## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The effects of low dose hydrocortisone and hydrocortisone plus fludrocortisone in adults with septic shock: a protocol for a systematic review and meta-analysis of individual participant data |
| **AUTHORS** | annane, djillali; PIRRACCHIO, Romain; Billot, Laurent; Waschka, Andre; Chevret, Sylvie; Cohen, Jeremy; Finfer, Simon; Gordon, Anthony; Hammond, Naomi; Myburgh, John; Venkatesh, Balasubramanian; Delaney, Anthony |

## VERSION 1 – REVIEW

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| **REVIEWER** | Amnon Schlegel, MD, PhD<br>University of Utah, USA |
| **REVIEW RETURNED** | 09-Jun-2020 |

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| **GENERAL COMMENTS** | The authors present a protocol for performing an individual-patient meta-analysis of hydrocortisone with or without fludrocortisone for septic shock. The protocol may arrive at some post-hoc insights that might serve as the basis for future trials.<br><br>Strengths:<br>1. Since ADRENAL and APROCCHSS arrived at conflicting aggregate results, and previous trials were similarly discordant, this individual subject analysis might reveal new hypotheses for future trials, and resolve the widely varying conclusions of the meta-analyses in refs. 8-15.<br>1. I hope this planned meta-analysis will serve to motivate attempting the authors' own scrapped FLUDRO trial (https://clinicaltrials.gov/ct2/show/NCT02069288), since it remains unknown whether mineralocorticoid activation alone would be clearly beneficial. The role of mineralocorticoid activation alone in treating septic shock is impossible to address without a trial of fludrocortisone alone (https://www.nejm.org/doi/full/10.1056/NEJMc1804993).<br>2.<br>3. The central weakness of the study (i.e., whether individual level data can be obtained across all the studies subjected to meta-analysis) is nicely conceded.<br>4. The meta-analysis will address whether dosing of hydrocortisone (bolus vs. continuous, duration and tapering) matter.<br>5. 28-day, 90-day, and 180-day mortality will be studied.<br>6. Appropriate statistical approaches (emerging consensus GLMM model approach applied in the "Data Analysis" section).<br><br>Concerns:<br>1. The highlights claim of priority (i.e. "the first") should be reconciled with the editors of BMJ Open: are priority statements |

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| | allowed? I confess I do not know. Likewise, the third point “the best assessment” should be moderated as “the best assessment with currently available data.”<br>2. Why oral hydrocortisone administration is excluded is unclear: this is a highly orally available drug, as is fludrocortisone, which is administered orally, only.<br>3. Chronic glucocorticoid use strikes me as an individual-patient detail that could be obtained and used to exclude subjects: they necessarily have iatrogenic central adrenal insufficiency and must be treated with stress-dose glucocorticoids anyway.<br>4. Similarly, persons taking fludrocortisone chronically for primary mineralocorticoid deficiency (i.e., as part of treatment of Addison disease or 21-alpha-hydroxylase deficiency), hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis), or for orthostatic hypotension lacking a clear biochemical diagnosis could be excluded. |

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| **REVIEWER** | Christian Scheer<br>Department of Anaesthesiology, University Medicine Greifswald, Germany |
| **REVIEW RETURNED** | 19-Jun-2020 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review the manuscript of Prof. Annane, Prof. Pirracchio and colleagues entitled "The effects of low dose hydrocortisone and hydrocortisone plus fludrocortisone in adults with septic shock: a protocol for a systematic review and meta-analysis of individual participant data"<br>The manuscript presents a protocol for a systematic review and meta-analysis of a very important and relevant topic. Such an investigation is absolutely welcome and could clarify an important question whether the usage of hydrocortison and fludrocortisone in adults with septic shock is evidence based or not.<br>The presented protocol is well written and the objective is very clear. General conditions including the risk of bias are extensively considered.<br>I have only minor comments.<br>I would like to encourage the authors to investigated not only patients with different severities based on total SOFA scores and lactate but also to look at differences regarding the needed catecholamine dosage. In other words, do patients with higher e.g. norepinephrine dosages benefit more from hydrocortisone/fludrocortisone than patients with less norepinephrine need? Maybe it is possible to give a norepinephrine threshold.<br>It would be also of interest, if patients who have especially cardiovascular dysfunction (high cardiovascular SOFA subscores) benefit more than patients with mainly other organ dysfunctions but maybe the same total SOFA score.<br>This investigation will shed light on many aspects and you will to a lot of analysis. Why will you not adjust for multiple testing? |

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| **REVIEWER** | Steven M. Lemieux<br>University of Saint Joseph School of Pharmacy and Physician Assistant Studies<br>United States of America |
| **REVIEW RETURNED** | 24-Jun-2020 |

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| **GENERAL COMMENTS** | This manuscript provides an exceptional overview of a protocol for a systematic review and individual patient data meta analysis that |

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| | will strive to provide clarity regarding the utility of corticosteroids in adult patients with septic shock. My comments are as follows:<br><br>-Analyzing variations in treatment response among subgroups of patients with differing times to the initiation of appropriate antimicrobial therapy would add valuable data. Similarly, analyzing variations in treatment response among subgroups of patients with differing times to the initiation of corticosteroids may also yield valuable information given the substantial differences observed in the time to initiation of corticosteroids in previously published literature (e.g. in ADRENAL, the average time to initiation of hydrocortisone was 20.9 hours with a standard deviation of 91.9 hours, whereas hydrocortisone was required to be administered within 24 hours in APROCCHSS).<br>-Additional effort should be made to ensure that septic shock patients who have a lactate > 2 mmol/L who are included in this individual patient data meta analysis do not exhibit hypovolemia in order to be consistent with the Sepsis-3 definition.<br>-Given that resolution of organ failure will be defined as a SOFA < 4, it is pertinent to provide additional details about how this will be determined if any component of a patient's SOFA score is missing.<br>-The investigators' search strategy includes a search of four databases (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Latin American & Caribbean Health Sciences Literature) rather than five as specified in the manuscript.<br>-In the analysis of number of days with hyperglycaemia as a secondary outcome, change the value of 180 g/dL to 180 mg/dL. |

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| **REVIEWER** | Fang Fang<br>West China Hospital, Sichuan University |
| **REVIEW RETURNED** | 25-Aug-2020 |

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| **GENERAL COMMENTS** | I have some comments and questions about a few aspects of this protocal.<br><br>1. In types of studies, "We will only include trials, which received an appropriate approval from a research ethics committee." I agree that a modern RCT should be approved by an ethics committee. However, corticosteroids used as adjuvant therapy for sepsis have been studied in RCTs for more than 50 years. The early RCTs are not forced to receive approval from the ethics committee. Thus, the authors may include these trials. Otherwise, they could do a sensitivity analysis to including trials which did not receive an appropriate approval from a research ethics committee<br>2. This study aims to assess the benefits and risks of hydrocortisone, with or without fludrocortisone for adults with septic shock.However, in types of participants, this study "trials that have included adults with sepsis or septic shock." Why will the authors incloud sepsis?<br>3. This study will search 5 five major electronic databases and annual meetings of<br>major critical care medicine symposia up to 2019. It is almost one year from now. The date should be updated to the end of 2020. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name
Amnon Schlegel, MD, PhD

Institution and Country
University of Utah, USA

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

Please leave your comments for the authors below The authors present a protocol for performing an individual-patient meta-analysis of hydrocortisone with or without fludrocortisone for septic shock. The protocol may arrive at some post-hoc insights that might serve as the basis for future trials.

Strengths:
1. Since ADRENAL and APROCCHSS arrived at conflicting aggregate results, and previous trials were similarly discordant, this individual subject analysis might reveal new hypotheses for future trials, and resolve the widely varying conclusions of the meta-analyses in refs. 8-15.
1. I hope this planned meta-analysis will serve to motivate attempting the authors' own scrapped FLUDRO trial (https://clicktime.symantec.com/3Y4KBa37MibAGuW1GE9zkLN6H2?u=https%3A%2F%2Fclinicaltrials.gov%2Fct2%2Fshow%2FNCT02069288), since it remains unknown whether mineralocorticoid activation alone would be clearly beneficial. The role of mineralocorticoid activation alone in treating septic shock is impossible to address without a trial of fludrocortisone alone (https://clicktime.symantec.com/34RSU2WdajtURavupweY1Hk6H2?u=https%3A%2F%2Fwww.nejm.org%2Fdoi%2Ffull%2F10.1056%2FNEJMc1804993).
2.
3. The central weakness of the study (i.e., whether individual level data can be obtained across all the studies subjected to meta-analysis) is nicely conceded.
4. The meta-analysis will address whether dosing of hydrocortisone (bolus vs. continuous, duration and tapering) matter.
5. 28-day, 90-day, and 180-day mortality will be studied.
6. Appropriate statistical approaches (emerging consensus GLMM model approach applied in the "Data Analysis" section).

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| Re: Thank you |

Concerns:
1. The highlights claim of priority (i.e. "the first") should be reconciled with the editors of BMJ Open: are priority statements allowed? I confess I do not know. Likewise, the third point "the best assessment" should be moderated as "the best assessment with currently available data."

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| Re: as suggested we have rephrased both sentences.<br>"This will be to the best of our knowledge the first individual-patient data meta-analysis on the use of hydrocortisone with or without fludrocortisone for septic shock." AND<br>"The analysis will provide the best assessment with currently available data on whether hydrocortisone…" |

2. Why oral hydrocortisone administration is excluded is unclear: this is a highly orally available drug, as is fludrocortisone, which is administered orally, only.

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| Re: In patients with septic shock (target population for this systematic review) the enteral route is not recommended whenever a drug can be administered intravenously, owing to the unpredictable risk of drug malabsorption in the context of gastric stasis and altered splanchnic perfusion. |

3. Chronic glucocorticoid use strikes me as an individual-patient detail that could be obtained and used to exclude subjects: they necessarily have iatrogenic central adrenal insufficiency and must be treated with stress-dose glucocorticoids anyway.

Re: We have added a subgroup analysis based on pre-existing conditions that might alter the HPA axis, rather than excluding these patients. The following sentence has been added page 17: “We will examine any variation in treatment response according to pre-existing conditions other than sepsis that are likely to be associated with altered hypothalamic-pituitary adrenal axis,”

4. Similarly, persons taking fludrocortisone chronically for primary mineralocorticoid deficiency (i.e., as part of treatment of Addison disease or 21-alpha-hydroxylase deficiency), hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis), or for orthostatic hypotension lacking a clear biochemical diagnosis could be excluded.
Re: We have added a subgroup analysis based on pre-existing conditions that might alter the HPA axis, rather than excluding these patients. The following sentence has been added page 17: “We will examine any variation in treatment response according to pre-existing conditions other than sepsis that are likely to be associated with altered hypothalamic-pituitary adrenal axis,”

Reviewer: 2
Reviewer Name
Christian Scheer

Institution and Country
Department of Anaesthesiology, University Medicine Greifswald, Germany

Please state any competing interests or state ‘None declared’:
None

Please leave your comments for the authors below Thank you for the opportunity to review the manuscript of Prof. Annane, Prof. Pirracchio and colleagues entitled "The effects of low dose hydrocortisone and hydrocortisone plus fludrocortisone in adults with septic shock: a protocol for a systematic review and meta-analysis of individual participant data"
The manuscript presents a protocol for a systematic review and meta-analysis of a very important and relevant topic. Such an investigation is absolutely welcome and could clarify an important question whether the usage of hydrocortison and fludrocortisone in adults with septic shock is evidence based or not.
The presented protocol is well written and the objective is very clear. General conditions including the risk of bias are extensively considered.

Re: thank you

I have only minor comments.
I would like to encourage the authors to investigated not only patients with different severities based on total SOFA scores and lactate but also to look at differences regarding the needed catecholamine dosage. In other words, do patients with higher e.g. norepinephrine dosages benefit more from hydrocortisone/fludrocortisone than patients with less norepinephrine need? Maybe it is possible to give a norepinephrine threshold.

Re: As highlighted by the reviewer this is an important question that we plan to address in subgroup analysis, as mentioned in the protocol page 16 section “subgroup analysis” “vasopressor-dependency (yes versus no, and by quartiles of baseline dose)” is the 3rd item of : “We will also examine any variation in response to treatment according to baseline prognosis factors including“

It would be also of interest, if patients who have especially cardiovascular dysfunction (high cardiovascular SOFA subscores) benefit more than patients with mainly other organ dysfunctions but maybe the same total SOFA score.

RE: we agree with the reviewer and have added this subgroup analysis (top of page 17)

This investigation will shed light on many aspects and you will to a lot of analysis. Why will you not adjust for multiple testing?

RE: We acknowledge the multiple tests and the increased risk of false positive findings. Our preference is not to formally adjust for multiplicity and instead have a clear outcome hierarchy (from primary to exploratory outcomes) together with a measured interpretation of significant findings. We have added the following sentence to the manuscript: "We will not adjust for multiple testing and consider findings from analyses other than the primary analysis of the primary outcome, as of exploratory nature." We have added the following 3 references 1. Rothman K.J. No adjustments are needed for multiple comparisons. Epidemiology. 1990; 1: 43-46; 2. Perneger T.V. What's wrong with Bonferroni adjustments. BMJ. 1998; 315: 1236-1238; 3. Feise R.J. Do multiple outcome measures require p-value adjustment?. BMC Med Res Methodol. 2002; 2: 8

Reviewer: 3
Reviewer Name
Steven M. Lemieux

Institution and Country
University of Saint Joseph School of Pharmacy and Physician Assistant Studies United States of America

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

Please leave your comments for the authors below This manuscript provides an exceptional overview of a protocol for a systematic review and individual patient data meta analysis that will strive to provide clarity regarding the utility of corticosteroids in adult patients with septic shock. My comments are as follows:

-Analyzing variations in treatment response among subgroups of patients with differing times to the initiation of appropriate antimicrobial therapy would add valuable data.

RE: we agree with the reviewer and have added this subgroup analysis (top of page 17)

Similarly, analyzing variations in treatment response among subgroups of patients with differing times to the initiation of corticosteroids may also yield valuable information given the substantial differences observed in the time to initiation of corticosteroids in previously published literature (e.g. in ADRENAL, the average time to initiation of hydrocortisone was 20.9 hours with a standard deviation of 91.9 hours, whereas hydrocortisone was required to be administered within 24 hours in APROCCHSS).

RE: we agree with the reviewer and have added this subgroup analysis (top of page 17) *:" We will examine any variation in treatment response according to timing of hydrocortisone initiation, i.e. within 24hours versus >24 hours of meeting trial's criteria of shock "*

-Additional effort should be made to ensure that septic shock patients who have a lactate > 2 mmol/L who are included in this individual patient data meta analysis do not exhibit hypovolemia in order to be consistent with the Sepsis-3 definition.

Re: as mentioned page 16, the first subgroup analysis will focus on patients with septic shock according to Sepsis 3 definition

-Given that resolution of organ failure will be defined as a SOFA < 4, it is pertinent to provide additional details about how this will be determined if any component of a patient's SOFA score is missing.

RE: given this is a secondary analysis, we will limit the analysis of SOFA scores to complete cases. We have added on bottom of page 15 the following sentence *"For the analysis on the outcome "recovery from organ failure" we will use only cases with complete data for SOFA score."*

-The investigators' search strategy includes a search of four databases (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Latin American & Caribbean Health Sciences Literature) rather than five as specified in the manuscript.

Re: this has been corrected

-In the analysis of number of days with hyperglycaemia as a secondary outcome, change the value of 180 g/dL to 180 mg/dL.

Re: this has been corrected

Reviewer: 4
Reviewer Name
Fang Fang

Institution and Country
West China Hospital, Sichuan University

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

Please leave your comments for the authors below I have some comments and questions about a few aspects of this protocal.

1. In types of studies, "We will only include trials, which received an appropriate approval from a research ethics committee." I agree that a modern RCT should be approved by an ethics committee. However, corticosteroids used as adjuvant therapy for sepsis have been studied in RCTs for more than 50 years. The early RCTs are not forced to receive approval from the ethics committee. Thus, the authors may include these trials. Otherwise, they could do a sensitivity analysis to including trials which did not receive an appropriate approval from a research ethics committee

Re: we respectfully disagree. Indeed, ethics in clinical research is mandated at the very least from the Declaration of Helsinki.

2. This study aims to assess the benefits and risks of hydrocortisone, with or without fludrocortisone for adults with septic shock. However, in types of participants, this study "trials that have included adults with sepsis or septic shock." Why will the authors incloud sepsis?

Re: Owing to the variability in the definition of sepsis and septic shock, and since we will use individual patients data we will be able to identify patients with septic shock as defined for this systematic analysis – see top of page 13 "Septic shock will be defined according to the definition used in each clinical trial. Each included patient will meet at least one of the following criteria
Systolic blood pressure <100 mmHg or mean arterial pressure <65 mm Hg after fluid resuscitation
Lactate > 2mmol/L
Requirement for vasopressors to maintain an adequate blood pressure.

3. This study will search 5 five major electronic databases and annual meetings of major critical care medicine symposia up to 2019. It is almost one year from now. The date should be updated to the end of 2020.

Re: we agree with the reviewer and search dates are from inception to September 2020. This information is included in Abstract and main text page 11

## VERSION 2 – REVIEW

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| **REVIEWER** | Amnon Schlegel, MD, PhD<br>University of Utah School of Medicine, USA |
| **REVIEW RETURNED** | 03-Oct-2020 |

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| **GENERAL COMMENTS** | The authors have addressed nearly all my concerns.<br><br>Regarding my point #4, the second solid bullet on p.17 addresses pre-existing glucocorticoid deficiency, but not mineralcorticoid deficiency (or chronic treatment with mineralocorticoid agonist, generally). Since this is a meta-analysis specifically hoping to assess the role of fludrocortisone in combination with hydrocortisone, the following bullet is incomplete:<br>"We will examine any variation in treatment response according to pre-existing conditions other than sepsis that are likely to be associated with altered hypothalamic-pituitary adrenal axis,"<br>I suggest changing this bullet to: "We will examine any variation in treatment response according to pre-existing conditions other than sepsis that are likely to be associated with altered hypothalamic-pituitary adrenal axis, the renin-angiotensing-aldosterone axis, or both:"<br>The bold mark-up draws your attention to my addition, but will be removed from the final version, of course. |

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| **REVIEWER** | Christian S. Scheer<br>Department of Anesthesiology, University Hospital of Greifswald, Greifswald, Germany |
| **REVIEW RETURNED** | 29-Sep-2020 |

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| **GENERAL COMMENTS** | Thank you very much for your adjustments and corrections.<br>I congratulate you on your well done protocol.<br>Good luck for your review and meta-analysis! |

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| **REVIEWER** | Steven M. Lemieux<br>University of Saint Joseph School of Pharmacy and Physician Assistant Studies<br>United States of America |
| **REVIEW RETURNED** | 06-Oct-2020 |

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| **GENERAL COMMENTS** | The authors were thorough in addressing both reviewer and editor feedback on this protocol for a systematic review and individual patient data meta analysis investigating the use of corticosteroids in septic shock. I have one comment to provide:<br>-In my original review of this protocol, I stated it would be essential to provide additional details regarding how resolution of organ failure would be determined if any component of a patient's SOFA score was missing given that resolution of organ failure is defined as a SOFA score of less than 4. In their response, the authors indicated they would limit their analysis to only cases with complete data for SOFA score. However, this clarification has not been added to the revised version of the protocol. Please add this information to the protocol so that these methods are made clear. |

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| **REVIEWER** | Fang Fang<br>West China Hospital, Sichuan University |
| **REVIEW RETURNED** | 29-Sep-2020 |

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| **GENERAL COMMENTS** | The authors have correctly responded to my concerns |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name
Amnon Schlegel, MD, PhD
Institution and Country
University of Utah School of Medicine, USA
Comments to the Author
The authors have addressed nearly all my concerns.

Regarding my point #4, the second solid bullet on p.17 addresses pre-existing glucocorticoid deficiency, but not mineralcorticoid deficiency (or chronic treatment with mineralocorticoid agonist, generally). Since this is a meta-analysis specifically hoping to assess the role of fludrocortisone in combination with hydrocortisone, the following bullet is incomplete:
"We will examine any variation in treatment response according to pre-existing conditions other than sepsis that are likely to be associated with altered hypothalamic-pituitary adrenal axis,"
I suggest changing this bullet to: "We will examine any variation in treatment response according to pre-existing conditions other than sepsis that are likely to be associated with altered hypothalamic-pituitary adrenal axis, **the renin-angiotensing-aldosterone axis, or both:**"
The bold mark-up draws your attention to my addition, but will be removed from the final version, of course.
Re: changed as proposed

Reviewer: 2
Reviewer Name
Christian S. Scheer
Institution and Country
Department of Anesthesiology, University Hospital of Greifswald, Greifswald, Germany

Comments to the Author
Thank you very much for your adjustments and corrections.
I congratulate you on your well done protocol.
Good luck for your review and meta-analysis!

Re: thank you

Reviewer: 3
Reviewer Name
Steven M. Lemieux
Institution and Country
University of Saint Joseph School of Pharmacy and Physician Assistant Studies United States of America

Comments to the Author
The authors were thorough in addressing both reviewer and editor feedback on this protocol for a systematic review and individual patient data meta analysis investigating the use of corticosteroids in septic shock. I have one comment to provide:
-In my original review of this protocol, I stated it would be essential to provide additional details regarding how resolution of organ failure would be determined if any component of a patient's SOFA score was missing given that resolution of organ failure is defined as a SOFA score of less than 4. In their response, the authors indicated they would limit their analysis to only cases with complete data for SOFA score. However, this clarification has not been added to the revised version of the protocol. Please add this information to the protocol so that these methods are made clear.

Re: added as requested (see penultimate paragraph page 15)

Reviewer: 4
Reviewer Name
Fang Fang
Institution and Country
West China Hospital, Sichuan University
Comments to the Author
The authors have correctly responded to my concerns

Re: thank you