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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

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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

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The **U**ti**l**i**t**y of **S**teroids in **Se**ptic **S**hock **i**ndividual **P**atient **D**ata **M**eta-**A**nalysis (ULYSSES IPDMA) Collaborators are listed in appendix 1

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Author contributions:

DA is the guarantor of the study. DA and RP were responsible for the conception of the study. DA and AD made substantial contributions to the conception and design of the study, drafting of the study protocol, substantial contributions to the analysis plan, revising the work critically for important intellectual content and providing approval for the final version to be published. LB and RP made substantial contributions to the trial design and

analytical plan, revising the work critically for important intellectual content and provided approval for the final version to be published. SC, AW, JC, SF, AG, NH, JM and BV made substantial contributions to the drafting of the study protocol, revised the work critically for important intellectual content and provided approval for the final version to be published.

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Abstract

Introduction

The benefits and risks of low dose hydrocortisone in patients with septic shock have been investigated in numerous randomized controlled trials and trial-level meta-analyses. Yet, the routine use of this treatment remains controversial. To overcome the limitations of previous meta-analyses inherent to the use of aggregate data, we will perform an individual patient data meta-analysis (IPDMA) on the effect of hydrocortisone with or without fludrocortisone compared to placebo or usual care on 90-day mortality and other outcomes in patients with septic shock.

Methods and analysis

To assess the benefits and risks of hydrocortisone, with or without fludrocortisone for adults with septic shock, we will search five major electronic databases (Cochrane Central Register of Controlled Trials-CENTRAL, MEDLINE, EMBASE and Latin American Caribbean Health Sciences Literature-LILACS), complimented by a search for unpublished trials. The primary analysis will compare hydrocortisone with or without fludrocortisone to placebo or no treatment in adult patients with septic shock. Secondary analyses will compare hydrocortisone to placebo (or usual care), hydrocortisone plus fludrocortisone to placebo (or usual care), and hydrocortisone versus hydrocortisone plus fludrocortisone. The primary outcome will be all cause mortality at 90-day. We will conduct both one-stage IPDMA using mixed-effect models and machine learning with targeted maximum likelihood analyses. We will assess the risk of bias related to unshared data and related to the quality of individual trial.

Ethics and dissemination

This individual patient data meta-analysis will use existing data from completed randomized clinical trials and will comply with the ethical and regulatory requirements regarding data sharing for each of the component trials. The findings of this study will be submitted for publication in a peer-review journal with straightforward policy for open access.

Key words:

adults – septic shock – corticosteroids - machine learning – individual patient data meta-analysis

Article Summary

Strengths and limitations of this study

- This will be the first individual-patient data meta-analysis on the use of hydrocortisone with or without fludrocortisone for septic shock.
- The use of individual patient data will allow estimation of subgroup effects based on patient level covariates.
- The analysis will provide the best assessment of the totality of available evidence on whether hydrocortisone with or without fludrocortisone confers benefits to patients with septic shock and to assess whether there is an optimal regimen for administration.
- The main limitations are regulatory barriers in accessing individual data from original trials, and technical barriers to combining individual patient data from the component trials.

Introduction

Rationale

Septic shock is a global health priority.[1] In 2017, there were about 49 million incident cases of sepsis worldwide and 11 million sepsis-related deaths, representing roughly one out of five of all global deaths.[2] There is a need for improved treatments for this unacceptably high mortality rate. The Surviving Sepsis Campaign[3] recommend that, in the first hour of sepsis recognition, physicians obtain blood cultures, administer broad-spectrum antibiotics, start appropriate fluid resuscitation, and begin vasopressors whenever needed. Beyond these core measures, there has been little change in the management of sepsis.

What has changed in recent years, has been the understanding that dysregulation of the host response to infection is key to understanding the pathophysiology of septic shock.[4] This dysregulated host response may be a therapeutic target to improve mortality in patients with septic shock. As early as the 1950s, physicians have used corticosteroids with clinical success in patients with severe infection not responding to antibiotic treatment.[5] Seventy years later, their use in the management of sepsis remains controversial. The fourth revision of the Surviving Sepsis Campaign guidelines suggested against the use of hydrocortisone except in patients poorly responsive to fluids and vasopressors.[3] Since this revision of the guidelines, two major trials have substantially contributed to the understanding of the benefits and risks of corticosteroids for adults with septic shock.[6 7] Both trials used a daily intravenous dose of 200 mg hydrocortisone for seven days without taper-off. The main differences in the trials' design included continuous infusion of hydrocortisone[7] versus intravenous bolus every 6 hours,[6] hydrocortisone alone [7] versus with fludrocortisone,[6] unspecified vasopressor-dependency [7] versus requirement for a minimal dose of ≥0.25 µg/kg/min or ≥1mg/h norepinephrine/epinephrine.,[6] and unspecified ventilator-dependency[7] versus need for mechanical ventilation. [6] These trials found similar benefits in terms of resolution of shock and organs dysfunction, of accelerating weaning off mechanical ventilation and reducing length of stay in the intensive care unit. They also found no evidence for serious adverse complications with corticosteroids. A mortality benefit with corticosteroids was only reported in APROCCHSS trial[7] but not in ADRENAL.[6]

Since 2018, eight trial-level meta-analyses have addressed the effects of corticosteroids in sepsis.[8-15] They have different designs including differences in trials eligibility criteria, search strategies and in statistical models. The number of included trials ranged from 14 to 61 and the number of participants ranged from 6,935 to 12,192. The relative risk (RR) of death in the short-term varied from 0.90 to 0.98, and the upper limit of the 95% confidence interval varied from 0.98 to 1.08. The magnitude and direction of the pooled RR of dying in the short-term were consistent across these meta-analyses in favoring corticosteroids but differed mainly by the presence of some imprecision in the point estimate. More recent meta-analyses found substantial heterogeneity in the results possibly explained by differences in type of participants (e.g. all ages versus adults only, all sepsis severity versus only septic shock or community-acquired pneumonia or sepsis and ARDS, and in treatments administration (hydrocortisone versus synthetic glucocorticoids, low versus high dose, short versus long course). Intravenous administration of hydrocortisone may be the most frequent prescribed regimen and people may use this drug in sepsis with or without shock.[16] A noteworthy limitation of these meta-analyses is the use of aggregate data, limiting the opportunity to harmonize outcome definitions across trials, adjust the estimated treatment effect on potential confounders and investigate different subgroups.

To address this significant drawback of earlier meta-analyses, we will perform a systematic review and individual patient data meta-analysis (IPDMA) from trials to assess the effect of intravenous hydrocortisone with or without fludrocortisone, compared to placebo or usual care on 90-day mortality and other outcomes in patients with septic shock.

Objectives

The primary objective of this IPDMA is to assess the effect on 90-day mortality of intravenous hydrocortisone therapy, with or without fludrocortisone, compared to placebo or usual care, in adults with septic shock.

Other objectives of this IPDMA include:

- To compare the effect on 90-day mortality of intravenous hydrocortisone therapy with or without fludrocortisone, for differing modes of hydrocortisone therapy;
    - Bolus compared to continuous infusion

- Tapered dosing compared to abrupt discontinuation
- Duration of treatment at full dose : fixed duration versus based on vasopressor-dependency

- To compare the effects of intravenous hydrocortisone therapy with or without fludrocortisone in adults with septic shock on secondary outcomes including 28-day and 180-day mortality, requirement for, and duration of organ support, resources utilization as measured by ICU and hospital length of stay, and serious adverse events.
- To compare the effect on 90-day mortality of intravenous hydrocortisone therapy with or without fludrocortisone in adults with septic shock in clinically important subgroups defined by;
  - age
  - sex
  - vasopressor-dependency
  - vasopressin administration
  - predicted mortality
  - SOFA score
  - arterial lactate concentrations and
  - etomidate exposure

Methods and analysis

This protocol follows the recommendations from the EQUATOR network statement on Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[17] and will allow the report of the completed study to comply with reporting items recommended in the PRISMA of Individual Participant Data (PRISMA IPD).[18]

Eligibility Criteria

Types of studies

We will consider only randomized trials. We will exclude quasi-randomized trials, trials with a crossover design or those for which the unit of randomization is not the patient. We will only include trials, which received an appropriate approval from a research ethics committee and where there was an appropriate method of obtaining consent.

Types of participants

We will consider trials that have included adults with sepsis or septic shock as defined in original studies. Trials of mixed population will be eligible whenever separate information will be available for the subset of patients with septic shock as defined in original studies. We will exclude trials in children or those performed in patients without sepsis.

Types of interventions and controls

We will consider trials in which the experimental intervention was intravenous hydrocortisone at a maximal daily dose of 400mg for at least 72 hours at full dose, whether given as intermittent bolus or as a continuous infusion, and whether tapered off or not. We will also consider trials that have investigated the combination of intravenous hydrocortisone and oral (or enteral) fludrocortisone. We will consider trials in which the comparator was a placebo, no treatment, or hydrocortisone alone when the experimental intervention was the combination of hydrocortisone to fludrocortisone. We will also consider trials that compared two doses of hydrocortisone or bolus versus continuous administration.

We will exclude trials that have investigated

1) corticosteroids other than hydrocortisone or fludrocortisone,
2) dosage of hydrocortisone higher than 400mg per day,
3) duration of hydrocortisone of less than 72 hours at full dose,
4) oral route of hydrocortisone.

We will also exclude trials for when we are unable to contact the primary author and/or sponsor or they refuse to share data. Nevertheless, in case of non-response or refusal, we will use published aggregated data and combine them to the IPDMA results in a sensitivity analysis, as described in the statistical plan.

Types of outcome measures

We will only consider trials for inclusion in this review that have information on crude mortality rates at any time point post randomisation.

Information sources

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, in progress). We will use the strategy of the recently completed Cochrane systematic review on the use of corticosteroids in sepsis.[9]

We will search the Cochrane Central Register of Controlled Trials (CENTRAL; 2019 Issue 12) using the search terms 'sepsis', 'septic shock', 'steroids' and 'corticosteroids'. We will also search (up to Dec 2019) MEDLINE, EMBASE and Latin American Caribbean Health Sciences Literature (LILACS) using the topic search terms in combination with the search strategy for identifying trials developed by The Cochrane Collaboration (Appendix 2).[19]

We will check the reference lists of all trials identified by these methods, and we will contact study authors to request individual published or unpublished data. We also will search the proceedings of annual meetings of major critical care medicine symposia, that is, Society of Critical Care Medicine (1998 to 2019), American Thoracic Society (1998 to 2019), International Symposium on Intensive Care and Emergency Medicine (1998 to 2019), American College of Chest Physicians and European Society of Intensive Care Medicine (1998 to 2019).

Search strategy

The full search strategy is available in Appendix 2

Study records

Selection processes and data management

We will perform all screening in duplicate with disagreements resolved by consensus and third-party adjudication when consensus could not be reached. After implementation of the search strategy, reviewers will work in pairs to screen all potentially relevant citations and references. Screening will be performed in two stages, initially reviewing titles and abstracts, and then full text for possibly relevant manuscripts. We will capture reasons for exclusion.

Obtaining individual patient data

One reviewer (DA) will contact the primary author and/or sponsor of all selected trials for potential agreement to share de-identified individual patient data from their trial for the purpose of this patient-level meta-analysis. They will define whether data will be freely available or only after application to and approval by a learned intermediary and whether we will require a data use agreement. In case of non-response or refusal, we will use published aggregated data and combine them to the IPDMA results in a sensitivity analysis. Data will be stored on a secure server hosted by University of Versailles SQY.

Data extraction and management

Two reviewers (RP and DA) will independently check data supplied for included trials for missing data, internal data consistency, randomization integrity (balance of patient characteristics at randomisation, pattern of randomisation), follow-up and censoring pattern. We will check summary tables with the trial protocol and latest trial report or publication. We will solve any discrepancies or unusual patterns with the study investigator. We will return a final copy of the form from each trial to the appropriate trial investigator for verification.

Data items

Specifically, with regards to the population of patients for the primary analysis, these will be adult patients with septic shock. Adults will be those 18 years or older at time of randomization. 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

1. Systolic blood pressure <100 mmHg or mean arterial pressure <65 mm Hg after fluid resuscitation
2. Lactate > 2mmol/L
3. Requirement for vasopressors to maintain an adequate blood pressure.

The intervention of interest is hydrocortisone, administered intravenously at a dose of less than 400mg per day, either in divided bolus doses, or as a continuous infusion. We will record the dose, the mode of administration, the duration of administration, and the mode of cessation, either tapered, or abruptly ceased. We will record whether fludrocortisone was administered, the dose and duration of administration. The details of the comparison group, either placebo or standard care will be recorded.

Outcomes and prioritization

The primary outcome measure for this meta-analysis will be 90-day all-cause mortality.

Secondary outcomes will include:

- All-cause mortality at ICU and hospital discharge, at 28 days and at 180 days,
- Time to resolution of organ failure (defined as a SOFA < 4), time to vasopressor withdrawal, and time to cessation of mechanical ventilation. We will also calculate organ-failure/vasopressor/mechanical ventilation free days (up to 28 day). Event free days will be calculated as the number of days alive from randomisation to day 28 and having a SOFA score<4, being off vasopressors, off mechanical ventilation. When death occurred before reaching a SOFA<4 or before being off vasopressor or mechanical ventilation, the number of event-free days will be zero. For these outcomes, we will consider only the first episode. Recovery from organ failure will be defined by a SOFA score<4 for at least 24 hours. Weaning from vasopressor will be defined by being off any dose of vasopressor/inotrope for at least 24 consecutive hours. Weaning from mechanical ventilation will be defined by being off any mode of respiratory support for at least 24 hours.
- Length of stay in the ICU and in the hospital,
- Superinfection, as defined by any new infection occurring >48 hours after randomization,
- Number of days with hyperglycaemia defined as, at least one episode of blood glucose levels >180g/dl in the corresponding 24 hours,

- Number of days with hypernatremia, defined as at least one episode of serum sodium concentration >150mmol/L in the corresponding 24 hours,
- Bleeding complications: gastroduodenal defined as any episode of gastroduodenal bleeding reported by the investigators of original studies, regardless the need for transfusion or haemostatic intervention
- Critical illness associated muscle weakness at the longest follow-up as defined in individual trials

Risk of bias in individual studies

Risk of bias will be assessed, independently and in duplicate, for each of the individual studies using a modified Cochrane risk of bias tool[20] that classifies risk of bias as "low", "probably low", "probably high", or "high" for each of the following domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting and other bias. We will rate the overall risk of bias as the highest risk attributed to any criterion. Reviewers will not contribute to risk of bias assessment for trials in which they have participated.

Data synthesis

Baseline patient characteristics will be presented by study and treatment group. For continuous variables, mean and standard deviation (SD) or median and interquartile range (IQR) will be reported, as appropriate. For categorical variables, the number of observations in each category and corresponding proportions will be reported. Patient characteristics across groups will be contrasted using nonparametric Kruskal-Wallis tests for continuous variables and chi-square or Fisher exact tests for categorical variables. Since earlier and later deaths may stem from qualitatively different processes, to provide a more comprehensive depiction of mortality, length of stay in the ICU or in the hospital will be reported in the overall population as well as in the subpopulation of survivors at day 90. All tests will be two-sided and conducted at significance level 0.05. No formal adjustment for multiple testing will be undertaken. Given the number of secondary outcomes and subgroup analyses to be performed, interpretation of p-values, beyond the primary outcome, will be undertaken very cautiously.

Data analysis

We will consider as the primary analysis, the comparison between hydrocortisone (with or without fludrocortisone) and placebo (or no treatment) on 90-day mortality for patients with septic shock,

Pre-specified secondary analyses will include all possible pairwise comparisons, namely, hydrocortisone versus placebo, hydrocortisone plus fludrocortisone versus placebo, hydrocortisone plus fludrocortisone versus hydrocortisone.

In order to increase the robustness of the results, we will perform two different statistical approaches, i.e. a one stage conventional meta-analysis and machine-learning targeted maximum likelihood analysis.

As suggested by different studies comparing one-stage to two-stage approaches[21 22] the conventional will be performed using a one-stage meta-analysis. In one-stage meta-analysis, all data from all studies are aggregated and the primary outcome is analyzed simultaneously by adopting a single statistical model that accounts for potential heterogeneity across studies.[23] Analyses will rely on generalized linear mixed effect models (GLMM) where both the intercept and the treatment effect will be treated as random variables with the study as the subject (i.e. a random study intercept and a random study-by-treatment interaction). For the primary outcome and for binary secondary outcomes, we will use a GLMM with a logit link function. Continuous secondary outcomes will be analysed using a GLMM with an identity link function. Our estimates of the average treatment effect will be adjusted for study (random effect), age, predicted mortality from SAPS2 or APACHE 2, SOFA, admission type (medical, elective surgery or emergent surgery), infection site infection type (hospital versus community acquired infection) and type of pathogen, baseline and increment in cortisol levels post corticotrophin, lactate levels, and need for mechanical ventilation (fixed effects). A study-by-treatment interaction term will be also be included in the model. For withdrawal of vasopressor therapy, withdrawal of mechanical ventilation, and recovery from organ failure (defined by a SOFA score <4 for at least 24 hours), cumulative event incidences will be estimated using a nonparametric estimator and will be compared using Gray's test, with death treated as a competing risk[24] and study used as random effect .[25]

We will also estimate the average treatment effect via a more flexible estimator, namely the targeted maximum likelihood estimator (TMLE).[26] In this analysis, different portions of the likelihood will be modelled using Super Learner and combined to produce a plug-in estimator of the average treatment effect that is consistent, double robust and asymptotically linear. We will use a Super Learner with a large library including

logistic regression models, stepwise regression models based on the Akaike information criterion, mixed logistic models with random effect to account for study-level and patient-level heterogeneity, multivariate adaptive regression splines, random forests, Bayesian generalized linear models, elastic net regularized generalized linear models, and gradient boosting, to estimate flexibly the relationship between mean outcome and covariates. For the pairwise comparisons between combinations of hydrocortisone, fludrocortisone and placebo, we will use network meta-analysis techniques[27] to assess the robustness of the results.

For binary outcomes, we will describe the average treatment effect using risk ratio (RR) or odds ratio (OR) estimate along with corresponding 95% CI and p-value. For continuous outcomes, we will describe the average treatment effect using mean difference (MD) estimate along with a corresponding 95% CI and p-value. We will test for qualitative interaction between treatment effect and subgroup of interest using the Gail and Simon interaction test.[28]

Subgroup analysis

We will perform, if data permit, the following subgroup analyses:

- We will examine treatment effect in the subgroup of patients meeting sepsis or septic shock criteria according to Sepsis 3 definition[4];
- We will also examine any variation in response to treatment according to baseline prognosis factors including
    - age (by quartiles),
    - sex,
    - vasopressor-dependency (yes versus no, and by quartiles of baseline dose),
    - vasopressin administration (yes or no),
    - predicted mortality from SAPSII or APACAHEII (by quartiles),
    - SOFA score (by quartiles),
    - arterial lactate levels (by quartiles) and
    - etomidate-free versus etomidate-exposed patients

- We will examine any variation in treatment response according to patient's adrenal status, i.e. responders to standard corticotrophin test (those whom stimulated cortisol levels increased by >9µg/dL from baseline value) versus non-responders to corticotrophin test, and
- we will examine any variation in response to treatment according to infection characteristics, i.e.
    - community versus hospital acquired,
    - medical vs. surgical, lung versus other sources of infection, and
    - gram negative versus gram positive versus polymicrobial.

Methods to assess bias

We will assess for the potential for publication bias or small study bias by inspection of funnel plots and the use of Egger's test. The potential bias introduced by the studies that could not be included in the analyses will be evaluated [29] by performing a two-stage meta-analysis aggregating the results obtained on shared data and treatment effect estimates published for unshared data, if data permit. Specifically, the available IPD will first be reduced to aggregated data using the modelling methods described above. Then, these aggregated data will be pooled with published aggregated data into a weighted average.[30 31] Heterogeneity will be assessed by using an estimate of Tau^2 generated from the one stage and two-stage models.

Confidence in cumulative evidence

We will present a summary of results and recommendations in accordance with the GRADE approach to assess the overall quality of the evidence.[32 33]

Consumer review:

This protocol is under review by sepsis survivors and stakeholders from the Australian Sepsis Network.[34]

Dissemination

We will report the findings according to the PRISMA-IPD statement.[18] We will share the findings from this IPDMA with primary authors and sponsors of included trials prior to submitting the results of this primary analysis for publication.

Publications Plan:

1. The study protocol including the statistical analysis plan will be published prior to publishing the results of the primary analysis
2. Upon completion of the primary analysis, the main manuscript will be submitted to one of the major clinical journals regardless of the results.
3. Sub-studies, as approved by the Executive Committee, can be published after the publication of the primary analysis. The Executive Committee will grant authorship depending on personal input but shall include appropriate acknowledgment of the included trials, site Investigators and the Clinical Trials Groups where appropriate.

Authorship Guidance:

In keeping with the ICMJE guidance (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), authors shall meet the following 4 criteria: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Authorships specifics:

For the principal publication the study will be conducted in the name of the **U**ti**l**i**ty** of Steroids in **Se**ptic **S**hock (ULYSSES) IPDMA investigators and acknowledge the included studies, and where appropriate, the Clinical Trials Groups. Where individuals' name is required for publication (e.g.: publication mast) the listing of authors

will be as follows: Prof Romain Pirracchio will be the first author, Prof Djillali Annane will be the second (listed as co-first) and corresponding author, followed by members of the writing committee, with Associate Professor Delaney as the senior author. The writing committee shall comprise the included trials' chief investigators and members of the executive committee who have contributed substantially to one or more of: trial design or management, or data analysis and meet the ICMJE criteria for authorship.[35]

Ethics

This planned IPDMA will use existing data from completed randomized controlled trials, reporting explicitly ethical approval of the original protocol and the process for obtaining patients consent.

Discussion

This IPDMA will provide the highest level of evidence about the benefit and risk of hydrocortisone therapy for adults with septic shock .[36 37] This collaborative group includes most of the principal investigators of trials on hydrocortisone for sepsis/septic shock, reducing the risk of sharing refusal. In contrast to trial-level meta-analyses, this IPDMA will permit clarifying the role of fludrocortisone and identifying the optimal modalities for corticosteroids administration in septic shock. In addition, it will help identifying subgroups of patients more likely to benefit from corticosteroids and those at high risk of harm. Finally, we will use the one-stage analysis and a machine learning with targeted maximum likelihood analysis (TMLE).[26] TMLE may reduce bias and increase efficiency and power when applied to treatment effect estimation in trials.[38] TMLE requires to model separately different parts of the likelihood. A wide variety of flexible regression algorithms including mixed-effect models may help mitigating the risk of model misspecification associated with standard regression approaches. The Super Learner (SL) [39] is an ensemble machine-learning algorithm that automatically constructs an optimal weighted combination estimator based on a collection of supplied candidate estimators. The SL yields an estimator that is mathematically guaranteed to perform essentially as well as or better than the best candidate among the ones it is built upon – this is significant since in practice which of the candidate estimators behaves best in a given problem and dataset is not known to the analyst.[39] In the context of IPDMA, as compared to GLMM, this approach may avoid any strong assumption about the functional form of the relationship between outcome and explanatory variables. It may help leverage the advantages of all candidate

learners such as GLMM. Finally, it may allow accounting for potential high-order interactions by including in the library highly flexible algorithms such as random forests. In this analysis, different portions of the likelihood will be modelled using SL and combined to produce a plug-in estimator of the average treatment effect that is consistent, double robust and asymptotically linear.

Conclusion.

This protocol outlines the rationale, methods, analysis plan and publication plan for an individual patient data meta-analysis to assess the effect of hydrocortisone, with and without fludrocortisone, on 90-day mortality and other outcomes in patients with septic shock.

Acknowledgment

We would like to thank the primary authors and sponsors that have provided access to their trial's database.

Conflict of interest

Djillali ANNANE: has received funding from French government to conduct trials that will be included in this systematic review (trials acronym: Ger-Inf-05; COIITSS, APROCCHS) – he received funding for FHU SEPSIS and RHU RECORDS research programs. The current IPDMA he was responsible for the Cochrane systematic review on corticosteroids for sepsis in children and adults, and this work will use part of data obtained in the Cochrane review.

Romain PIRRACCHIO : no conflict of interest

Laurent BILLOT : no conflict of interest

André WASCHKA : no conflict of interest

Sylvie CHEVRET : no conflict of interest

Jeremy COHEN: no conflict of interest

Simon FINFER: no conflict of interest

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Naomi HAMMOND: no conflict of interest

John MYBURGH: no conflict of interest

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Anthony DELANEY: no conflict of interest

Data statements

Data may be accessed only by written request to the primary author of individual studies that will be included in this individual patient data meta-analysis.

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Appendix 1

The **U**ti**l**i**t**y of **S**teroids in **Se**ptic **S**hock **i**ndividual **P**atient **D**ata **M**eta-**A**nalysis (ULYSSES IPDMA) Collaborators

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Appendix 1: Search strategy

1 Search strategy for CENTRAL

#1 MeSH descriptor: [Sepsis] explode all trees

#2 MeSH descriptor: [Shock, Septic] explode all trees

#3 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees

#4 MeSH descriptor: [Central Nervous System Bacterial Infections] explode all trees and with qualifier(s): [blood - BL, complications - CO, drug therapy - DT]

#5 MeSH descriptor: [Pneumonia] explode all trees

#6 MeSH descriptor: [Community-Acquired Infections] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#7 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#8 MeSH descriptor: [Acute Lung Injury] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#9 sepsis or (septic* NEAR/3 shock*)

#10 (bacterem* or bacteraem* or pyrexia or septicaem* or septicem*)

#11 SIRS or (Inflammatory next Response next Syndrome*)

#12 bacteria* NEAR infect* NEAR (blood* or serum or invas* or severe or systemic)

#13 ((community next acquired) or severe) NEAR pneumonia

#14 (acute or adult) NEAR/2 (respiratory NEAR/2 distress)

#15 (acute or adult) NEAR/2 (lung NEAR/2 injury)

#16 ARDS

#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees

#19 MeSH descriptor: [Hydrocortisone] explode all trees

#20 MeSH descriptor: [Cortisone] explode all trees

#21 MeSH descriptor: [Steroids] explode all trees

#22 corticosteroid* or steroid* or cortison* or hydrocortison*

#23 methylprednisolon* or (methyl next prednisolon*) or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*

#24 #18 or #19 or #20 or #21 or #22 or #23

#25 #17 and #24

#26 #25 in Trials

2 Search strategy for MEDLINE (Ovid SP)

1 exp Sepsis/

2 exp Shock, Septic/

3 Systemic Inflammatory Response Syndrome/

4 exp Bacteremia/

5 Bacterial Infections/bl, dt, co

6 Pneumonia/co, dt

7 Community-Acquired Infections/co, dt

8 Respiratory Distress Syndrome, Adult/co, dt

9 Acute Lung Injury/co, dt

10 (sepsis or septic*).mp.

11 (bacter?em* or septic?em* or pyrexia).mp.

12 (SIRS or Inflammatory Response Syndrome*).mp.

13 (bacteria* adj6 infect* adj6 (blood* or serum or invas* or severe or systemic)).mp.

14 ((community-acquired or severe) adj3 pneumonia).mp.

15 ((acute or adult) adj2 (respiratory adj2 distress)).mp.

16 ARDS.mp.

17 ((acute or adult) adj2 (lung adj2 injury)).mp.

18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 exp Adrenal Cortex Hormones/

20 exp Hydrocortisone/

21 (corticosteroid* or steroid* or cortison* or hydrocortison*).mp.

22 (methylprednisolon* or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*).mp.

23 19 or 20 or 21 or 22

24 18 and 23

25 ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

26 24 and 25

3 Search strategy for Embase (Ovid SP)

1 exp sepsis/

2 exp septic shock/

3 pneumonia/co, dt [Complication, Drug Therapy]

4 adult respiratory distress syndrome/co, dt [Complication, Drug Therapy]

5 acute lung injury/co, dt [Complication, Drug Therapy]

6 systemic inflammatory response syndrome/co, dt [Complication, Drug Therapy]

7 community acquired infection/co, dt [Complication, Drug Therapy]

8 (sepsis or (septic* adj5 shock) or (bacter?em* or pyrexia or septic?em*) or (SIRS or Inflammatory Response Syndrome*)).mp.

9 (bacteria* adj2 infect* adj2 (blood* or serum or invas* or severe or systemic)).mp.

10 (((community-acquired or severe) adj2 pneumonia) or ((acute or adult) adj1 (respiratory adj1 distress)) or ((acute or adult) adj1 (lung adj1 injury)) or ARDS).mp.

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12 steroid/

13 corticosteroid/

14 cortisone/

15 hydrocortisone/

16 (corticosteroid* or steroid* or cortison* or hydrocortison* or (methylprednisolon* or methyl prednisolon* or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*)).mp.

17 12 or 13 or 14 or 15 or 16

18 11 and 17

19 ((placebo or randomized controlled trial).sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animal not human).sh.

20 18 and 19

4 Search strategy for LILACS (via BIREME)

(sepsis OR septic$ OR SEPSIS OR SEPTIC OR SIRS OR "septic shock" OR "SEPTIC SHOCK/" OR SEPTICEMIA OR PNEUMONIA OR bact* OR "adult respiratory distress syndrome" OR "acute lung injury" OR "systemic inflammatory response syndrome" OR "bacterial infection" OR "community acquired infection") (corticosteroid* OR steroid* OR glucocorticoid* OR CORTCOSTEROID* OR GLUCOCORTICOID/ OR STEROID OR MINERALOCORTICOID OR cortison* OR hydrocortison* OR fludrocortison* OR betamethason* OR methylprednisolon* OR prednison* OR dexamethason*)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	3
Support:			
Sources	5a	Indicate sources of financial or other support for the review	3
Sponsor	5b	Provide name for the review funder and/or sponsor	3
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	3
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the	9,10

		review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11, appendix 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11,12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12,13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13,14
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14,15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15,16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	17

Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17

BMJ Open

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

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Complete List of Authors:	annane, djillali; Versailles Saint-Quentin-en-Yvelines University, School of medicine; Universite Paris-Saclay PIRRACCHIO, Romain; Zuckerberg San Francisco General Hospital and Trauma Center Billot, Laurent; The George Institute for Global Health, Statistics Division Waschka, Andre; University of California Berkeley Chevret, Sylvie; University of Paris Cohen, Jeremy; University of Queensland, Finfer, Simon; The George Institute for Global Health Gordon, Anthony; Imperial College London, 1. Section of Anaesthetics, Pain Medicine and Intensive Care Hammond, Naomi ; George Institute for Global Health, Myburgh, John; University of New South Wales, St George Clinical School Venkatesh, Balasubramanian; Royal Brisbane and Women's Hospital Delaney, Anthony; The George Institute for Global Health
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Emergency medicine, Infectious diseases, Pharmacology and therapeutics
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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

Registration:

Prospero registration number CRD42017062198

Authors:

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DA is the guarantor of the study. DA and RP were responsible for the conception of the study. DA and AD made substantial contributions to the conception and design of the study, drafting of the study protocol, substantial contributions to the analysis plan, revising the work critically for important intellectual content and providing approval for the final version to be published. LB and RP made substantial contributions to the trial design and analytical plan, revising the work critically for important intellectual content and provided approval for the final version to be published. SC, AW, JC, SF, AG, NH, JM and BV made substantial contributions to the drafting of

the study protocol, revised the work critically for important intellectual content and provided approval for the final version to be published.

Ammendments:

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Abstract

Introduction

The benefits and risks of low dose hydrocortisone in patients with septic shock have been investigated in numerous randomized controlled trials and trial-level meta-analyses. Yet, the routine use of this treatment remains controversial. To overcome the limitations of previous meta-analyses inherent to the use of aggregate data, we will perform an individual patient data meta-analysis (IPDMA) on the effect of hydrocortisone with or without fludrocortisone compared to placebo or usual care on 90-day mortality and other outcomes in patients with septic shock.

Methods and analysis

To assess the benefits and risks of hydrocortisone, with or without fludrocortisone for adults with septic shock, we will search major electronic databases from inception to September 2020 (Cochrane Central Register of Controlled Trials-CENTRAL, MEDLINE, EMBASE and Latin American Caribbean Health Sciences Literature-LILACS), complimented by a search for unpublished trials. The primary analysis will compare hydrocortisone with or without fludrocortisone to placebo or no treatment in adult patients with septic shock. Secondary analyses will compare hydrocortisone to placebo (or usual care), hydrocortisone plus fludrocortisone to placebo (or usual care), and hydrocortisone versus hydrocortisone plus fludrocortisone. The primary outcome will be all cause mortality at 90-day. We will conduct both one-stage IPDMA using mixed-effect models and machine learning with targeted maximum likelihood analyses. We will assess the risk of bias related to unshared data and related to the quality of individual trial.

Ethics and dissemination

This individual patient data meta-analysis will use existing data from completed randomized clinical trials and will comply with the ethical and regulatory requirements regarding data sharing for each of the component trials. The findings of this study will be submitted for publication in a peer-review journal with straightforward policy for open access.

The protocol for this systematic review has been registered on PROPSPERO on April 6th 2017

Key words:

adults – septic shock – corticosteroids - machine learning – individual patient data meta-analysis

Article Summary

Strengths and limitations of this study

- 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.
- The use of individual patient data will allow estimation of subgroup effects based on patient level covariates.
- The analysis will provide the best assessment with currently available data on whether hydrocortisone with or without fludrocortisone confers benefits to patients with septic shock and to assess whether there is an optimal regimen for administration.
- The main limitations are regulatory barriers in accessing individual data from original trials, and technical barriers to combining individual patient data from the component trials.

Introduction

Rationale

Septic shock is a global health priority.[1] In 2017, there were about 49 million incident cases of sepsis worldwide and 11 million sepsis-related deaths, representing roughly one out of five of all global deaths.[2] There is a need for improved treatments for this unacceptably high mortality rate. The Surviving Sepsis Campaign[3] recommend that, in the first hour of sepsis recognition, physicians obtain blood cultures, administer broad-spectrum antibiotics, start appropriate fluid resuscitation, and begin vasopressors whenever needed. Beyond these core measures, there has been little change in the management of sepsis.

What has changed in recent years, has been the understanding that dysregulation of the host response to infection is key to understanding the pathophysiology of septic shock.[4] This dysregulated host response may be a therapeutic target to improve mortality in patients with septic shock. As early as the 1950s, physicians have used corticosteroids with clinical success in patients with severe infection not responding to antibiotic treatment.[5] Seventy years later, their use in the management of sepsis remains controversial. The fourth revision of the Surviving Sepsis Campaign guidelines suggested against the use of hydrocortisone except in patients poorly responsive to fluids and vasopressors.[3] Since this revision of the guidelines, two major trials have substantially contributed to the understanding of the benefits and risks of corticosteroids for adults with septic shock.[6 7] Both trials used a daily intravenous dose of 200 mg hydrocortisone for seven days without taper-off. The main differences in the trials' design included continuous infusion of hydrocortisone[7] versus intravenous bolus every 6 hours,[6] hydrocortisone alone [7] versus with fludrocortisone,[6] unspecified vasopressor-dependency [7] versus requirement for a minimal dose of ≥0.25 µg/kg/min or ≥1mg/h norepinephrine/epinephrine.,[6] and unspecified ventilator-dependency[7] versus need for mechanical ventilation. [6] These trials found similar benefits in terms of resolution of shock and organs dysfunction, of accelerating weaning off mechanical ventilation and reducing length of stay in the intensive care unit. They also found no evidence for serious adverse complications with corticosteroids. A mortality benefit with corticosteroids was only reported in APROCCHSS trial[7] but not in ADRENAL.[6]

Since 2018, eight trial-level meta-analyses have addressed the effects of corticosteroids in sepsis.[8-15] They have different designs including differences in trials eligibility criteria, search strategies and in statistical models. The number of included trials ranged from 14 to 61 and the number of participants ranged from 6,935 to 12,192. The relative risk (RR) of death in the short-term varied from 0.90 to 0.98, and the upper limit of the 95% confidence interval varied from 0.98 to 1.08. The magnitude and direction of the pooled RR of dying in the short-term were consistent across these meta-analyses in favoring corticosteroids but differed mainly by the presence of some imprecision in the point estimate. More recent meta-analyses found substantial heterogeneity in the results possibly explained by differences in type of participants (e.g. all ages versus adults only, all sepsis severity versus only septic shock or community-acquired pneumonia or sepsis and ARDS, and in treatments administration (hydrocortisone versus synthetic glucocorticoids, low versus high dose, short versus long course). Intravenous administration of hydrocortisone may be the most frequent prescribed regimen and people may use this drug in sepsis with or without shock.[16] A noteworthy limitation of these meta-analyses is the use of aggregate data, limiting the opportunity to harmonize outcome definitions across trials, adjust the estimated treatment effect on potential confounders and investigate different subgroups.

To address this significant drawback of earlier meta-analyses, we will perform a systematic review and individual patient data meta-analysis (IPDMA) from trials to assess the effect of intravenous hydrocortisone with or without fludrocortisone, compared to placebo or usual care on 90-day mortality and other outcomes in patients with septic shock.

Objectives

The primary objective of this IPDMA is to assess the effect on 90-day mortality of intravenous hydrocortisone therapy, with or without fludrocortisone, compared to placebo or usual care, in adults with septic shock.

Other objectives of this IPDMA include:

- To compare the effect on 90-day mortality of intravenous hydrocortisone therapy with or without fludrocortisone, for differing modes of hydrocortisone therapy;
    - Bolus compared to continuous infusion

- Tapered dosing compared to abrupt discontinuation
- Duration of treatment at full dose : fixed duration versus based on vasopressor-dependency

- To compare the effects of intravenous hydrocortisone therapy with or without fludrocortisone in adults with septic shock on secondary outcomes including 28-day and 180-day mortality, requirement for, and duration of organ support, resources utilization as measured by ICU and hospital length of stay, and serious adverse events.
- To compare the effect on 90-day mortality of intravenous hydrocortisone therapy with or without fludrocortisone in adults with septic shock in clinically important subgroups defined by;
  - age
  - sex
  - vasopressor-dependency
  - vasopressin administration
  - predicted mortality
  - SOFA score
  - arterial lactate concentrations and
  - etomidate exposure

Methods and analysis

This protocol follows the recommendations from the EQUATOR network statement on Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[17] and will allow the report of the completed study to comply with reporting items recommended in the PRISMA of Individual Participant Data (PRISMA IPD).[18]

Eligibility Criteria

Types of studies

We will consider only randomized trials. We will exclude quasi-randomized trials, trials with a crossover design or those for which the unit of randomization is not the patient. We will only include trials, which received an appropriate approval from a research ethics committee and where there was an appropriate method of obtaining consent.

Types of participants

We will consider trials that have included adults with sepsis or septic shock as defined in original studies. Trials of mixed population will be eligible whenever separate information will be available for the subset of patients with septic shock as defined in original studies. We will exclude trials in children or those performed in patients without sepsis.

Types of interventions and controls

We will consider trials in which the experimental intervention was intravenous hydrocortisone at a maximal daily dose of 400mg for at least 72 hours at full dose, whether given as intermittent bolus or as a continuous infusion, and whether tapered off or not. We will also consider trials that have investigated the combination of intravenous hydrocortisone and oral (or enteral) fludrocortisone. We will consider trials in which the comparator was a placebo, no treatment, or hydrocortisone alone when the experimental intervention was the combination of hydrocortisone to fludrocortisone. We will also consider trials that compared two doses of hydrocortisone or bolus versus continuous administration.

We will exclude trials that have investigated

1) corticosteroids other than hydrocortisone or fludrocortisone,
2) dosage of hydrocortisone higher than 400mg per day,
3) duration of hydrocortisone of less than 72 hours at full dose,
4) oral route of hydrocortisone.

We will also exclude trials for when we are unable to contact the primary author and/or sponsor or they refuse to share data. Nevertheless, in case of non-response or refusal, we will use published aggregated data and combine them to the IPDMA results in a sensitivity analysis, as described in the statistical plan.

Types of outcome measures

We will only consider trials for inclusion in this review that have information on crude mortality rates at any time point post randomisation.

Information sources

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, in progress). We will use the strategy of the recently completed Cochrane systematic review on the use of corticosteroids in sepsis.[9]

We will search the Cochrane Central Register of Controlled Trials (CENTRAL; 2020 Issue 9) using the search terms 'sepsis', 'septic shock', 'steroids' and 'corticosteroids'. We will also search (up to September 2020) MEDLINE, EMBASE and Latin American Caribbean Health Sciences Literature (LILACS) using the topic search terms in combination with the search strategy for identifying trials developed by The Cochrane Collaboration (Appendix 1).[19]

We will check the reference lists of all trials identified by these methods, and we will contact study authors to request individual published or unpublished data. We also will search the proceedings of annual meetings of major critical care medicine symposia, that is, Society of Critical Care Medicine (1998 to 2020), American Thoracic Society (1998 to 2020), International Symposium on Intensive Care and Emergency Medicine (1998 to 2020), American College of Chest Physicians and European Society of Intensive Care Medicine (1998 to 2020).

Search strategy

The full search strategy is available in Appendix 1

Study records

Selection processes and data management

We will perform all screening in duplicate with disagreements resolved by consensus and third-party adjudication when consensus could not be reached. After implementation of the search strategy, reviewers will work in pairs to screen all potentially relevant citations and references. Screening will be performed in two stages, initially reviewing titles and abstracts, and then full text for possibly relevant manuscripts. We will capture reasons for exclusion.

Obtaining individual patient data

One reviewer (DA) will contact the primary author and/or sponsor of all selected trials for potential agreement to share de-identified individual patient data from their trial for the purpose of this patient-level meta-analysis. They will define whether data will be freely available or only after application to and approval by a learned intermediary and whether we will require a data use agreement. In case of non-response or refusal, we will use published aggregated data and combine them to the IPDMA results in a sensitivity analysis. Data will be stored on a secure server hosted by University of Versailles SQY.

Data extraction and management

Two reviewers (RP and DA) will independently check data supplied for included trials for missing data, internal data consistency, randomization integrity (balance of patient characteristics at randomisation, pattern of randomisation), follow-up and censoring pattern. We will check summary tables with the trial protocol and latest trial report or publication. We will solve any discrepancies or unusual patterns with the study investigator. We will return a final copy of the form from each trial to the appropriate trial investigator for verification.

Data items

Specifically, with regards to the population of patients for the primary analysis, these will be adult patients with septic shock. Adults will be those 18 years or older at time of randomization. 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

1. Systolic blood pressure <100 mmHg or mean arterial pressure <65 mm Hg after fluid resuscitation
2. Lactate > 2mmol/L
3. Requirement for vasopressors to maintain an adequate blood pressure.

The intervention of interest is hydrocortisone, administered intravenously at a dose of less than 400mg per day, either in divided bolus doses, or as a continuous infusion. We will record the dose, the mode of administration, the duration of administration, and the mode of cessation, either tapered, or abruptly ceased. We will record whether fludrocortisone was administered, the dose and duration of administration. The details of the comparison group, either placebo or standard care will be recorded.

Outcomes and prioritization

The primary outcome measure for this meta-analysis will be 90-day all-cause mortality.

Secondary outcomes will include:

- All-cause mortality at ICU and hospital discharge, at 28 days and at 180 days,
- Time to resolution of organ failure (defined as a SOFA < 4), time to vasopressor withdrawal, and time to cessation of mechanical ventilation. We will also calculate organ-failure/vasopressor/mechanical ventilation free days (up to 28 day). Event free days will be calculated as the number of days alive from randomisation to day 28 and having a SOFA score<4, being off vasopressors, off mechanical ventilation. When death occurred before reaching a SOFA<4 or before being off vasopressor or mechanical ventilation, the number of event-free days will be zero. For these outcomes, we will consider only the first episode. Recovery from organ failure will be defined by a SOFA score<4 for at least 24 hours. Weaning from vasopressor will be defined by being off any dose of vasopressor/inotrope for at least 24 consecutive hours. Weaning from mechanical ventilation will be defined by being off any mode of respiratory support for at least 24 hours.
- Length of stay in the ICU and in the hospital,
- Superinfection, as defined by any new infection occurring >48 hours after randomization,
- Number of days with hyperglycaemia defined as, at least one episode of blood glucose levels >180mg/dl in the corresponding 24 hours,

- Number of days with hypernatremia, defined as at least one episode of serum sodium concentration >150mmol/L in the corresponding 24 hours,
- Bleeding complications: gastroduodenal defined as any episode of gastroduodenal bleeding reported by the investigators of original studies, regardless the need for transfusion or haemostatic intervention
- Critical illness associated muscle weakness at the longest follow-up as defined in individual trials

Risk of bias in individual studies

Risk of bias will be assessed, independently and in duplicate, for each of the individual studies using a modified Cochrane risk of bias tool[20] that classifies risk of bias as "low", "probably low", "probably high", or "high" for each of the following domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting and other bias. We will rate the overall risk of bias as the highest risk attributed to any criterion. Reviewers will not contribute to risk of bias assessment for trials in which they have participated.

Data synthesis

Baseline patient characteristics will be presented by study and treatment group. For continuous variables, mean and standard deviation (SD) or median and interquartile range (IQR) will be reported, as appropriate. For categorical variables, the number of observations in each category and corresponding proportions will be reported. Patient characteristics across groups will be contrasted using nonparametric Kruskal-Wallis tests for continuous variables and chi-square or Fisher exact tests for categorical variables. Since earlier and later deaths may stem from qualitatively different processes, to provide a more comprehensive depiction of mortality, length of stay in the ICU or in the hospital will be reported in the overall population as well as in the subpopulation of survivors at day 90. All tests will be two-sided and conducted at significance level 0.05. No formal adjustment for multiple testing will be undertaken. Given the number of secondary outcomes and subgroup analyses to be performed, interpretation of p-values, beyond the primary outcome, will be undertaken very cautiously.

Data analysis

We will consider as the primary analysis, the comparison between hydrocortisone (with or without fludrocortisone) and placebo (or no treatment) on 90-day mortality for patients with septic shock,

Pre-specified secondary analyses will include all possible pairwise comparisons, namely, hydrocortisone versus placebo, hydrocortisone plus fludrocortisone versus placebo, hydrocortisone plus fludrocortisone versus hydrocortisone.

In order to increase the robustness of the results, we will perform two different statistical approaches, i.e. a one stage conventional meta-analysis and machine-learning targeted maximum likelihood analysis.

As suggested by different studies comparing one-stage to two-stage approaches[21 22] the conventional will be performed using a one-stage meta-analysis. In one-stage meta-analysis, all data from all studies are aggregated and the primary outcome is analyzed simultaneously by adopting a single statistical model that accounts for potential heterogeneity across studies.[23] Analyses will rely on generalized linear mixed effect models (GLMM) where both the intercept and the treatment effect will be treated as random variables with the study as the subject (i.e. a random study intercept and a random study-by-treatment interaction). For the primary outcome and for binary secondary outcomes, we will use a GLMM with a logit link function. Continuous secondary outcomes will be analysed using a GLMM with an identity link function. Our estimates of the average treatment effect will be adjusted for study (random effect), age, predicted mortality from SAPS2 or APACHE 2, SOFA, admission type (medical, elective surgery or emergent surgery), infection site infection type (hospital versus community acquired infection) and type of pathogen, baseline and increment in cortisol levels post corticotrophin, lactate levels, and need for mechanical ventilation (fixed effects). A study-by-treatment interaction term will be also be included in the model. For withdrawal of vasopressor therapy, withdrawal of mechanical ventilation, and recovery from organ failure (defined by a SOFA score <4 for at least 24 hours), cumulative event incidences will be estimated using a nonparametric estimator and will be compared using Gray's test, with death treated as a competing risk[24] and study used as random effect .[25] 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.[26-28]

We will also estimate the average treatment effect via a more flexible estimator, namely the targeted maximum likelihood estimator (TMLE).[29] In this analysis, different portions of the likelihood will be modelled

using Super Learner and combined to produce a plug-in estimator of the average treatment effect that is consistent, double robust and asymptotically linear. We will use a Super Learner with a large library including logistic regression models, stepwise regression models based on the Akaike information criterion, mixed logistic models with random effect to account for study-level and patient-level heterogeneity, multivariate adaptive regression splines, random forests, Bayesian generalized linear models, elastic net regularized generalized linear models, and gradient boosting, to estimate flexibly the relationship between mean outcome and covariates. For the pairwise comparisons between combinations of hydrocortisone, fludrocortisone and placebo, we will use network meta-analysis techniques[30] to assess the robustness of the results.

For binary outcomes, we will describe the average treatment effect using risk ratio (RR) or odds ratio (OR) estimate along with corresponding 95% CI and p-value. For continuous outcomes, we will describe the average treatment effect using mean difference (MD) estimate along with a corresponding 95% CI and p-value. We will test for qualitative interaction between treatment effect and subgroup of interest using the Gail and Simon interaction test.[31]

Subgroup analysis

We will perform, if data permit, the following subgroup analyses:

- We will examine treatment effect in the subgroup of patients meeting sepsis or septic shock criteria according to Sepsis 3 definition[4];
- We will also examine any variation in response to treatment according to baseline prognosis factors including
    - age (by quartiles),
    - sex,
    - vasopressor-dependency (yes versus no, and by quartiles of baseline dose),
    - vasopressin administration (yes or no),
    - predicted mortality from SAPSII or APACAHEII (by quartiles),
    - SOFA score and each of its component (by quartiles),
    - arterial lactate levels (by quartiles) and

- etomidate-free versus etomidate-exposed patients
- appropriate antibiotic treatment

- We will examine any variation in treatment response according to patient's adrenal status, i.e. responders to standard corticotrophin test (those whom stimulated cortisol levels increased by >9µg/dL from baseline value) versus non-responders to corticotrophin test,
- 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,
- 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, and
- we will examine any variation in response to treatment according to infection characteristics, i.e.
  - community versus hospital acquired,
  - medical vs. surgical, lung versus other sources of infection, and
  - gram negative versus gram positive versus polymicrobial.

Methods to assess bias

We will assess for the potential for publication bias or small study bias by inspection of funnel plots and the use of Egger's test. The potential bias introduced by the studies that could not be included in the analyses will be evaluated [32] by performing a two-stage meta-analysis aggregating the results obtained on shared data and treatment effect estimates published for unshared data, if data permit. Specifically, the available IPD will first be reduced to aggregated data using the modelling methods described above. Then, these aggregated data will be pooled with published aggregated data into a weighted average.[33 34] Heterogeneity will be assessed by using an estimate of Tau^2 generated from the one stage and two-stage models.

Confidence in cumulative evidence

We will present a summary of results and recommendations in accordance with the GRADE approach to assess the overall quality of the evidence.[35 36]

Patient and Public involvment:

This protocol is under review by sepsis survivors and stakeholders from the Australian Sepsis Network.[37]

Ethics and Dissemination

Ethics

This planned IPDMA will use existing data from completed randomized controlled trials, reporting explicitly ethical approval of the original protocol and the process for obtaining patients consent.

Publications Plan:

We will report the findings according to the PRISMA-IPD statement.[18] We will share the findings from this IPDMA with primary authors and sponsors of included trials prior to submitting the results of this primary analysis for publication.

1. The study protocol including the statistical analysis plan will be published prior to publishing the results of the primary analysis
2. Upon completion of the primary analysis, the main manuscript will be submitted to one of the major clinical journals regardless of the results.
3. Sub-studies, as approved by the Executive Committee, can be published after the publication of the primary analysis. The Executive Committee will grant authorship depending on personal input but shall include appropriate acknowledgment of the included trials, site Investigators and the Clinical Trials Groups where appropriate.

Authorship Guidance:

In keeping with the ICMJE guidance (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), authors shall meet the following 4 criteria: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Authorships specifics:

For the principal publication the study will be conducted in the name of the **U**ti**l**i**t**y of Steroids in **Se**ptic **S**hock (ULYSSES) IPDMA investigators and acknowledge the included studies, and where appropriate, the Clinical Trials Groups. Where individuals' name is required for publication (e.g.: publication mast) the listing of authors will be as follows: Prof Romain Pirracchio will be the first author, Prof Djillali Annane will be the second (listed as co-first) and corresponding author, followed by members of the writing committee, with Associate Professor Delaney as the senior author. The writing committee shall comprise the included trials' chief investigators and members of the executive committee who have contributed substantially to one or more of: trial design or management, or data analysis and meet the ICMJE criteria for authorship.[38]

Discussion

This IPDMA will provide the highest level of evidence about the benefit and risk of hydrocortisone therapy for adults with septic shock .[39 40] This collaborative group includes most of the principal investigators of trials on hydrocortisone for sepsis/septic shock, reducing the risk of sharing refusal. In contrast to trial-level meta-analyses, this IPDMA will permit clarifying the role of fludrocortisone and identifying the optimal modalities for corticosteroids administration in septic shock. In addition, it will help identifying subgroups of patients more likely to benefit from corticosteroids and those at high risk of harm. Finally, we will use the one-stage analysis and a machine learning with targeted maximum likelihood analysis (TMLE).[29] TMLE may reduce bias and increase efficiency and power when applied to treatment effect estimation in trials.[41] TMLE requires to model

separately different parts of the likelihood. A wide variety of flexible regression algorithms including mixed-effect models may help mitigating the risk of model misspecification associated with standard regression approaches. The Super Learner (SL) [42] is an ensemble machine-learning algorithm that automatically constructs an optimal weighted combination estimator based on a collection of supplied candidate estimators. The SL yields an estimator that is mathematically guaranteed to perform essentially as well as or better than the best candidate among the ones it is built upon – this is significant since in practice which of the candidate estimators behaves best in a given problem and dataset is not known to the analyst.[42] In the context of IPDMA, as compared to GLMM, this approach may avoid any strong assumption about the functional form of the relationship between outcome and explanatory variables. It may help leverage the advantages of all candidate learners such as GLMM. Finally, it may allow accounting for potential high-order interactions by including in the library highly flexible algorithms such as random forests. In this analysis, different portions of the likelihood will be modelled using SL and combined to produce a plug-in estimator of the average treatment effect that is consistent, double robust and asymptotically linear.

Acknowledgment

We would like to thank the primary authors and sponsors that have provided access to their trial's database.

Conflict of interest

Djillali ANNANE: has received funding from French government to conduct trials that will be included in this systematic review (trials acronym: Ger-Inf-05; COIITSS, APROCCHS) – he received funding for FHU SEPSIS and RHU RECORDS research programs. The current IPDMA he was responsible for the Cochrane systematic review on corticosteroids for sepsis in children and adults, and this work will use part of data obtained in the Cochrane review.

Romain PIRRACCHIO : no conflict of interest

Laurent BILLOT : no conflict of interest

André WASCHKA : no conflict of interest

Sylvie CHEVRET : no conflict of interest

Jeremy COHEN: no conflict of interest

Simon FINFER: no conflict of interest

Anthony C. GORDON: has received funding from an NIHR Research Professorship (RP-2015-06-18), consulting fees paid to his institution from GlaxoSmithKline and Bristol Myers Squibb, and personal consulting fees from Baxter Healthcare

Naomi HAMMOND: no conflict of interest

John MYBURGH: no conflict of interest

Balasubramanian VENKATESH: no conflict of interest

Anthony DELANEY: no conflict of interest

Data statements

Data may be accessed only by written request to the primary author of individual studies that will be included in this individual patient data meta-analysis.

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The **U**ti**l**i**t**y of **S**teroids in **Se**ptic **S**hock **i**ndividual **P**atient **D**ata **M**eta-**A**nalysis (ULYSSES IPDMA) Collaborators

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Appendix 1: Search strategy

1 Search strategy for CENTRAL

#1 MeSH descriptor: [Sepsis] explode all trees

#2 MeSH descriptor: [Shock, Septic] explode all trees

#3 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees

#4 MeSH descriptor: [Central Nervous System Bacterial Infections] explode all trees and with qualifier(s): [blood - BL, complications - CO, drug therapy - DT]

#5 MeSH descriptor: [Pneumonia] explode all trees

#6 MeSH descriptor: [Community-Acquired Infections] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#7 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#8 MeSH descriptor: [Acute Lung Injury] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#9 sepsis or (septic* NEAR/3 shock*)

#10 (bacterem* or bacteraem* or pyrexia or septicaem* or septicem*)

#11 SIRS or (Inflammatory next Response next Syndrome*)

#12 bacteria* NEAR infect* NEAR (blood* or serum or invas* or severe or systemic)

#13 ((community next acquired) or severe) NEAR pneumonia

#14 (acute or adult) NEAR/2 (respiratory NEAR/2 distress)

#15 (acute or adult) NEAR/2 (lung NEAR/2 injury)

#16 ARDS

#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees

#19 MeSH descriptor: [Hydrocortisone] explode all trees

#20 MeSH descriptor: [Cortisone] explode all trees

#21 MeSH descriptor: [Steroids] explode all trees

#22 corticosteroid* or steroid* or cortison* or hydrocortison*

#23 methylprednisolon* or (methyl next prednisolon*) or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*

#24 #18 or #19 or #20 or #21 or #22 or #23

#25 #17 and #24

#26 #25 in Trials

2 Search strategy for MEDLINE (Ovid SP)

1 exp Sepsis/

2 exp Shock, Septic/

3 Systemic Inflammatory Response Syndrome/

4 exp Bacteremia/

5 Bacterial Infections/bl, dt, co

6 Pneumonia/co, dt

7 Community-Acquired Infections/co, dt

8 Respiratory Distress Syndrome, Adult/co, dt

9 Acute Lung Injury/co, dt

10 (sepsis or septic*).mp.

11 (bacter?em* or septic?em* or pyrexia).mp.

12 (SIRS or Inflammatory Response Syndrome*).mp.

13 (bacteria* adj6 infect* adj6 (blood* or serum or invas* or severe or systemic)).mp.

14 ((community-acquired or severe) adj3 pneumonia).mp.

15 ((acute or adult) adj2 (respiratory adj2 distress)).mp.

16 ARDS.mp.

17 ((acute or adult) adj2 (lung adj2 injury)).mp.

18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 exp Adrenal Cortex Hormones/

20 exp Hydrocortisone/

21 (corticosteroid* or steroid* or cortison* or hydrocortison*).mp.

22 (methylprednisolon* or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*).mp.

23 19 or 20 or 21 or 22

24 18 and 23

25 ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

26 24 and 25

3 Search strategy for Embase (Ovid SP)

1 exp sepsis/

2 exp septic shock/

3 pneumonia/co, dt [Complication, Drug Therapy]

4 adult respiratory distress syndrome/co, dt [Complication, Drug Therapy]

5 acute lung injury/co, dt [Complication, Drug Therapy]

6 systemic inflammatory response syndrome/co, dt [Complication, Drug Therapy]

7 community acquired infection/co, dt [Complication, Drug Therapy]

8 (sepsis or (septic* adj5 shock) or (bacter?em* or pyrexia or septic?em*) or (SIRS or Inflammatory Response Syndrome*)).mp.

9 (bacteria* adj2 infect* adj2 (blood* or serum or invas* or severe or systemic)).mp.

10 (((community-acquired or severe) adj2 pneumonia) or ((acute or adult) adj1 (respiratory adj1 distress)) or ((acute or adult) adj1 (lung adj1 injury)) or ARDS).mp.

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12 steroid/

13 corticosteroid/

14 cortisone/

15 hydrocortisone/

16 (corticosteroid* or steroid* or cortison* or hydrocortison* or (methylprednisolon* or methyl prednisolon* or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*)).mp.

17 12 or 13 or 14 or 15 or 16

18 11 and 17

19 ((placebo or randomized controlled trial).sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animal not human).sh.

20 18 and 19

4 Search strategy for LILACS (via BIREME)

(sepsis OR septic$ OR SEPSIS OR SEPTIC OR SIRS OR "septic shock" OR "SEPTIC SHOCK/" OR SEPTICEMIA OR PNEUMONIA OR bact* OR "adult respiratory distress syndrome" OR "acute lung injury" OR "systemic inflammatory response syndrome" OR "bacterial infection" OR "community acquired infection") (corticosteroid* OR steroid* OR glucocorticoid* OR CORTCOSTEROID* OR GLUCOCORTICOID/ OR STEROID OR MINERALOCORTICOID OR cortison* OR hydrocortison* OR fludrocortison* OR betamethason* OR methylprednisolon* OR prednison* OR dexamethason*)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	3
Support:			
Sources	5a	Indicate sources of financial or other support for the review	3
Sponsor	5b	Provide name for the review funder and/or sponsor	3
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	3
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the	9,10

		review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11, appendix 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11,12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12,13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13,14
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14,15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15,16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	17

Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17

BMJ Open

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

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Emergency medicine, Infectious diseases, Pharmacology and therapeutics
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Clinical trials < THERAPEUTICS, CLINICAL PHARMACOLOGY

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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

Registration:

Prospero registration number CRD42017062198

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Abstract

Introduction

The benefits and risks of low dose hydrocortisone in patients with septic shock have been investigated in numerous randomized controlled trials and trial-level meta-analyses. Yet, the routine use of this treatment remains controversial. To overcome the limitations of previous meta-analyses inherent to the use of aggregate data, we will perform an individual patient data meta-analysis (IPDMA) on the effect of hydrocortisone with or without fludrocortisone compared to placebo or usual care on 90-day mortality and other outcomes in patients with septic shock.

Methods and analysis

To assess the benefits and risks of hydrocortisone, with or without fludrocortisone for adults with septic shock, we will search major electronic databases from inception to September 2020 (Cochrane Central Register of Controlled Trials-CENTRAL, MEDLINE, EMBASE and Latin American Caribbean Health Sciences Literature-LILACS), complimented by a search for unpublished trials. The primary analysis will compare hydrocortisone with or without fludrocortisone to placebo or no treatment in adult patients with septic shock. Secondary analyses will compare hydrocortisone to placebo (or usual care), hydrocortisone plus fludrocortisone to placebo (or usual care), and hydrocortisone versus hydrocortisone plus fludrocortisone. The primary outcome will be all cause mortality at 90-day. We will conduct both one-stage IPDMA using mixed-effect models and machine learning with targeted maximum likelihood analyses. We will assess the risk of bias related to unshared data and related to the quality of individual trial.

Ethics and dissemination

This individual patient data meta-analysis will use existing data from completed randomized clinical trials and will comply with the ethical and regulatory requirements regarding data sharing for each of the component trials. The findings of this study will be submitted for publication in a peer-review journal with straightforward policy for open access.

The protocol for this systematic review has been registered on PROPSPERO on April 6th 2017, Prospero registration number CRD42017062198

Key words:

adults – septic shock – corticosteroids - machine learning – individual patient data meta-analysis

Article Summary

Strengths and limitations of this study

- 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.
- The use of individual patient data will allow estimation of subgroup effects based on patient level covariates.
- The analysis will provide the best assessment with currently available data on whether hydrocortisone with or without fludrocortisone confers benefits to patients with septic shock and to assess whether there is an optimal regimen for administration.
- The main limitations are regulatory barriers in accessing individual data from original trials, and technical barriers to combining individual patient data from the component trials.

Introduction

Rationale

Septic shock is a global health priority.[1] In 2017, there were about 49 million incident cases of sepsis worldwide and 11 million sepsis-related deaths, representing roughly one out of five of all global deaths.[2] There is a need for improved treatments for this unacceptably high mortality rate. The Surviving Sepsis Campaign[3] recommend that, in the first hour of sepsis recognition, physicians obtain blood cultures, administer broad-spectrum antibiotics, start appropriate fluid resuscitation, and begin vasopressors whenever needed. Beyond these core measures, there has been little change in the management of sepsis.

What has changed in recent years, has been the understanding that dysregulation of the host response to infection is key to understanding the pathophysiology of septic shock.[4] This dysregulated host response may be a therapeutic target to improve mortality in patients with septic shock. As early as the 1950s, physicians have used corticosteroids with clinical success in patients with severe infection not responding to antibiotic treatment.[5] Seventy years later, their use in the management of sepsis remains controversial. The fourth revision of the Surviving Sepsis Campaign guidelines suggested against the use of hydrocortisone except in patients poorly responsive to fluids and vasopressors.[3] Since this revision of the guidelines, two major trials have substantially contributed to the understanding of the benefits and risks of corticosteroids for adults with septic shock.[6 7] Both trials used a daily intravenous dose of 200 mg hydrocortisone for seven days without taper-off. The main differences in the trials' design included continuous infusion of hydrocortisone[7] versus intravenous bolus every 6 hours,[6] hydrocortisone alone [7] versus with fludrocortisone,[6] unspecified vasopressor-dependency [7] versus requirement for a minimal dose of ≥0.25 µg/kg/min or ≥1mg/h norepinephrine/epinephrine.,[6] and unspecified ventilator-dependency[7] versus need for mechanical ventilation. [6] These trials found similar benefits in terms of resolution of shock and organs dysfunction, of accelerating weaning off mechanical ventilation and reducing length of stay in the intensive care unit. They also found no evidence for serious adverse complications with corticosteroids. A mortality benefit with corticosteroids was only reported in APROCCHSS trial[7] but not in ADRENAL.[6]

Since 2018, eight trial-level meta-analyses have addressed the effects of corticosteroids in sepsis.[8-15] They have different designs including differences in trials eligibility criteria, search strategies and in statistical models. The number of included trials ranged from 14 to 61 and the number of participants ranged from 6,935 to 12,192. The relative risk (RR) of death in the short-term varied from 0.90 to 0.98, and the upper limit of the 95% confidence interval varied from 0.98 to 1.08. The magnitude and direction of the pooled RR of dying in the short-term were consistent across these meta-analyses in favoring corticosteroids but differed mainly by the presence of some imprecision in the point estimate. More recent meta-analyses found substantial heterogeneity in the results possibly explained by differences in type of participants (e.g. all ages versus adults only, all sepsis severity versus only septic shock or community-acquired pneumonia or sepsis and ARDS, and in treatments administration (hydrocortisone versus synthetic glucocorticoids, low versus high dose, short versus long course). Intravenous administration of hydrocortisone may be the most frequent prescribed regimen and people may use this drug in sepsis with or without shock.[16] A noteworthy limitation of these meta-analyses is the use of aggregate data, limiting the opportunity to harmonize outcome definitions across trials, adjust the estimated treatment effect on potential confounders and investigate different subgroups.

To address this significant drawback of earlier meta-analyses, we will perform a systematic review and individual patient data meta-analysis (IPDMA) from trials to assess the effect of intravenous hydrocortisone with or without fludrocortisone, compared to placebo or usual care on 90-day mortality and other outcomes in patients with septic shock.

Objectives

The primary objective of this IPDMA is to assess the effect on 90-day mortality of intravenous hydrocortisone therapy, with or without fludrocortisone, compared to placebo or usual care, in adults with septic shock.

Other objectives of this IPDMA include:

- To compare the effect on 90-day mortality of intravenous hydrocortisone therapy with or without fludrocortisone, for differing modes of hydrocortisone therapy;
    - Bolus compared to continuous infusion

- Tapered dosing compared to abrupt discontinuation
- Duration of treatment at full dose : fixed duration versus based on vasopressor-dependency

- To compare the effects of intravenous hydrocortisone therapy with or without fludrocortisone in adults with septic shock on secondary outcomes including 28-day and 180-day mortality, requirement for, and duration of organ support, resources utilization as measured by ICU and hospital length of stay, and serious adverse events.
- To compare the effect on 90-day mortality of intravenous hydrocortisone therapy with or without fludrocortisone in adults with septic shock in clinically important subgroups defined by;
  - age
  - sex
  - vasopressor-dependency
  - vasopressin administration
  - predicted mortality
  - SOFA score
  - arterial lactate concentrations and
  - etomidate exposure

Methods and analysis

This protocol follows the recommendations from the EQUATOR network statement on Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[17] and will allow the report of the completed study to comply with reporting items recommended in the PRISMA of Individual Participant Data (PRISMA IPD).[18]

Eligibility Criteria

Types of studies

We will consider only randomized trials. We will exclude quasi-randomized trials, trials with a crossover design or those for which the unit of randomization is not the patient. We will only include trials, which received an appropriate approval from a research ethics committee and where there was an appropriate method of obtaining consent.

Types of participants

We will consider trials that have included adults with sepsis or septic shock as defined in original studies. Trials of mixed population will be eligible whenever separate information will be available for the subset of patients with septic shock as defined in original studies. We will exclude trials in children or those performed in patients without sepsis.

Types of interventions and controls

We will consider trials in which the experimental intervention was intravenous hydrocortisone at a maximal daily dose of 400mg for at least 72 hours at full dose, whether given as intermittent bolus or as a continuous infusion, and whether tapered off or not. We will also consider trials that have investigated the combination of intravenous hydrocortisone and oral (or enteral) fludrocortisone. We will consider trials in which the comparator was a placebo, no treatment, or hydrocortisone alone when the experimental intervention was the combination of hydrocortisone to fludrocortisone. We will also consider trials that compared two doses of hydrocortisone or bolus versus continuous administration.

We will exclude trials that have investigated

1) corticosteroids other than hydrocortisone or fludrocortisone,
2) dosage of hydrocortisone higher than 400mg per day,
3) duration of hydrocortisone of less than 72 hours at full dose,
4) oral route of hydrocortisone.

We will also exclude trials for when we are unable to contact the primary author and/or sponsor or they refuse to share data. Nevertheless, in case of non-response or refusal, we will use published aggregated data and combine them to the IPDMA results in a sensitivity analysis, as described in the statistical plan.

Types of outcome measures

We will only consider trials for inclusion in this review that have information on crude mortality rates at any time point post randomisation.

Information sources

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, in progress). We will use the strategy of the recently completed Cochrane systematic review on the use of corticosteroids in sepsis.[9]

We will search the Cochrane Central Register of Controlled Trials (CENTRAL; 2020 Issue 9) using the search terms 'sepsis', 'septic shock', 'steroids' and 'corticosteroids'. We will also search (up to September 2020) MEDLINE, EMBASE and Latin American Caribbean Health Sciences Literature (LILACS) using the topic search terms in combination with the search strategy for identifying trials developed by The Cochrane Collaboration (Appendix 1).[19]

We will check the reference lists of all trials identified by these methods, and we will contact study authors to request individual published or unpublished data. We also will search the proceedings of annual meetings of major critical care medicine symposia, that is, Society of Critical Care Medicine (1998 to 2020), American Thoracic Society (1998 to 2020), International Symposium on Intensive Care and Emergency Medicine (1998 to 2020), American College of Chest Physicians and European Society of Intensive Care Medicine (1998 to 2020).

Search strategy

The full search strategy is available in Appendix 1

Study records

Selection processes and data management

We will perform all screening in duplicate with disagreements resolved by consensus and third-party adjudication when consensus could not be reached. After implementation of the search strategy, reviewers will work in pairs to screen all potentially relevant citations and references. Screening will be performed in two stages, initially reviewing titles and abstracts, and then full text for possibly relevant manuscripts. We will capture reasons for exclusion.

Obtaining individual patient data

One reviewer (DA) will contact the primary author and/or sponsor of all selected trials for potential agreement to share de-identified individual patient data from their trial for the purpose of this patient-level meta-analysis. They will define whether data will be freely available or only after application to and approval by a learned intermediary and whether we will require a data use agreement. In case of non-response or refusal, we will use published aggregated data and combine them to the IPDMA results in a sensitivity analysis. Data will be stored on a secure server hosted by University of Versailles SQY.

Data extraction and management

Two reviewers (RP and DA) will independently check data supplied for included trials for missing data, internal data consistency, randomization integrity (balance of patient characteristics at randomisation, pattern of randomisation), follow-up and censoring pattern. We will check summary tables with the trial protocol and latest trial report or publication. We will solve any discrepancies or unusual patterns with the study investigator. We will return a final copy of the form from each trial to the appropriate trial investigator for verification.

Data items

Specifically, with regards to the population of patients for the primary analysis, these will be adult patients with septic shock. Adults will be those 18 years or older at time of randomization. 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

1. Systolic blood pressure <100 mmHg or mean arterial pressure <65 mm Hg after fluid resuscitation
2. Lactate > 2mmol/L
3. Requirement for vasopressors to maintain an adequate blood pressure.

The intervention of interest is hydrocortisone, administered intravenously at a dose of less than 400mg per day, either in divided bolus doses, or as a continuous infusion. We will record the dose, the mode of administration, the duration of administration, and the mode of cessation, either tapered, or abruptly ceased. We will record whether fludrocortisone was administered, the dose and duration of administration. The details of the comparison group, either placebo or standard care will be recorded.

Outcomes and prioritization

The primary outcome measure for this meta-analysis will be 90-day all-cause mortality.

Secondary outcomes will include:

- All-cause mortality at ICU and hospital discharge, at 28 days and at 180 days,
- Time to resolution of organ failure (defined as a SOFA < 4), time to vasopressor withdrawal, and time to cessation of mechanical ventilation. We will also calculate organ-failure/vasopressor/mechanical ventilation free days (up to 28 day). Event free days will be calculated as the number of days alive from randomisation to day 28 and having a SOFA score<4, being off vasopressors, off mechanical ventilation. When death occurred before reaching a SOFA<4 or before being off vasopressor or mechanical ventilation, the number of event-free days will be zero. For these outcomes, we will consider only the first episode. Recovery from organ failure will be defined by a SOFA score<4 for at least 24 hours. Weaning from vasopressor will be defined by being off any dose of vasopressor/inotrope for at least 24 consecutive hours. Weaning from mechanical ventilation will be defined by being off any mode of respiratory support for at least 24 hours.
- Length of stay in the ICU and in the hospital,
- Superinfection, as defined by any new infection occurring >48 hours after randomization,
- Number of days with hyperglycaemia defined as, at least one episode of blood glucose levels >180mg/dl in the corresponding 24 hours,

- Number of days with hypernatremia, defined as at least one episode of serum sodium concentration >150mmol/L in the corresponding 24 hours,
- Bleeding complications: gastroduodenal defined as any episode of gastroduodenal bleeding reported by the investigators of original studies, regardless the need for transfusion or haemostatic intervention
- Critical illness associated muscle weakness at the longest follow-up as defined in individual trials

Risk of bias in individual studies

Risk of bias will be assessed, independently and in duplicate, for each of the individual studies using a modified Cochrane risk of bias tool[20] that classifies risk of bias as "low", "probably low", "probably high", or "high" for each of the following domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting and other bias. We will rate the overall risk of bias as the highest risk attributed to any criterion. Reviewers will not contribute to risk of bias assessment for trials in which they have participated.

Data synthesis

Baseline patient characteristics will be presented by study and treatment group. For continuous variables, mean and standard deviation (SD) or median and interquartile range (IQR) will be reported, as appropriate. For categorical variables, the number of observations in each category and corresponding proportions will be reported. Patient characteristics across groups will be contrasted using nonparametric Kruskal-Wallis tests for continuous variables and chi-square or Fisher exact tests for categorical variables. Since earlier and later deaths may stem from qualitatively different processes, to provide a more comprehensive depiction of mortality, length of stay in the ICU or in the hospital will be reported in the overall population as well as in the subpopulation of survivors at day 90. All tests will be two-sided and conducted at significance level 0.05. No formal adjustment for multiple testing will be undertaken. Given the number of secondary outcomes and subgroup analyses to be performed, interpretation of p-values, beyond the primary outcome, will be undertaken very cautiously.

Data analysis

We will consider as the primary analysis, the comparison between hydrocortisone (with or without fludrocortisone) and placebo (or no treatment) on 90-day mortality for patients with septic shock,

Pre-specified secondary analyses will include all possible pairwise comparisons, namely, hydrocortisone versus placebo, hydrocortisone plus fludrocortisone versus placebo, hydrocortisone plus fludrocortisone versus hydrocortisone.

In order to increase the robustness of the results, we will perform two different statistical approaches, i.e. a one stage conventional meta-analysis and machine-learning targeted maximum likelihood analysis.

As suggested by different studies comparing one-stage to two-stage approaches[21 22] the conventional will be performed using a one-stage meta-analysis. In one-stage meta-analysis, all data from all studies are aggregated and the primary outcome is analyzed simultaneously by adopting a single statistical model that accounts for potential heterogeneity across studies.[23] Analyses will rely on generalized linear mixed effect models (GLMM) where both the intercept and the treatment effect will be treated as random variables with the study as the subject (i.e. a random study intercept and a random study-by-treatment interaction). For the primary outcome and for binary secondary outcomes, we will use a GLMM with a logit link function. Continuous secondary outcomes will be analysed using a GLMM with an identity link function. Our estimates of the average treatment effect will be adjusted for study (random effect), age, predicted mortality from SAPS2 or APACHE 2, SOFA, admission type (medical, elective surgery or emergent surgery), infection site infection type (hospital versus community acquired infection) and type of pathogen, baseline and increment in cortisol levels post corticotrophin, lactate levels, and need for mechanical ventilation (fixed effects). A study-by-treatment interaction term will be also be included in the model. For withdrawal of vasopressor therapy, withdrawal of mechanical ventilation, and recovery from organ failure (defined by a SOFA score <4 for at least 24 hours, we will use only cases with complete data for SOFA score), cumulative event incidences will be estimated using a nonparametric estimator and will be compared using Gray's test, with death treated as a competing risk[24] and study used as random effect .[25] 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.[26-28]

We will also estimate the average treatment effect via a more flexible estimator, namely the targeted maximum likelihood estimator (TMLE).[29] In this analysis, different portions of the likelihood will be modelled

using Super Learner and combined to produce a plug-in estimator of the average treatment effect that is consistent, double robust and asymptotically linear. We will use a Super Learner with a large library including logistic regression models, stepwise regression models based on the Akaike information criterion, mixed logistic models with random effect to account for study-level and patient-level heterogeneity, multivariate adaptive regression splines, random forests, Bayesian generalized linear models, elastic net regularized generalized linear models, and gradient boosting, to estimate flexibly the relationship between mean outcome and covariates. For the pairwise comparisons between combinations of hydrocortisone, fludrocortisone and placebo, we will use network meta-analysis techniques[30] to assess the robustness of the results.

For binary outcomes, we will describe the average treatment effect using risk ratio (RR) or odds ratio (OR) estimate along with corresponding 95% CI and p-value. For continuous outcomes, we will describe the average treatment effect using mean difference (MD) estimate along with a corresponding 95% CI and p-value. We will test for qualitative interaction between treatment effect and subgroup of interest using the Gail and Simon interaction test.[31]

Subgroup analysis

We will perform, if data permit, the following subgroup analyses:

- We will examine treatment effect in the subgroup of patients meeting sepsis or septic shock criteria according to Sepsis 3 definition[4];
- We will also examine any variation in response to treatment according to baseline prognosis factors including
    - age (by quartiles),
    - sex,
    - vasopressor-dependency (yes versus no, and by quartiles of baseline dose),
    - vasopressin administration (yes or no),
    - predicted mortality from SAPSII or APACAHEII (by quartiles),
    - SOFA score and each of its component (by quartiles),
    - arterial lactate levels (by quartiles) and

- etomidate-free versus etomidate-exposed patients
- appropriate antibiotic treatment

- We will examine any variation in treatment response according to patient's adrenal status, i.e. responders to standard corticotrophin test (those whom stimulated cortisol levels increased by >9µg/dL from baseline value) versus non-responders to corticotrophin test,
- 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-angiotensin-aldosterone axis, or both 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, and
- we will examine any variation in response to treatment according to infection characteristics, i.e.
  - community versus hospital acquired,
  - medical vs. surgical, lung versus other sources of infection, and
  - gram negative versus gram positive versus polymicrobial.

Methods to assess bias

We will assess for the potential for publication bias or small study bias by inspection of funnel plots and the use of Egger's test. The potential bias introduced by the studies that could not be included in the analyses will be evaluated [32] by performing a two-stage meta-analysis aggregating the results obtained on shared data and treatment effect estimates published for unshared data, if data permit. Specifically, the available IPD will first be reduced to aggregated data using the modelling methods described above. Then, these aggregated data will be pooled with published aggregated data into a weighted average.[33 34] Heterogeneity will be assessed by using an estimate of Tau^2 generated from the one stage and two-stage models.

Confidence in cumulative evidence

We will present a summary of results and recommendations in accordance with the GRADE approach to assess the overall quality of the evidence.[35 36]

Patient and Public involvement:

This protocol is under review by sepsis survivors and stakeholders from the Australian Sepsis Network.[37]

Ethics and Dissemination

Ethics

This planned IPDMA will use existing data from completed randomized controlled trials, reporting explicitly ethical approval of the original protocol and the process for obtaining patients consent.

Publications Plan:

We will report the findings according to the PRISMA-IPD statement.[18] We will share the findings from this IPDMA with primary authors and sponsors of included trials prior to submitting the results of this primary analysis for publication.

1. The study protocol including the statistical analysis plan will be published prior to publishing the results of the primary analysis
2. Upon completion of the primary analysis, the main manuscript will be submitted to one of the major clinical journals regardless of the results.
3. Sub-studies, as approved by the Executive Committee, can be published after the publication of the primary analysis. The Executive Committee will grant authorship depending on personal input but shall include appropriate acknowledgment of the included trials, site Investigators and the Clinical Trials Groups where appropriate.

Authorship Guidance:

In keeping with the ICMJE guidance (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), authors shall meet the following 4 criteria: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Authorships specifics:

For the principal publication the study will be conducted in the name of the **U**ti**l**i**t**y of Steroids in **Se**ptic **S**hock (ULYSSES) IPDMA investigators and acknowledge the included studies, and where appropriate, the Clinical Trials Groups. Where individuals' name is required for publication (e.g.: publication mast) the listing of authors will be as follows: Prof Romain Pirracchio will be the first author, Prof Djillali Annane will be the second (listed as co-first) and corresponding author, followed by members of the writing committee, with Associate Professor Delaney as the senior author. The writing committee shall comprise the included trials' chief investigators and members of the executive committee who have contributed substantially to one or more of: trial design or management, or data analysis and meet the ICMJE criteria for authorship.[38]

Discussion

This IPDMA will provide the highest level of evidence about the benefit and risk of hydrocortisone therapy for adults with septic shock .[39 40] This collaborative group includes most of the principal investigators of trials on hydrocortisone for sepsis/septic shock, reducing the risk of sharing refusal. In contrast to trial-level meta-analyses, this IPDMA will permit clarifying the role of fludrocortisone and identifying the optimal modalities for corticosteroids administration in septic shock. In addition, it will help identifying subgroups of patients more likely to benefit from corticosteroids and those at high risk of harm. Finally, we will use the one-stage analysis and a machine learning with targeted maximum likelihood analysis (TMLE).[29] TMLE may reduce bias and

increase efficiency and power when applied to treatment effect estimation in trials.[41] TMLE requires to model separately different parts of the likelihood. A wide variety of flexible regression algorithms including mixed-effect models may help mitigating the risk of model misspecification associated with standard regression approaches. The Super Learner (SL) [42] is an ensemble machine-learning algorithm that automatically constructs an optimal weighted combination estimator based on a collection of supplied candidate estimators. The SL yields an estimator that is mathematically guaranteed to perform essentially as well as or better than the best candidate among the ones it is built upon – this is significant since in practice which of the candidate estimators behaves best in a given problem and dataset is not known to the analyst.[42] In the context of IPDMA, as compared to GLMM, this approach may avoid any strong assumption about the functional form of the relationship between outcome and explanatory variables. It may help leverage the advantages of all candidate learners such as GLMM. Finally, it may allow accounting for potential high-order interactions by including in the library highly flexible algorithms such as random forests. In this analysis, different portions of the likelihood will be modelled using SL and combined to produce a plug-in estimator of the average treatment effect that is consistent, double robust and asymptotically linear.

Acknowledgment

We would like to thank the primary authors and sponsors that have provided access to their trial's database.

Conflict of interest

Djillali ANNANE: has received funding from French government to conduct trials that will be included in this systematic review (trials acronym: Ger-Inf-05; COIITSS, APROCCHS) – he received funding for FHU SEPSIS and RHU RECORDS research programs. The current IPDMA he was responsible for the Cochrane systematic review on corticosteroids for sepsis in children and adults, and this work will use part of data obtained in the Cochrane review.

Romain PIRRACCHIO : no conflict of interest

Laurent BILLOT : no conflict of interest

André WASCHKA : no conflict of interest

Sylvie CHEVRET : no conflict of interest

Jeremy COHEN: no conflict of interest

Simon FINFER: no conflict of interest

Anthony C. GORDON: has received funding from an NIHR Research Professorship (RP-2015-06-18), consulting fees paid to his institution from GlaxoSmithKline and Bristol Myers Squibb, and personal consulting fees from Baxter Healthcare

Naomi HAMMOND: no conflict of interest

John MYBURGH: no conflict of interest

Balasubramanian VENKATESH: no conflict of interest

Anthony DELANEY: no conflict of interest

Data statements

Data may be accessed only by written request to the primary author of individual studies that will be included in this individual patient data meta-analysis.

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The **U**ti**l**i**t**y of **S**teroids in **Se**ptic **S**hock **i**ndividual **P**atient **D**ata **M**eta-**A**nalysis (ULYSSES IPDMA) Collaborators

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Appendix 1: Search strategy

1 Search strategy for CENTRAL

#1 MeSH descriptor: [Sepsis] explode all trees

#2 MeSH descriptor: [Shock, Septic] explode all trees

#3 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees

#4 MeSH descriptor: [Central Nervous System Bacterial Infections] explode all trees and with qualifier(s): [blood - BL, complications - CO, drug therapy - DT]

#5 MeSH descriptor: [Pneumonia] explode all trees

#6 MeSH descriptor: [Community-Acquired Infections] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#7 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#8 MeSH descriptor: [Acute Lung Injury] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#9 sepsis or (septic* NEAR/3 shock*)

#10 (bacterem* or bacteraem* or pyrexia or septicaem* or septicem*)

#11 SIRS or (Inflammatory next Response next Syndrome*)

#12 bacteria* NEAR infect* NEAR (blood* or serum or invas* or severe or systemic)

#13 ((community next acquired) or severe) NEAR pneumonia

#14 (acute or adult) NEAR/2 (respiratory NEAR/2 distress)

#15 (acute or adult) NEAR/2 (lung NEAR/2 injury)

#16 ARDS

#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees

#19 MeSH descriptor: [Hydrocortisone] explode all trees

#20 MeSH descriptor: [Cortisone] explode all trees

#21 MeSH descriptor: [Steroids] explode all trees

#22 corticosteroid* or steroid* or cortison* or hydrocortison*

#23 methylprednisolon* or (methyl next prednisolon*) or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*

#24 #18 or #19 or #20 or #21 or #22 or #23

#25 #17 and #24

#26 #25 in Trials

2 Search strategy for MEDLINE (Ovid SP)

1 exp Sepsis/

2 exp Shock, Septic/

3 Systemic Inflammatory Response Syndrome/

4 exp Bacteremia/

5 Bacterial Infections/bl, dt, co

6 Pneumonia/co, dt

7 Community-Acquired Infections/co, dt

8 Respiratory Distress Syndrome, Adult/co, dt

9 Acute Lung Injury/co, dt

10 (sepsis or septic*).mp.

11 (bacter?em* or septic?em* or pyrexia).mp.

12 (SIRS or Inflammatory Response Syndrome*).mp.

13 (bacteria* adj6 infect* adj6 (blood* or serum or invas* or severe or systemic)).mp.

14 ((community-acquired or severe) adj3 pneumonia).mp.

15 ((acute or adult) adj2 (respiratory adj2 distress)).mp.

16 ARDS.mp.

17 ((acute or adult) adj2 (lung adj2 injury)).mp.

18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 exp Adrenal Cortex Hormones/

20 exp Hydrocortisone/

21 (corticosteroid* or steroid* or cortison* or hydrocortison*).mp.

22 (methylprednisolon* or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*).mp.

23 19 or 20 or 21 or 22

24 18 and 23

25 ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

26 24 and 25

3 Search strategy for Embase (Ovid SP)

1 exp sepsis/

2 exp septic shock/

3 pneumonia/co, dt [Complication, Drug Therapy]

4 adult respiratory distress syndrome/co, dt [Complication, Drug Therapy]

5 acute lung injury/co, dt [Complication, Drug Therapy]

6 systemic inflammatory response syndrome/co, dt [Complication, Drug Therapy]

7 community acquired infection/co, dt [Complication, Drug Therapy]

8 (sepsis or (septic* adj5 shock) or (bacter?em* or pyrexia or septic?em*) or (SIRS or Inflammatory Response Syndrome*)).mp.

9 (bacteria* adj2 infect* adj2 (blood* or serum or invas* or severe or systemic)).mp.

10 (((community-acquired or severe) adj2 pneumonia) or ((acute or adult) adj1 (respiratory adj1 distress)) or ((acute or adult) adj1 (lung adj1 injury)) or ARDS).mp.

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12 steroid/

13 corticosteroid/

14 cortisone/

15 hydrocortisone/

16 (corticosteroid* or steroid* or cortison* or hydrocortison* or (methylprednisolon* or methyl prednisolon* or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid*)).mp.

17 12 or 13 or 14 or 15 or 16

18 11 and 17

19 ((placebo or randomized controlled trial).sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animal not human).sh.

20 18 and 19

4 Search strategy for LILACS (via BIREME)

(sepsis OR septic$ OR SEPSIS OR SEPTIC OR SIRS OR "septic shock" OR "SEPTIC SHOCK/" OR SEPTICEMIA OR PNEUMONIA OR bact* OR "adult respiratory distress syndrome" OR "acute lung injury" OR "systemic inflammatory response syndrome" OR "bacterial infection" OR "community acquired infection") (corticosteroid* OR steroid* OR glucocorticoid* OR CORTCOSTEROID* OR GLUCOCORTICOID/ OR STEROID OR MINERALOCORTICOID OR cortison* OR hydrocortison* OR fludrocortison* OR betamethason* OR methylprednisolon* OR prednison* OR dexamethason*)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	3
Support:			
Sources	5a	Indicate sources of financial or other support for the review	3
Sponsor	5b	Provide name for the review funder and/or sponsor	3
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	3
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the	9,10

		review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	11, appendix 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11,12
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12,13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13,14
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14,15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15,16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	17

Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17