Author's response to reviews

Title: Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection: a meta-analysis of randomised controlled trials

Authors:

Matthias Briel (brielm@uhbs.ch)
Remy Boscacci (remy.boscacci@insel.ch)
Hansjakob Furrer (hansjakob.furrer@insel.ch)
Heiner C Bucher (hbucher@uhbs.ch)

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Author's response to reviews: see over
Dear Editor

We would like to thank you for reviewing our manuscript and for reconsidering a revised version for publication in BMC Infectious Diseases. We carefully addressed all the points raised by the reviewers in the point by point reply and thank them for their work. We also went through the manuscript formatting checklist to ensure that the revised manuscript conforms to all of the points. All contributors have approved this revised version of the manuscript and fulfil criteria for authorship.

We hope that this revision meets your and the reviewers’ expectations and that it can be accepted for publication in the present form. We are looking forward to your reply.

Yours sincerely

Dr. Matthias Briel
Basel Institute for Clinical Epidemiology
University Hospital Basel
CH-4031 Basel, Switzerland

Phone 0041-61-265 3100
Fax 0041-61-265 3109
Email brielm@uhbs.ch
Point by point reply:
MS: 1993399006731207
First revision: Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection: a meta-analysis of randomised controlled trials

Comments from Reviewer #1 (Raymond A Smego)

Minor Essential Revisions:

1.) Suggest re-wording Objective statement in the Abstract: To review the effects of adjunctive corticosteroids on overall mortality and the need for mechanical ventilation in HIV-infected patients.

Reply: We re-phrased the first paragraph of the Abstract as the reviewer suggested and added information to define the term “substantial hypoxemia”. In the revised manuscript it reads now as follows (page 2):

The objective of this study was to review the effects of adjunctive corticosteroids on overall mortality and the need for mechanical ventilation in HIV-infected patients with Pneumocystis jiroveci pneumonia (PCP) and substantial hypoxemia (arterial oxygen partial pressure <70 mmHg or alveolar-arterial gradient >35 mmHg on room air).

2.) Methods, Study Selection and Data Abstraction, sentence 2: Suggest re-wording: We exclude trials with patients with no or mild hypoxemia.

Reply: We re-worded the respective sentence as the reviewer suggested. Page 4, paragraph 2, sentence 2 of the revised manuscript:

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.

3.) Discussion, page 8, line 1: Suggest changing to: There has been some concern.

Reply: We changed the respective sentence as the reviewer suggested. Page 7, paragraph 2, sentence 1 of the revised manuscript:

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 [22,23].

4.) Discussion, page 8, last word: Would change missing to lacking.
Reply: We changed “missing” to “lacking”; Page 7, paragraph 3, last sentence (Discussion) of the revised manuscript:

Moreover, corticosteroids might also be beneficial for non-HIV-infected patients with severe PCP [25], but evidence from randomised controlled trials is still lacking.

5.) Suggest changing systematic review to meta-analysis on page 8 (Conclusions).

Reply: We re-phrased the first sentence of the Conclusion section (page 8, revised manuscript) accordingly:

This meta-analysis confirmed and quantified the benefit of adjunctive corticosteroid therapy in HIV-infected patients with moderate-severe PCP.

6.) Results, Overall Mortality, line 1: Delete statistically.

Reply: We deleted “statistically” on page 5, paragraph 3, sentence 1.

7.) Suggest deleting table of excluded trials.

Reply: We would prefer to keep the table as a supplemental file, because we want to make our study selection more transparent to the reader. Reviewer #3 appreciated the table and considered it helpful.
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Comments from Reviewer #2 (Thomas Benfield)

Discretionary Revisions:

The authors might add in the discussion that a proven beneficial effect of early antiretroviral therapy during acute PCP awaits the results of controlled clinical trials, i.e. available data is from observational studies. Therefore the NNT may be biased.

Reply: The reviewer is correct, there is no evidence of benefit from RCTs for early antiretroviral treatment in patients with PCP. Estimates from observational studies indicate that mortality in patients with severe PCP was much lower when HAART was started early (Morris A et al. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe Pneumocystis carinii pneumonia AIDS, 2003 Jan 3;17(1):73-80). We believe, however, that the estimate of 10% for mortality from PCP [21] is a realistic one to illustrate the expected benefit from use of corticosteroids with HAART available. Therefore we would like to keep the current wording.
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Comments from Reviewer #3 (Henry Koziel)

Minor Essential Revisions:

1.) Abstract: Under the “Conclusions” section, the authors should define “substantial hypoxemia.” The term “substantial hypoxemia” is too vague. Providing the pO2 and/or A-a gradient would provide more useful information.

Reply: Please see reply to point 1.), Reviewer #1.

Discretionary Revisions:

2.) The Table provided as supplemental information, indicating the 2 excluded studies is helpful. However, I would encourage the authors to expand the table to also include the 6 studies included in the meta-analysis. In addition to the specific parameters reported in the author’s Table of Excluded Trials, the new table should also include the number of subjects randomised to each treatment group, the corticosteroid dosing regimen and schedule used in the study, the timing for initiating corticosteroid, need for mechanical ventilation, 1-month mortality and 3-4 month mortality. If space allows, the new table should be included in the body of the manuscript rather than as Supplemental data. Such a table would very clearly highlight the essential information reported by each published randomised study, and allow the readers to better appreciate the variability in the clinical approach to corticosteroid use (as the consensus recommendation for the corticosteroid dosing is based on the largest randomised study, but the optimal corticosteroid dosing schedule has not yet been established).

Reply: In our Table 1 (Characteristics of included trials) we included information about the number of subjects randomised to each treatment group, the corticosteroid dosing regimen and schedule used in each trial, the timing for initiating corticosteroids, and clinical outcomes at specific time-points for each trial. We think that the Table of excluded studies should primarily make our study selection more transparent, but in our view it does not contribute essential information. Therefore we would like to suggest it as a supplemental file.