

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

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| TITLE (PROVISIONAL) | Corticosteroids in sepsis: An updated systematic review and meta-analysis (protocol) |
| AUTHORS | Rochweg, Bram; Oczkowski, Simon; Siemieniuk, Reed; Menon, Kusum; Szczeklik, W; English, Shane; Agoritsas, Thomas; Belley-Coté, E; D'Aragon, Frédérick; Alhazzani, Waleed; Duan, Erick; Gossack-Keenan, Kira; Sevransky, Jon; Vandvik, Per; Venkatesh, Bala; Guyatt, Gordon; Annane, D |

VERSION 1 - REVIEW

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| REVIEWER | Peter Dodek Center for Health Evaluation and Outcome Sciences, St. Paul's Hospital and University of British Columbia, Canada I am a member of the RapidRecs team that will be developing a guideline based on this systematic review and meta-analysis. |
| REVIEW RETURNED | 24-Mar-2017 |

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| GENERAL COMMENTS | <p>General: This manuscript describes the protocol to be used for an updated systematic review and meta-analysis of the effect of corticosteroids for sepsis. The authors have addressed all of the items required in the PRISMA 2009 checklist, but there are several issues to be clarified.</p> <p>Specific:</p> <ol style="list-style-type: none">1. Title: It would be helpful to inform the reader that septic shock will also be examined. So perhaps the title could be, "Corticosteroids in sepsis and septic shock:".2. Abstract, line 8: delete, "represents" and substitute, "is". Delete "However".3. Abstract, line 12: please clarify which year the authors are referring to.4. Abstract, lines 18-20: Please clarify if the same search strategy as used in the previous study will be used in this one.5. Abstract, line 22: delete, "were" and substitute, "have been"; please define, "semi-independent".6. Abstract, line 38: delete, "were" and substitute, "have been".7. Abstract, line 40: insert, "updated" after "...summarize the".8. Page 4: The background seems long—parts of it could be moved to the very short Discussion section (e.g. details about the description of the intervention and how it works).9. Page 4, line 9: delete "vascular smooth muscle"10. Page 4, line 12: it would be helpful to define "septic shock" after the first time this term is used.11. Page 4, line 20: in light of the controversy about the changing incidence of sepsis, please cite one of the articles on this controversy (e.g. Rhee et al. Critical Care (2015) 19:338. DOI |
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| | <p>10.1186/s13054-015-1048-9).</p> <p>12. Page 4, line 38: Please cite some of the individual published trials at the end of this line and at the end of line 40.</p> <p>13. Page 4, line 44: Please clarify whether the main problem is true “cortisol deficiency” or decreased sensitivity of cortisol receptors, or both.</p> <p>14. Page 4, line 51: Please delete, “in the adrenal medulla”</p> <p>15. Page 4, line 56: Please insert, “agents that have” between “with” and “both”, and substitute, “activity” for “containing corticosteroids”.</p> <p>16. Page 5, line 6: Please insert, “administration of” between “for” and “corticosteroids”</p> <p>17. Page 5, line 12: “...suggested that steroids...”</p> <p>18. Page 5, line 13: “...in the evidence, and were limited by...”</p> <p>19. Page 5, line 16: “...suggested that patients...”</p> <p>20. Page 5, line 19: “...most recently published review (reference here), one additional...”. Delete “published” on that line.</p> <p>21. Page 5, line 20: please check the format for citation #13—it seems too ‘bulky’</p> <p>22. Page 5, line 26: Please substitute, “clinically” for “patient”</p> <p>23. Page 5, line 44: “...meta-analysis of all published RCTs that have investigated...”</p> <p>24. Page 6: Please delete “Types of” from subheadings</p> |
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| REVIEWER | <p>Neill Adhikari Sunnybrook Health Sciences Centre and University of Toronto, Canada</p> <p>I am on the BMJ RapidRecs panel for this topic and have provided input on the review protocol. My role as a reviewer was pre-approved by the BMJ Open editor.</p> |
| REVIEW RETURNED | 26-Mar-2017 |

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| GENERAL COMMENTS | <p>Rochwerg and colleagues have written a clear protocol for a systematic review of corticosteroids for sepsis, building on a previous high-quality Cochrane review.</p> <p>Minor comments:</p> <p>1) Suggest clarifying that the start date for the new search will be a database entry date of September 2014 or later (rather than a publication date of September 2014 or later, since there can be a delay of months between publication and database entry for smaller non-English journals).</p> <p>2) On page 8, change ‘Study weights will be measured using the inverse variance method’ to ‘Study weights will be generated using the inverse variance method’.</p> <p>3) In the subgroup section on page 9, I think the sign in the last sentence referring to the p-value threshold should be <.</p> <p>4) Consider referencing PMID 1303622 when referring to sepsis definitions used by trial authors, rather than only the 2001 and 2016 papers.</p> |
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| REVIEWER | <p>Matthias Briel University Hospital Basel, Switzerland</p> <p>I have published together with some of the authors (Siemieniuk R, Vandvik P, Guyatt G) in the past.</p> |
| REVIEW RETURNED | 31-Mar-2017 |

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| GENERAL COMMENTS | <p>Rochwerg and colleagues present a protocol of an update of a systematic review and meta-analysis that examines corticosteroids in patients with sepsis in randomized controlled trials. Overall, the protocol is comprehensive, well written and structured, and addresses an important clinical question. The rationale for the update is clearly presented and the methods appear sound. I have only a few minor comments and suggestions for improvement:</p> <p>Abstract:</p> <ul style="list-style-type: none"> - There is a discrepancy between a date mentioned in the abstract (“...Cochrane review on the same topic was comprehensive to October 2014.”) and one mentioned on page 7 (“...comprehensive to September 2014.”) - In the description of the guideline panel the methodologists are missing. - You could include in the first sentence of the third Methods paragraph that you plan to use a random effect model for pooling effect estimates. <p>Background:</p> <ul style="list-style-type: none"> - There is a typo in the first sentence of para 2 on page 5 – one “published” should be deleted. <p>Methods:</p> <ul style="list-style-type: none"> - Type of outcome measures: It remains unclear what you exactly mean by “28-day, 30-day, hospital, ICU mortality” – is it that you plan to use “28-day or 30-day hospital or ICU mortality (whatever is available)”? Please be more precise. - Why do you plan to use a “modified version of the Cochrane RoB tool”? In what way is it modified? - Page 8, second paragraph: The last number in the enumeration should be (4) instead of (2). <p>Discussion:</p> <ul style="list-style-type: none"> - Strengths and limitations of the systematic review could be briefly discussed. |
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| REVIEWER | Srinivas Murthy University of British Columbia Vancouver, Canada |
| REVIEW RETURNED | 28-Apr-2017 |

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| GENERAL COMMENTS | <p>The authors of this manuscript report their protocol for a systematic review and meta-analysis for the timely question of the role of corticosteroids in critically ill children and adults with sepsis. This builds upon multiple prior reviews, including a 2014 Cochrane review, examining the same question. The need for this review, which shares authors and design elements from the 2014 review, is to integrate new and upcoming randomized data, relevant to the question, so as to facilitate expedient reporting of systematic review/meta-analysis level data to the larger community. Hence, this is a valuable initiative.</p> <p>The protocol is well-written, the research team is experienced, and the reporting satisfies the criteria for systematic review protocols in terms of items described and analysis plans outlined. Some minor</p> |
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| | <p>comments for revision:</p> <ul style="list-style-type: none"> -Please include a PRISMA-P checklist, instead of PRISMA (available here: http://www.prisma-statement.org/Extensions/Protocols.aspx), for this protocol manuscript -The motivation for updating this review is clear, given new and accumulating evidence. However, given the imminent arrival of larger randomized data (NCT01448109, now completed recruitment), please outline a plan for ensuring that the results of the proposed review are able to be updated in a reasonably timely fashion. -the search strategy outlined in the appendix has no year limitations, but the text (page 7, line 6) states searches will be from September 2014 onwards. Please clarify. -Further, it is unclear from the Methods section if the quantitative analyses will be exclusive to included studies post-2014, or to all studies, including those in the original Cochrane review. Given the expanded outcome measures in this protocol, including quality-of-life, I presume that the authors will be performing primary data collection from pre-2014 studies, simply using the search results from the Cochrane review, but this should be clarified. <p>Typographic changes:</p> <ul style="list-style-type: none"> -Page 5, line 19: extra 'published' -Page 8, Line 14: re-number the RoB categories |
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Peter Dodek

Institution and Country

Center for Health Evaluation and Outcome Sciences, St. Paul's Hospital and University of British Columbia, Canada

Please state any competing interests or state 'None declared':

I am a member of the RapidRecs team that will be developing a guideline based on this systematic review and meta-analysis.

Please leave your comments for the authors below

General: This manuscript describes the protocol to be used for an updated systematic review and meta-analysis of the effect of corticosteroids for sepsis. The authors have addressed all of the items required in the PRISMA 2009 checklist, but there are several issues to be clarified.

**Thanks for your careful review of our protocol manuscript.

Specific:

1. Title: It would be helpful to inform the reader that septic shock will also be examined. So perhaps the title could be, "Corticosteroids in sepsis and septic shock:".

**In keeping with the new Sepsis-3 definitions, sepsis as a broader term includes septic shock. As such, we have not altered the title.

2. Abstract, line 8: delete, "represents" and substitute, "is". Delete "However". **Revised as suggested.

3. Abstract, line 12: please clarify which year the authors are referring to. **This has been revised for clarity and now reads (new wording underlined),

"Several large randomized controlled trials have been published recently prompting a re-evaluation of the available literature."

4. Abstract, lines 18-20: Please clarify if the same search strategy as used in the previous study will be used in this one.

**Thanks. Due to space limitations, we did not modify in the abstract but did add explicit clarification in the search section of the methods which now reads (new wording underlined),

"A search and screening process from a Cochrane review on the same topic was credible and comprehensive to September 2014. Using the same search strategy, we will search Medline, EMBASE, LILACS, and the Cochrane trial registry for RCTs..."

5. Abstract, line 22: delete, “were” and substitute, “have been”; please define, “semi-independent”.

**Revised as suggested. Due to space limitations we did not define semi-independent in the abstract but did add the following sentence to the methods under the Guideline Panel and Patient Involvement heading,

“The panel is considered semi-independent of the systematic review team as four individuals are members of both.”

6. Abstract, line 38: delete, “were” and substitute, “have been”.

**Revised as suggested.

7. Abstract, line 40: insert, ...summarize “updated” after “ the”.

**Revised as suggested.

8. Page 4: The background seems long—parts of it could be moved to the very short Discussion section (e.g. details about the description of the intervention and how it works).

**We appreciate the reviewer’s perspective and realize this may relate to style when considering protocol manuscripts. Our group’s preference is to leave this information in the background, in effect, setting the stage for the importance of this updated review.

9. Page 4, line 9: delete “vascular smooth muscle” **Revised as suggested.

10. Page 4, line 12: it would be helpful to define “septic shock” after the first time this term is used. **We have added the following sentence to the introduction,

“Septic shock is defined by the need for vasopressors to maintain a mean arterial pressure over 65mm Hg or greater and a serum lactate greater than 2 mmol/L in the absence of hypovolemia.”

11. Page 4, line 20: in light of the controversy about the changing incidence of sepsis, please cite one of the articles on this controversy (e.g. Rhee et al. Critical Care (2015) 19:338. DOI 10.1186/s13054-015-1048-9).

**Added as suggested.

12. Page 4, line 38: Please cite some of the individual published trials at the end of this line and at the end of line 40.

**Added as suggested.

13. Page 4, line 44: Please clarify whether the main problem is true “cortisol deficiency” or decreased sensitivity of cortisol receptors, or both.

**Unfortunately we are unsure which is the ‘main’ problem in this situation. As such, we have intentionally left vague but described the potential mechanisms.

14. Page 4, line 51: Please delete, “in the adrenal medulla” **Revised as suggested.

15. Page 4, line 56: Please insert, “agents that have” between “with” and “both”, and substitute, “activity” for “containing corticosteroids”.

**Revised as suggested.

16. Page 5, line 6: Please insert, “administration of” between “for” and “corticosteroids” **Revised as suggested.

17. Page 5, line 12: “...suggested...” that steroids

**Revised as suggested.

18. Page 5, line 13: “...in the evidence,...” and were limited by **Revised as suggested.

19. Page 5, line 16: “...suggested...” that patients

**Revised as suggested.

20. Page 5, line 19: "...most recently published..." review (reference here), one additional
Delete

"published" on that line.

**Revised as suggested.

21. Page 5, line 20: please check the format for citation #13—it seems too 'bulky' **Revised as suggested.

22. Page 5, line 26: Please substitute, "clinically" for "patient"

**Revised as suggested.

23. Page 5, line 44: "...meta -analysis of all..."published RCTs that have investigated

**Revised as suggested.

24. Page 6: Please delete "Types of" from subheadings

**Revised as suggested.

Reviewer: 2

Reviewer Name

Neill Adhikari

Institution and Country

Sunnybrook Health Sciences Centre and University of Toronto, Canada

Please state any competing interests or state 'None declared':

I am on the BMJ RapidRecs panel for this topic and have provided input on the review protocol. My role as a reviewer was pre-approved by the BMJ Open editor.

Please leave your comments for the authors below

Rochweg and colleagues have written a clear protocol for a systematic review of corticosteroids for sepsis, building on a previous high-quality Cochrane review.

Minor comments:

1) Suggest clarifying that the start date for the new search will be a database entry date of September 2014 or later (rather than a publication date of September 2014 or later, since there can be a delay of months between publication and database entry for smaller non-English journals).

**Thank you. We have clarified and the section in the methods now reads (new wording underlined),

“Using the same search strategy, we will search Medline, EMBASE, LILACS, and the Cochrane trial registry for RCTs investigating the use of corticosteroids in patients with sepsis from a database entry date of September 2014.”

2) On page 8, change ‘Study weights will be measured using the inverse variance method’ to ‘Study weights will be generated using the inverse variance method’.

**Revised as suggested.

3) In the subgroup section on page 9, I think the sign in the last sentence referring to the p-value threshold should be <.

**This has been corrected.

4) Consider referencing PMID 1303622 when referring to sepsis definitions used by trial authors, rather than only the 2001 and 2016 papers.

**Added as suggested.

Reviewer: 3

Reviewer Name

Matthias Briel

Institution and Country

University Hospital Basel, Switzerland

Please state any competing interests or state 'None declared':

I have published together with some of the authors (Siemieniuk R, Vandvik P, Guyatt G) in the past.

Please leave your comments for the authors below

Rochweg and colleagues present a protocol of an update of a systematic review and meta-analysis that examines corticosteroids in patients with sepsis in randomized controlled trials. Overall, the protocol is comprehensive, well written and structured, and addresses an important clinical question. The rationale for the update is clearly presented and the methods appear sound. I have only a few minor comments and suggestions for improvement:

Abstract:

- There is a discrepancy...Cochranebetwreviewena ondatethementionedsametopicin the abstract (“was comprehensive...comprehensivetoOctober2014toSeptember.”)andone 2014mentioned.”) on page 7 (“

**Thanks. We have revised the wording on page 7 to match the abstract (October 2014). We have structured our search to go back to September 2014 in order to not miss a potential gap in database indexing.

- In the description of the guideline panel the methodologists are missing.

**Added to the abstract as suggested.

- You could include in the first sentence of the third Methods paragraph that you plan to use a random effect model for pooling effect estimates.

**Added to the abstract as suggested.

Background:

- There is a typo in the first sentence of para 2 on page 5 – one “published” should be deleted.

**Thanks. This has been corrected.

Methods:

- Type of outcome measures: It remains unclear what you exactly mean by “28-day, 30-day, hospital, ICU mortality” – is it that you plan to use “28-day or 30-day hospital or ICU mortality (whatever is available)”? Please be more precise.

**For short term mortality we had intended to include whichever of these was reported in the individual trials. We have clarified this as suggested.

- Why do you plan to use a “modified version of the Cochrane RoB tool”? In what way is it modified?

**The Evidence Partners modified Cochrane RoB tool which is referenced after this sentence removes the option of ‘unclear’ from the Cochrane RoB domain assessments. Instead, each RoB domain is assessed as low, probably low, probably high, or high. Work from members of our research group found the ‘unclear’ option to be unhelpful to readers and that most systematic reviewers are able to judge these unclear assessments as probably low or probably high based on the information available (PMID: 22200346). These ratings are described on page 8.

- Page 8, second paragraph: The last number in the enumeration should be (4) instead of (2).

**Revised as suggested.

Discussion:

- Strengths and limitations of the systematic review could be briefly discussed.

**The discussion has been restructured to include strength and limitations as suggested by the reviewer. The 2nd paragraph now reads,

“Strengths of this protocol include a comprehensive search strategy of published and unpublished literature, a priori subgroup analysis plan, and inclusion of GRADE methodology to characterize the certainty in evidence and confidence in the estimates of effect. Results of this review will be accompanied by a BMJ Rapid Recommendation for front line clinicians. Limitations relate to the anticipated clinical heterogeneity of patients, corticosteroid regimes and outcome assessments from included studies.”

Reviewer: 4

Reviewer Name

Srinivas Murthy

Institution and Country

University of British Columbia

Vancouver, Canada

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

The authors of this manuscript report their protocol for a systematic review and meta-analysis for the timely question of the role of corticosteroids in critically ill children and adults with sepsis. This builds upon multiple prior reviews, including a 2014 Cochrane review, examining the same question. The need for this review, which shares authors and design elements from the 2014 review, is to integrate new and upcoming randomized data, relevant to the question, so as to facilitate expedient reporting of systematic review/meta-analysis level data to the larger community. Hence, this is a valuable initiative.

The protocol is well-written, the research team is experienced, and the reporting satisfies the criteria for systematic review protocols in terms of items described and analysis plans outlined. Some minor comments for revision:

-Please include a PRISMA-P checklist, instead of PRISMA (available here: <http://www.prisma-statement.org/Extensions/Protocols.aspx>), for this protocol manuscript

**We have completed the PRISMA-P checklist and uploaded the file as requested.

-The motivation for updating this review is clear, given new and accumulating evidence. However, given the imminent arrival of larger randomized data (NCT01448109, now completed recruitment), please outline a plan for ensuring that the results of the proposed review are able to be updated in a reasonably timely fashion.

****We plan to update the systematic review once these trial results are available. We have added a sentence to the discussion which now reads,**

“Also, as future trial results become available (eg. NCT01448109) we will be able to rapidly incorporate the results into this evidence summary.”

-the search strategy outlined in the appendix has no year limitations, but the text (page 7, line 6) states searches will be from September 2014 onwards. Please clarify.

****The search strategy in the appendix was run with limits only examining the relevant databases from September 2014 onwards. These limits do not show up in the actual search strategy itself but we have tried to clearly outline the search plan in the methods.**

-Further, it is unclear from the Methods section if the quantitative analyses will be exclusive to included studies post-2014, or to all studies, including those in the original Cochrane review. Given the expanded outcome measures in this protocol, including quality-of-life, I presume that the authors will be performing primary data collection from pre-2014 studies, simply using the search results from the Cochrane review, but this should be clarified.

****The reviewer is correct in their assumption. For de novo outcomes and subgroups we will go back to the individual studies that were included in the Cochrane review for further data abstraction. We have included the following sentence in the ‘data extraction’ section of the methods,**

“We will perform data collection on studies included in the previous review only for outcomes or subgroups that were not previously reported.”

Typographic changes:

-Page 5, line 19: extra 'published'

****Revised as suggested.**

-Page 8, Line 14: re-number the RoB categories

**Revised as suggested.

We are grateful for the opportunity to improve the presentation of our work and hope that we have addressed the suggestions and concerns raised through the peer -review and editorial review process.