazole
- Recruitment: October 1988 - May 1990
- Study centers: 3
- Country: Denmark, Netherlands
- Setting: Tertiary care
- % male: 95
- Median age (range): 37 (26-68)
- Baseline characteristics similar for each group: Yes

**Interventions**
- Adjunctive methylprednisolone (i.v.), 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

### Risk of bias

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<td>Unclear</td>
<td>B - Unclear</td>
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</table>

### Walmsley 1995

**Methods**
- Prospective, randomized, parallel group trial with blinding of patients and care-givers. No blinded outcome assessment. Max. follow-up for clinical outcomes 6 months.
- Sample size calculation performed.
- Trial completed as planned.
Walmsley 1995  *(Continued)*

<table>
<thead>
<tr>
<th>Participants</th>
<th>78 patients with AIDS and confirmed 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. Diagnosis of PCP: bronchoalveolar lavage, biopsy, sputum. Baseline treatment for PCP: 82% trimethoprim-sulfamethoxazole, 17% Pentamidine, 1% Dapsone for 21 days. Recruitment: August 1986 - January 1991 Study centers: 3 Country: Canada Setting: Tertiary care % male: 99 Mean age: 37 Baseline characteristics similar for each group: Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Adjunctive methylprednisolon (i.v.), 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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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 &gt;70 mmHg on room air by day 10 of therapy. 2. Adverse drug reactions 3. Time to improvement of chest radiographs 4. Superinfections during acute therapy 5. Opportunistic infections or malignancies in the 6 months after treatment</td>
</tr>
<tr>
<td>Notes</td>
<td>There was no statistically significant difference in the primary endpoint between randomized groups. The study was published 4 years after its completion.</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

**Characteristics of excluded studies** *(ordered by study ID)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeantils 1993</td>
<td>Small pilot study on 10 patients with no or mild hypoxemia (arterial partial pressure of oxygen above 70 mmHg) and a follow-up of only 3 days; no mortality</td>
</tr>
<tr>
<td>Montaner 1993</td>
<td>Study on a subgroup of patients from the already included study Montaner 1990</td>
</tr>
</tbody>
</table>
### Comparison 1. Adjunctive corticosteroids versus no such treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Death at 1 month</td>
<td>6</td>
<td>489</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.56 [0.32, 0.98]</td>
</tr>
<tr>
<td>2 Death at 3-4 months</td>
<td>6</td>
<td>489</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.68 [0.50, 0.94]</td>
</tr>
<tr>
<td>3 Need for mechanical ventilation at 1 month</td>
<td>3</td>
<td>388</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.38 [0.20, 0.73]</td>
</tr>
</tbody>
</table>

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

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

**Comparison:** 1 Adjunctive corticosteroids versus no such treatment

**Outcome:** 1 Death at 1 month

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozzette 1990</td>
<td>13/123</td>
<td>28/128</td>
<td>28.1 %</td>
<td>0.48</td>
<td>0.26, 0.89</td>
</tr>
<tr>
<td>Clement 1989</td>
<td>9/19</td>
<td>9/22</td>
<td>25.7 %</td>
<td>1.16</td>
<td>0.58, 2.31</td>
</tr>
<tr>
<td>Gagnon 1990</td>
<td>3/12</td>
<td>9/11</td>
<td>17.6 %</td>
<td>0.31</td>
<td>0.11, 0.85</td>
</tr>
<tr>
<td>Montaner 1990</td>
<td>1/18</td>
<td>0/19</td>
<td>3.0 %</td>
<td>3.16</td>
<td>0.14, 72.84</td>
</tr>
<tr>
<td>Nielsen 1992</td>
<td>2/30</td>
<td>9/29</td>
<td>11.1 %</td>
<td>0.21</td>
<td>0.05, 0.91</td>
</tr>
<tr>
<td>Walmsley 1995</td>
<td>4/40</td>
<td>6/38</td>
<td>14.6 %</td>
<td>0.63</td>
<td>0.19, 2.07</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>242</strong></td>
<td><strong>247</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.56 [0.32, 0.98]</strong></td>
</tr>
</tbody>
</table>

Total events: 32 (Treatment), 61 (Control)

Heterogeneity: Tau² = 0.19; Chi² = 8.83, df = 5 (P = 0.12); I² = 43%

Test for overall effect: Z = 2.03 (P = 0.043)
### Analysis 1.2. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 2 Death at 3-4 months.

Review: Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection

Comparison: 1 Adjunctive corticosteroids versus no such treatment

Outcome: 2 Death at 3-4 months

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozette 1990</td>
<td>20/123</td>
<td>33/128</td>
<td>41.1 % 0.63 [0.38, 1.04]</td>
<td>41.1 %</td>
<td>0.63 [0.38, 1.04]</td>
</tr>
<tr>
<td>Clement 1989</td>
<td>9/19</td>
<td>9/22</td>
<td>21.3 % 1.16 [0.58, 2.31]</td>
<td>21.3 %</td>
<td>1.16 [0.58, 2.31]</td>
</tr>
<tr>
<td>Gagnon 1990</td>
<td>5/12</td>
<td>9/11</td>
<td>19.3 % 0.51 [0.25, 1.05]</td>
<td>19.3 %</td>
<td>0.51 [0.25, 1.05]</td>
</tr>
<tr>
<td>Montaner 1990</td>
<td>2/18</td>
<td>1/19</td>
<td>1.9 % 2.11 [0.21, 21.32]</td>
<td>1.9 %</td>
<td>2.11 [0.21, 21.32]</td>
</tr>
<tr>
<td>Nielsen 1992</td>
<td>4/30</td>
<td>9/29</td>
<td>9.0 % 0.43 [0.15, 1.24]</td>
<td>9.0 %</td>
<td>0.43 [0.15, 1.24]</td>
</tr>
<tr>
<td>Walmsley 1995</td>
<td>4/40</td>
<td>6/38</td>
<td>7.2 % 0.63 [0.19, 2.07]</td>
<td>7.2 %</td>
<td>0.63 [0.19, 2.07]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>242</strong></td>
<td><strong>247</strong></td>
<td>100.0 % 0.68 [0.50, 0.94]</td>
<td>100.0 %</td>
<td>0.68 [0.50, 0.94]</td>
</tr>
</tbody>
</table>

Total events: 44 (Treatment), 67 (Control)

Heterogeneity: Tau² = 0.0, Chi² = 4.64, df = 5 (P = 0.46); I² =0.0%

Test for overall effect: Z = 2.36 (P = 0.018)
Analysis 1.3. Comparison 1 Adjunctive corticosteroids versus no such treatment, Outcome 3 Need for mechanical ventilation at 1 month.

Review: Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection

Comparison: 1 Adjunctive corticosteroids versus no such treatment

Outcome: 3 Need for mechanical ventilation at 1 month

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozzette 1990</td>
<td>5/123</td>
<td>15/128</td>
<td>0.35 [ 0.13, 0.93 ]</td>
<td>42.6%</td>
<td></td>
</tr>
<tr>
<td>Nielsen 1992</td>
<td>3/30</td>
<td>12/29</td>
<td>0.24 [ 0.08, 0.77 ]</td>
<td>30.6%</td>
<td></td>
</tr>
<tr>
<td>Walmsley 1995</td>
<td>4/40</td>
<td>5/38</td>
<td>0.76 [ 0.22, 2.62 ]</td>
<td>26.8%</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>193</td>
<td>195</td>
<td>0.38 [ 0.20, 0.73 ]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 12 (Treatment), 32 (Control)

Heterogeneity: Tau² = 0.0; Chi² = 1.83, df = 2 (P = 0.40); I² = 0.0%

Test for overall effect: Z = 2.94 (P = 0.0033)

WHAT’S NEW

Last assessed as up-to-date: 23 May 2006.

Date | Event | Description
--- | --- | ---
29 October 2008 | Amended | Converted to new review format.

HISTORY

Review first published: Issue 3, 2006

Date | Event | Description
--- | --- | ---
24 May 2006 | New citation required and conclusions have changed | Substantive amendment
CONTRIBUTIONS OF AUTHORS

MB and HCB conceived of the study and performed the literature search. MB, HCB, RB and HF checked eligibility and quality of trials, and extracted the necessary data. 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.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans