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Corticosteroids in sepsis: An updated systematic review and meta-analysis (protocol)

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Abstract

Introduction: Sepsis is associated with a dysregulated host response to infection and impaired endogenous corticosteroid metabolism. As such, therapeutic use of exogenous corticosteroids represents a promising adjunctive intervention. However, despite a large number of trials examining this research question, uncertainty persists regarding the effect of corticosteroids on survival in sepsis. Several large randomized controlled trials have been published within the last year prompting a re-evaluation of the available literature.

Methods and Analysis: A rigorous and reproducible search and screening process from a Cochrane review on the same topic was comprehensive to October 2014. We will search Medline, EMBASE, LILACS, the Cochrane trial registry, and clinicaltrials.gov for eligible randomized controlled trials investigating the use of corticosteroids in patients with sepsis from September 2014.

Outcomes were chosen by a semi-independent guideline panel, created in the context of a parallel BMJ Rapid Recommendation on the topic. This panel includes clinicians, content experts, and patient representatives, who will help identify patient-important outcomes that are critical for deciding whether to use or not use corticosteroids in sepsis. Two reviewers will independently screen and identify eligible studies; a third reviewer will resolve any disagreements.

We will use Review Manager (RevMan) to pool effect estimates from included studies for each outcome. We will present the results as relative risk with 95% confidence intervals (CI) for dichotomous outcomes and as mean difference or standardized mean difference for continuous outcomes with 95% CI. We will assess the certainty of evidence at the outcome level using the Grading of Recommendations, Assessment, Development and Evaluation approach. We will conduct *a priori* subgroup analyses, which were chosen by the parallel BMJ Rapid Recommendation panel.

Ethics and Dissemination: The aim of this systematic review is to summarize the evidence on the efficacy and safety of corticosteroids in patients with sepsis.

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Keywords

Sepsis; systematic review; corticosteroids; shock; intensive care; meta-analysis

Strengths

- systematic and comprehensive search
- multi-disciplinary team including oversight and input from semi-independent BMJ RapidRec panel which includes patient and carer representatives
- the results of this review will directly inform BMJ RapidRec clinical practice guideline recommendation
- application of GRADE methodology to assess certainty in summarized estimates of effect

Limitations

- anticipated clinical heterogeneity in individual study populations and intervention (including dosing, timing and formulation of corticosteroids)

Background

Description of the condition

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. The primary immune mechanisms include hyper-stimulation of the inflammatory cascade and upregulation of related cytokines (including TNF-α, IL-1, IL-6). Hemodynamic instability secondary to vascular smooth muscle vasodilation and dysregulation of coagulation and fibrinolysis are key contributors to tissue hypoperfusion and organ injury [2]. Multiple organ failure is often present in septic shock and is the most common cause of death.

The incidence of sepsis varies from 900,000 to 3 million cases in the United States per year depending on the epidemiological methodology employed [3]. In-hospital mortality of sepsis ranges from 14.7% to 30% in children and adults [3, 4]. Although hospital mortality rates from sepsis may have declined over the last 20 years, the incidence of sepsis seems to be increasing [5].

Description of intervention

The sympathetic nervous system is activated by external stressors, such as sepsis, leading to the release of endogenous catecholamines and cortisol from the adrenal glands. Cortisol is the major endogenous glucocorticoid in the body and down-regulates production of inflammatory cytokines through inhibition of NF-KB [6]. Cortisol also has other physiologic effects in the body including increasing glucose levels (through enhanced hepatic gluconeogenesis and decreased peripheral glucose uptake), and increasing blood pressure (via increasing sensitivity to catecholamines).

Corticosteroids are synthetic cortisol compounds, which exert similar effects to their endogenous counterparts. In addition to glucocorticoid activity, many synthetic corticosteroids also have mineralocorticoid components that serve as substrate precursors for catecholamine synthesis [7]. Some of the corticosteroids that have been investigated in the setting of sepsis include hydrocortisone, methylprednisolone, and prednisone. Dosing regimes vary considerably with some studies giving large doses over 2-3 days and then stopping and others giving lower doses over 1-2 weeks with a gradual taper.

How the intervention might work

Cortisol deficiency in sepsis is likely multifactorial, usually reversible, and results in an inadequate amount of cortisol at the tissue level [8]. Likewise, tissue resistance to corticosteroids is multifactorial and may involve alteration in the number or function of glucocorticoid receptors, cortisol metabolism or access to tissues. The result of removing this ‘check’ on the host immune response is unregulated activation of the inflammatory cascade leading to end organ dysfunction. Also, the relative deficiency of mineralocorticoids in the adrenal medulla may further contribute to systemic hypoperfusion, a subsequent decrease in oxygenated blood delivery to the periphery and further end-organ damage.

Exogenous supplementation with both glucocorticoid and mineralcorticoid containing corticosteroids is therefore a promising therapeutic option in patients with sepsis.

Why it is important to do this review

Despite strong physiologic rationale for corticosteroids in sepsis, uncertainty regarding the overall clinical effectiveness and the challenge of identifying patients who may benefit from their use has ultimately led to a high degree of practice variation [9, 10]. In the 55 years since the first randomized controlled trial (RCT) of corticosteroids in sepsis, their utility remains debated in the management of critically ill patients. The most recent systematic review suggested steroids may reduce mortality in sepsis, although conclusions were based on low certainty in the evidence, limited by imprecision, inconsistency and the potential for publication bias [11]. Results from this review suggested patients with septic shock and those treated with a low dose and long course of corticosteroids had the highest likelihood of benefit.

Since the most recently published review, an additional large RCT published was published [12] and another is planned for publication shortly [13]. Our updated systematic review and meta-analysis will include these two new trials, and any others identified in the updated search, in order to improve precision of the pooled point estimates of the treatment effect of corticosteroids in patients with sepsis. The new trials will provide data for at least 1600 additional patients from what we expect are trials at low risk of bias. This will substantially improve the power to detect patient-important effects; the previous review included 4200 patients from trials with various degrees of credibility.

This systematic review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation program (www.magicproject.org) and *The BMJ* [14]. The aim of the project is to respond to new potentially practice-changing evidence and provide a trustworthy practice guideline in a timely manner. The anticipated publication of the APROCCHSS trial [15], a multicentre trial that randomised 1241 patients with septic shock to receive hydrocortisone and fludrocortisone or placebo is the trigger for this updated review. This systematic review will inform a parallel clinical practice guideline which will be published in a multi-layered electronic format on *The BMJ* and MAGICapp.

Objectives

We plan to conduct a systematic review and meta-analysis of all RCTs that investigated the use of corticosteroids in critically ill patients with sepsis.

Methods

Types of studies

We plan to include all RCTs reporting the use of corticosteroids in critically ill patients with sepsis. We will exclude case reports, case series, and observational studies. We will not impose any methodological quality or language restrictions to the studies included, and will appraise their risk of bias (see corresponding section below).

Types of participants

The population of interest includes all adult and children (excluding premature infants due to higher rates of adrenal insufficiency in this population [16]) who were diagnosed with sepsis, severe sepsis or septic shock according to appropriate criteria [1, 17]. We will include data from trials enrolling patients with acute respiratory distress syndrome (ARDS) if patients with sepsis are reported separately.

Types of interventions and comparators

The intervention of interest is the administration of systemic corticosteroids, including but not limited to, cortisone, hydrocortisone, methylprednisolone, betamethasone, fludrocortisone, and dexamethasone. We will only include RCTs with a placebo or no corticosteroid comparator group.

For the purposes of this review, high-dose corticosteroids will be considered any dose greater than 400 mg/day of hydrocortisone or equivalent. Similarly, long duration of corticosteroid treatment will be considered greater than or equal to 3 days. These operational definitions are rationalized based on a change in philosophy regarding the role of corticosteroids in sepsis that occurred in the late 1990s. Older studies administered very high dose and short duration corticosteroids attempting to maximize their anti-inflammatory effect, whereas newer studies used lower dose and longer duration corticosteroids with the intent of compensating for a dysfunctional hypothalamic-pituitary axis response to stress.

Types of outcome measures

Patient important outcomes have been chosen by a semi-independent parallel BMJ Rapid Recommendation guideline panel and include the outcomes that are critical for choosing whether to use corticosteroids in sepsis [18].

The outcomes are:

- short-term mortality
    - 90-day mortality
    - 28-day, 30-day, hospital, ICU mortality
- long-term mortality (closest to 1 year)
- number of participants with shock reversal at day 7 (stable hemodynamic status over 24 hours after withdrawal of vasopressors)
- organ dysfunction at day 7 (using total SOFA score)
- intensive care unit (ICU) length of stay
- hospital length of stay
- adverse events associated with corticosteroids including ICU-acquired neuromuscular weakness, gastrointestinal bleeding, neuropsychiatric effects, hypernatremia, superinfection, vascular events (stroke, myocardial infarction) and clinically significant hyperglycemia
- Quality of life (using validated indices such as SF-36) at 1 year

Search methods for identification of studies
A search and screening process from a Cochrane review on the same topic was credible and comprehensive to September 2014 [19]. We will therefore search Medline, EMBASE, LILACS, and the Cochrane trial registry for RCTs investigating the use of corticosteroids in patients with sepsis from September 2014. We will not use any language restrictions. See appendix for MEDLINE search strategy. Keyword search terms include corticosteroids, sepsis and septic shock.

Searching other resources
We will search the references of review articles and systematic reviews on the same topic for eligible articles. In addition, we will search for unpublished or ongoing trials on the WHO international clinical trials registry (WHO ICTRP), current controlled trials metaregister of controlled trials, and clinicaltrials.gov database. Two reviewers will search conference proceedings from the Society of Critical Care Medicine, American Thoracic Society, and the European Society of Intensive Care Medicine (2014 and onwards).

Data collection and analysis
Upon implementation of our search strategy, reviewers working in pairs will independently screen all citations and references using specific eligibility criteria. If disagreements between the two primary reviewers cannot be resolved by discussion and consensus, a third reviewer will make the final determination of trial eligibility. We will attempt to contact study authors to obtain missing information necessary to judge trial eligibility.

Data extraction and management
Data extraction will be done independently and in duplicate using pre-designed data abstraction forms. Abstracted data will include study title, first author, relevant demographic data, details of the intervention and control, primary and secondary outcome data, and information on methodological quality for each study. A third reviewer will resolve inconsistent data extraction between the two reviewers.

Assessment of risk of bias in included studies
Two reviewers will independently assess the risk of bias for each included study using the modified version of the Cochrane Collaboration tool [20]. Risk of bias assessment will be performed for individual studies separately for each outcome. A third reviewer will resolve disagreements.

The included RCTs will be assessed for sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and missing participant data. Sequence generation will be considered adequate if the study explicitly described an appropriate randomization procedure to generate an unpredictable sequence of allocation, including computerized randomization, use of random number tables and coin-tossing. Concealment of allocation will be considered adequate if specific methods to protect allocation were documented and implemented. Performance bias will be considered low if a study reported participant, caregiver and/or researcher blinding. Blinding of outcome

assessment will be considered adequate if outcome assessors and adjudicators were blinded. Within-study selective reporting of outcomes will be examined by reviewing the *a priori* study protocol, if available. If the study protocol is not available, we will compare the outcomes listed in the methods section with the reported outcomes in the results section.

A description for each domain assessed will be included along with comments if necessary and a final judgment for each outcome within each study and categorized as: (1) Low risk of bias, where bias is not present or if present, unlikely to affect outcomes, (2) Probably low risk of bias, (3) Probably high risk of bias, or (2) High risk of bias, where outcomes are likely to be significantly affected by bias. We will consider the highest risk of bias for any criteria as the overall risk of bias for the study.

Measures of treatment effect

We will use RevMan 5.3 software to conduct meta-analyses. We will use the method of DerSimonian and Laird for random effects model to pool effect sizes for each outcome. Study weights will be measured using the inverse variance method. We will present the results as relative risk (RR) with 95% confidence intervals (CI) for dichotomous outcomes and as mean difference (MD) or standardized mean difference (SMD) for continuous outcomes with 95% CI. We plan to perform random effect analysis for all outcomes of interest.

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to quantify the absolute magnitude of effect. We will use representative and trustworthy observational studies to measure baseline risk and apply the relative effect measured from the meta-analysis to obtain absolute differences (risk difference or mean difference) with a 95% CI. The risk difference with 95% CI will be derived from pooled risk ratios and its 95% CI utilizing assumed control risk for each outcome [21].

Dealing with missing data

Where possible, if missing data are encountered we will attempt to contact the individual study authors for additional information. If this is not possible, we will analyze the available data and report on the potential impact of missing data on the results in the discussion section. We will perform a complete case analysis as the primary analysis for all outcomes and perform sensitivity analyses with increasingly extreme assumptions for missing participant data [22].

Assessment of reporting biases

We will look for potential publication bias using a funnel plot if more than 10 trials are included. For continuous outcomes, the Egger test [23] will be used to detect funnel plot asymmetry. For dichotomous outcomes, the arcsine test will be used. All analyses will be performed using RevMan or R.

Subgroup analysis and investigation of heterogeneity

We will assess for heterogeneity between studies using the chi-squared test for homogeneity, where $p < 0.10$ indicates substantial heterogeneity, and the I^2 statistic, in addition to visual inspection of the forest plots for magnitude of differences. If subgroup effects are credible, we will present the outcomes separately for each subgroup [24]. If serious heterogeneity remains, we will rate down our certainty in the effect estimate [25].

We will conduct *a priori* subgroup analyses, which were chosen by the parallel BMJ Rapid Recommendation panel (hypothesized direction of effect in parentheses):

- risk of bias (corticosteroids more effective in trials with high risk of bias),
- treatment dose (corticosteroids more effective in trials with lower doses),
- treatment duration (corticosteroids more effective in trials with longer duration),
- treatment molecule (corticosteroids more effective in trials with drugs having more mineralocorticoid activity),
- sepsis population subtype (sepsis, septic shock, pneumosepsis) (corticosteroids most effective in patients with pneumonia and those with septic shock, and least effective in patients with non-pneumonia sepsis without shock),
- age of patients (corticosteroids more effective in studies enrolling children [<18 years old] than adults),
- and presence of critical illness related corticosteroid insufficiency (CIRCI) (corticosteroids more effective in trials identifying and enrolling patients with CIRCI).

For subgroup analyses, we will perform meta-regression if a sufficient number of studies are found (generally greater than 10). If not, we will use the chi-square test for each subgroup hypothesis, and then meta-regression if more than one is found to be statistically significant (using a p-value threshold of > 0.10).

Sensitivity analysis

Sensitivity analysis will be performed excluding studies only reported as abstracts.

Assessing the certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the certainty of evidence for each outcome [26]. The GRADE system classifies the certainty of the aggregate body of evidence as high, moderate, low, or very low. The evidence will be evaluated using the following criteria: 1) study design and rigour of its execution (ie, individual study risk of bias), 2) the extent to which the evidence could be applied to patients of interest (ie, directness), 3) the consistency of results, 4) the analysis of the results (ie. precision), and 5) whether there is a likelihood of publication bias.

For each outcome, a final overall certainty of evidence will be summarized for the intervention taking into consideration both desirable and undesirable outcomes. An evidence profile will be included in the results showing the GRADE assessments and pooled analysis per outcome.

Guideline Panel and Patient Involvement

According to the *BMJ* Rapid Recommendations process [18], the guideline panel has already provided critical oversight and identified populations, subgroups, and outcomes of interest for this review. The panel includes content experts, methodologists, and patients or carers with personal experience with sepsis. All patients receive personal training and support to optimise contributions throughout the guideline development process. The patient panel members will be invited to lead the interpretation of the results based on what they expect the typical patient values and preferences to be, as well as the variation between patients.

Discussion

Despite a large body of evidence, the role of corticosteroids in sepsis remains controversial. Given the forthcoming availability of new data addressing this research question, an updated systematic review and meta-analysis is needed to generate the best summary of evidence in order to help guideline developers and to assist bedside clinicians. This systematic review will summarize the RCT data on the efficacy and safety of corticosteroid use in critically ill patients with sepsis. The certainty of evidence will be assessed using the GRADE approach to characterize the confidence in the estimate of effect. Results of this review will be accompanied by a BMJ rapid review guideline recommendation for front line clinicians.

Abbreviations

EMBASE, Excerpta Medica database; ICU, intensive care unit; RR, relative risk; CI, confidence interval; MD, mean difference; SMD, standardized mean difference; GRADE, grading of recommendations assessment development and evaluation; CIRCI, critical illness related corticosteroid deficiencey; TNF, tumour necrosis factor; IL, interleukin; HPA, hypothalamic-pituitary-adrenal; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone; NF-Kβ, nuclear factor kappa-light-chain enhancer; I-CAM, intracellular adhesion molecule; RCT, randomized controlled trial; ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment score; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform; MD, mean difference; SMD, standardized mean difference; ACR, assumed control risk; NNT, number needed to treat

Competing interests

The authors declare that they have no financial competing interests.

Authors' contributions

BR, RS, TA, PV & GG conceived the idea for this systematic review. All authors developed the methodology for the systematic review. The manuscript was drafted by BR and revised by all authors. BR and SO will screen potential studies, perform duplicate independent data abstraction, risk of bias assessment and GRADE assessment with help from RS, TA, WS, WA, ED, FD, EBC and KGK. BR will conduct the data synthesis. BR is the guarantor of the review.

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Appendix. Search strategy for MEDLINE (Ovid SP)

1. exp Sepsis/
2. exp Shock, Septic/
3. (sepsis or septic shock).mp.
4. 1 or 2 or 3
5. exp Adrenal Cortex Hormones/
6. (corticosteroid* or steroid*).mp.
7. 6 or 5
8. 4 and 7
9. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.
ab. or trial.ti.) not (animals not (humans and animals)).sh.
10. 8 and 9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	N/A
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	N/A
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	N/A
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	N/A
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	N/A
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Corticosteroids in sepsis: An updated systematic review and meta-analysis (protocol)

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Primary Subject Heading:	Intensive care
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Corticosteroids in sepsis: An updated systematic review and meta-analysis (protocol)

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Abstract

Introduction: Sepsis is associated with a dysregulated host response to infection and impaired endogenous corticosteroid metabolism. As such, therapeutic use of exogenous corticosteroids is a promising adjunctive intervention. Despite a large number of trials examining this research question, uncertainty persists regarding the effect of corticosteroids on survival in sepsis. Several large randomized controlled trials have been published recently prompting a re-evaluation of the available literature.

Methods and Analysis: A rigorous and reproducible search and screening process from a Cochrane review on the same topic was comprehensive to October 2014. We will search Medline, EMBASE, LILACS, the Cochrane trial registry, and clinicaltrials.gov for eligible randomized controlled trials investigating the use of corticosteroids in patients with sepsis from September 2014.

Outcomes have been chosen by a semi-independent guideline panel, created in the context of a parallel BMJ Rapid Recommendation on the topic. This panel includes clinicians, content experts, methodologists, and patient representatives, who will help identify patient-important outcomes that are critical for deciding whether to use or not use corticosteroids in sepsis. Two reviewers will independently screen and identify eligible studies; a third reviewer will resolve any disagreements.

We will use Review Manager (RevMan) to pool effect estimates from included studies for each outcome using a random effect model. We will present the results as relative risk with 95% confidence intervals (CI) for dichotomous outcomes and as mean difference or standardized mean difference for continuous outcomes with 95% CI. We will assess the certainty of evidence at the outcome level using the Grading of Recommendations, Assessment, Development and Evaluation approach. We will conduct *a priori* subgroup analyses, which have been chosen by the parallel BMJ Rapid Recommendation panel.

Ethics and Dissemination: The aim of this systematic review is to summarize the updated evidence on the efficacy and safety of corticosteroids in patients with sepsis.

PROSPERO ID: CRD42017058537

Keywords

Sepsis; systematic review; corticosteroids; shock; intensive care; meta-analysis

Strengths

- systematic and comprehensive search
- multi-disciplinary team including oversight and input from semi-independent BMJ RapidRec panel which includes patient and carer representatives
- the results of this review will directly inform BMJ RapidRec clinical practice guideline recommendation
- application of GRADE methodology to assess certainty in summarized estimates of effect

Limitations

- anticipated clinical heterogeneity in individual study populations and intervention (including dosing, timing and formulation of corticosteroids)

Background

Description of the condition

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. The primary immune mechanisms include hyper-stimulation of the inflammatory cascade and upregulation of related cytokines (including TNF-α, IL-1, IL-6). Hemodynamic instability secondary to vasodilation and dysregulation of coagulation and fibrinolysis are key contributors to tissue hypoperfusion and organ injury [2]. Septic shock is defined by the need for vasopressors to maintain a mean arterial pressure over 65mm Hg or greater and a serum lactate greater than 2 mmol/L in the absence of hypovolemia.

The incidence of sepsis varies from 900,000 to 3 million cases in the United States per year depending on the epidemiological methodology employed [3, 4]. In-hospital mortality of sepsis ranges from 14.7% to 30% in children and adults [3, 5]. Although hospital mortality rates from sepsis may have declined over the last 20 years, the incidence of sepsis seems to be increasing [6].

Description of intervention

The sympathetic nervous system is activated by external stressors, such as sepsis, leading to the release of endogenous catecholamines and cortisol from the adrenal glands. Cortisol is the major endogenous glucocorticoid in the body and down-regulates production of inflammatory cytokines through inhibition of NF-KB [7]. Cortisol also has other physiologic effects in the body including increasing glucose levels (through enhanced hepatic gluconeogenesis and decreased peripheral glucose uptake), and increasing blood pressure (via increasing sensitivity to catecholamines).

Corticosteroids are synthetic cortisol compounds, which exert similar effects to their endogenous counterparts. In addition to glucocorticoid activity, many synthetic corticosteroids also have mineralocorticoid components that serve as substrate precursors for catecholamine synthesis [8]. Some of the corticosteroids that have been investigated in the setting of sepsis include hydrocortisone[9-16], methylprednisolone[17-20], and prednisone[21, 22]. Dosing regimes vary considerably with some studies giving large doses over 2-3 days and then stopping and others giving lower doses over 1-2 weeks with a gradual taper.

How the intervention might work

Cortisol deficiency in sepsis is likely multifactorial, usually reversible, and results in an inadequate amount of cortisol at the tissue level [23]. Likewise, tissue resistance to corticosteroids is multifactorial and may involve alteration in the number or function of glucocorticoid receptors, cortisol metabolism or access to tissues. The result of removing this ‘check’ on the host immune response is unregulated activation of the inflammatory cascade leading to end organ dysfunction. Also, the relative deficiency of mineralocorticoids may further contribute to systemic hypoperfusion, a subsequent decrease in oxygenated blood delivery to the periphery and further end-organ damage.

Exogenous supplementation with agents that have both glucocorticoid and mineralcorticoid activity is therefore a promising therapeutic option in patients with sepsis.

Why it is important to do this review

Despite strong physiologic rationale for administration of corticosteroids in sepsis, uncertainty regarding the overall clinical effectiveness and the challenge of identifying patients who may benefit from their use has ultimately led to a high degree of practice variation [24, 25]. In the 55 years since the first randomized controlled trial (RCT) of corticosteroids in sepsis, their utility remains debated in the management of critically ill patients. The most recent systematic review suggested that steroids may reduce mortality in sepsis, although conclusions were based on low certainty in the evidence, and were limited by imprecision, inconsistency and the potential for publication bias [26]. Results from this review suggested that patients with septic shock and those treated with a low dose and long course of corticosteroids had the highest likelihood of benefit.

Since the most recently published review, an additional large RCT was published [27] and another is planned for publication shortly [28]. Our updated systematic review and meta-analysis will include these two new trials, and any others identified in the updated search, in order to improve precision of the pooled point estimates of the treatment effect of corticosteroids in patients with sepsis. The new trials will provide data for at least 1600 additional patients from what we expect are trials at low risk of bias. This will substantially improve the power to detect clinically important effects; the previous review included 4200 patients from trials with various degrees of credibility.

This systematic review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation program (www.magicproject.org) and *The BMJ* [29]. The aim of the project is to respond to new potentially practice-changing evidence and provide a trustworthy practice guideline in a timely manner. The anticipated publication of the APROCCHSS trial [30], a multicentre trial that randomised 1241 patients with septic shock to receive hydrocortisone and fludrocortisone or placebo is the trigger for this updated review. This systematic review will inform a parallel clinical practice guideline which will be published in a multi-layered electronic format on *The BMJ* and MAGICapp.

Objectives

We plan to conduct a systematic review and meta-analysis of all published RCTs that have investigated the use of corticosteroids in critically ill patients with sepsis.

Methods

Studies

We plan to include all RCTs reporting the use of corticosteroids in critically ill patients with sepsis. We will exclude case reports, case series, and observational studies. We will not impose any methodological quality or language restrictions to the studies included, and will appraise their risk of bias (see corresponding section below).

Participants
The population of interest includes all adult and children (excluding premature infants due to higher rates of adrenal insufficiency in this population [31]) who were diagnosed with sepsis, severe sepsis or septic shock according to appropriate criteria [1, 32, 33]. We will include data from trials enrolling patients with acute respiratory distress syndrome (ARDS) if patients with sepsis are reported separately.

Interventions and comparators
The intervention of interest is the administration of systemic corticosteroids, including but not limited to, cortisone, hydrocortisone, methylprednisolone, betamethasone, fludrocortisone, and dexamethasone. We will only include RCTs with a placebo or no corticosteroid comparator group.

For the purposes of this review, high-dose corticosteroids will be considered any dose greater than 400 mg/day of hydrocortisone or equivalent. Similarly, long duration of corticosteroid treatment will be considered greater than or equal to 3 days. These operational definitions are rationalized based on a change in philosophy regarding the role of corticosteroids in sepsis that occurred in the late 1990s. Older studies administered very high dose and short duration corticosteroids attempting to maximize their anti-inflammatory effect, whereas newer studies used lower dose and longer duration corticosteroids with the intent of compensating for a dysfunctional hypothalamic-pituitary axis response to stress.

Outcome measures
Patient important outcomes have been chosen by a semi-independent parallel BMJ Rapid Recommendation guideline panel and include the outcomes that are critical for choosing whether to use corticosteroids in sepsis [34].

The outcomes are:

- short-term mortality
    - 90-day mortality
    - 28-day, 30-day, hospital, ICU mortality (whichever is available)
- long-term mortality (closest to 1 year)
- number of participants with shock reversal at day 7 (stable hemodynamic status over 24 hours after withdrawal of vasopressors)
- organ dysfunction at day 7 (using total SOFA score)
- intensive care unit (ICU) length of stay
- hospital length of stay
- adverse events associated with corticosteroids including ICU-acquired neuromuscular weakness, gastrointestinal bleeding, neuropsychiatric effects, hypernatremia, superinfection, vascular events (stroke, myocardial infarction) and clinically significant hyperglycemia
- Quality of life (using validated indices such as SF-36) at 1 year

Search methods for identification of studies

A search and screening process from a Cochrane review on the same topic was credible and comprehensive to October 2014 [35]. Using the same search strategy, we will search Medline, EMBASE, LILACS, and the Cochrane trial registry for RCTs investigating the use of corticosteroids in patients with sepsis from a database entry date of September 2014. We will not use any language restrictions. See appendix for MEDLINE search strategy. Keyword search terms include corticosteroids, sepsis and septic shock.

Searching other resources

We will search the references of review articles and systematic reviews on the same topic for eligible articles. In addition, we will search for unpublished or ongoing trials on the WHO international clinical trials registry (WHO ICTRP), current controlled trials metaregister of controlled trials, and clinicaltrials.gov database. Two reviewers will search conference proceedings from the Society of Critical Care Medicine, American Thoracic Society, and the European Society of Intensive Care Medicine (2014 and onwards).

Data collection and analysis

Upon implementation of our search strategy, reviewers working in pairs will independently screen all citations and references using specific eligibility criteria. If disagreements between the two primary reviewers cannot be resolved by discussion and consensus, a third reviewer will make the final determination of trial eligibility. We will attempt to contact study authors to obtain missing information necessary to judge trial eligibility.

Data extraction and management

Data extraction will be done independently and in duplicate using pre-designed data abstraction forms. Abstracted data will include study title, first author, relevant demographic data, details of the intervention and control, primary and secondary outcome data, and information on methodological quality for each study. A third reviewer will resolve inconsistent data extraction between the two reviewers. We will perform data collection on studies included in the previous review [35] only for outcomes or subgroups that were not previously reported.

Assessment of risk of bias in included studies

Two reviewers will independently assess the risk of bias for each included study using the modified version of the Cochrane Collaboration tool [36]. Risk of bias assessment will be performed for individual studies separately for each outcome. A third reviewer will resolve disagreements.

The included RCTs will be assessed for sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and missing participant data. Sequence generation will be considered adequate if the study explicitly described an appropriate randomization procedure to generate an unpredictable sequence of allocation, including computerized randomization, use of random number tables and coin-tossing. Concealment of allocation will be considered adequate if specific methods to protect

allocation were documented and implemented. Performance bias will be considered low if a study reported participant, caregiver and/or researcher blinding. Blinding of outcome assessment will be considered adequate if outcome assessors and adjudicators were blinded. Within-study selective reporting of outcomes will be examined by reviewing the *a priori* study protocol, if available. If the study protocol is not available, we will compare the outcomes listed in the methods section with the reported outcomes in the results section.

A description for each domain assessed will be included along with comments if necessary and a final judgment for each outcome within each study and categorized as: (1) Low risk of bias, where bias is not present or if present, unlikely to affect outcomes, (2) Probably low risk of bias, (3) Probably high risk of bias, or (4) High risk of bias, where outcomes are likely to be significantly affected by bias. We will consider the highest risk of bias for any criteria as the overall risk of bias for the study.

Measures of treatment effect

We will use RevMan 5.3 software to conduct meta-analyses. We will use the method of DerSimonian and Laird for random effects model to pool effect sizes for each outcome. Study weights will be generated using the inverse variance method. We will present the results as relative risk (RR) with 95% confidence intervals (CI) for dichotomous outcomes and as mean difference (MD) or standardized mean difference (SMD) for continuous outcomes with 95% CI. We plan to perform random effect analysis for all outcomes of interest.

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to quantify the absolute magnitude of effect. We will use representative and trustworthy observational studies to measure baseline risk and apply the relative effect measured from the meta-analysis to obtain absolute differences (risk difference or mean difference) with a 95% CI. The risk difference with 95% CI will be derived from pooled risk ratios and its 95% CI utilizing assumed control risk for each outcome [37].

Dealing with missing data

Where possible, if missing data are encountered we will attempt to contact the individual study authors for additional information. If this is not possible, we will analyze the available data and report on the potential impact of missing data on the results in the discussion section. We will perform a complete case analysis as the primary analysis for all outcomes and perform sensitivity analyses with increasingly extreme assumptions for missing participant data [38].

Assessment of reporting biases

We will look for potential publication bias using a funnel plot if more than 10 trials are included. For continuous outcomes, the Egger test [39] will be used to detect funnel plot asymmetry. For dichotomous outcomes, the arcsine test will be used. All analyses will be performed using RevMan or R.

Subgroup analysis and investigation of heterogeneity

We will assess for heterogeneity between studies using the chi-squared test for homogeneity, where $p < 0.10$ indicates substantial heterogeneity, and the I^2 statistic, in addition to visual inspection of the forest plots for magnitude of differences. If subgroup effects are credible, we will present the outcomes separately for each subgroup [40]. If serious heterogeneity remains, we will rate down our certainty in the effect estimate [41].

We will conduct *a priori* subgroup analyses, which were chosen by the parallel BMJ Rapid Recommendation panel (hypothesized direction of effect in parentheses):

- risk of bias (corticosteroids more effective in trials with high risk of bias),
- treatment dose (corticosteroids more effective in trials with lower doses),
- treatment duration (corticosteroids more effective in trials with longer duration),
- treatment molecule (corticosteroids more effective in trials with drugs having more mineralocorticoid activity),
- sepsis population subtype (sepsis, septic shock, pneumosepsis) (corticosteroids most effective in patients with pneumonia and those with septic shock, and least effective in patients with non-pneumonia sepsis without shock),
- age of patients (corticosteroids more effective in studies enrolling children [<18 years old] than adults),
- and presence of critical illness related corticosteroid insufficiency (CIRCI) (corticosteroids more effective in trials identifying and enrolling patients with CIRCI).

For subgroup analyses, we will perform meta-regression if a sufficient number of studies are found (generally greater than 10). If not, we will use the chi-square test for each subgroup hypothesis, and then meta-regression if more than one is found to be statistically significant (using a p-value threshold of < 0.10).

Sensitivity analysis

Sensitivity analysis will be performed excluding studies only reported as abstracts.

Assessing the certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the certainty of evidence for each outcome [42]. The GRADE system classifies the certainty of the aggregate body of evidence as high, moderate, low, or very low. The evidence will be evaluated using the following criteria: 1) study design and rigour of its execution (ie, individual study risk of bias), 2) the extent to which the evidence could be applied to patients of interest (ie, directness), 3) the consistency of results, 4) the analysis of the results (ie. precision), and 5) whether there is a likelihood of publication bias.

For each outcome, a final overall certainty of evidence will be summarized for the intervention taking into consideration both desirable and undesirable outcomes. An evidence profile will be included in the results showing the GRADE assessments and pooled analysis per outcome.

Guideline Panel and Patient Involvement

According to the *BMJ* Rapid Recommendations process [34], the guideline panel has already provided critical oversight and identified populations, subgroups, and outcomes of interest for this review. The panel includes content experts, methodologists, and patients or carers with personal experience with sepsis. The panel is considered semi-independent of the systematic review team as four individuals are members of both. All patients receive personal training and support to optimise contributions throughout the guideline development process. The patient panel members will be invited to lead the interpretation of the results based on what they expect the typical patient values and preferences to be, as well as the variation between patients.

Discussion

Despite a large body of evidence, the role of corticosteroids in sepsis remains controversial. Given the forthcoming availability of new data addressing this research question, an updated systematic review and meta-analysis is needed to generate the best summary of evidence in order to help guideline developers and to assist bedside clinicians. This systematic review will summarize the RCT data on the efficacy and safety of corticosteroid use in critically ill patients with sepsis. Also, as future trial results become available (eg. NCT01448109) we will be able to rapidly incorporate the results into this evidence summary.

Strengths of this protocol include a comprehensive search strategy of published and unpublished literature, *a priori* subgroup analysis plan, and inclusion of GRADE methodology to characterize the certainty in evidence and confidence in the estimates of effect. Results of this review will be accompanied by a BMJ Rapid Recommendation [34, 43-45] for front line clinicians . Limitations relate to the anticipated clinical heterogeneity of patients, corticosteroid regimes and outcome assessments from included studies.

Abbreviations

EMBASE, Excerpta Medica database; ICU, intensive care unit; RR, relative risk; CI, confidence interval; MD, mean difference; SMD, standardized mean difference; GRADE, grading of recommendations assessment development and evaluation; CIRCI, critical illness related corticosteroid deficiencey; TNF, tumour necrosis factor; IL, interleukin; HPA, hypothalamic-pituitary-adrenal; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone; NF-Kβ, nuclear factor kappa-light-chain enhancer; I-CAM, intracellular adhesion molecule; RCT, randomized controlled trial; ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment score; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform; MD, mean difference; SMD, standardized mean difference; ACR, assumed control risk; NNT, number needed to treat

Competing interests

The authors declare that they have no financial competing interests.

Authors' contributions

BR, RS, TA, PV & GG conceived the idea for this systematic review. BR, SO, RS, KM, WS, SE, TA, EBC, FD, WA, ED, KGK, JS, PV, BV, GG and DA developed the methodology for the systematic review. The protocol manuscript was drafted by BR and revised by SO, RS, KM, WS, SE, TA, EBC, FD, WA, ED, KGK, JS, PV, BV, GG and DA. BR and SO will plan to screen potential studies, perform duplicate independent data abstraction, risk of bias assessment and GRADE assessment with help from RS, TA, WS, WA, ED, FD, EBC and KGK. BR will conduct the data synthesis. BR is the guarantor of the review.

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Appendix. Search strategy for MEDLINE (Ovid SP)

1. exp Sepsis/
2. exp Shock, Septic/
3. (sepsis or septic shock).mp.
4. 1 or 2 or 3
5. exp Adrenal Cortex Hormones/
6. (corticosteroid* or steroid*).mp.
7. 6 or 5
8. 4 and 7
9. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.
ab. or trial.ti.) not (animals not (humans and animals)).sh.
10. 8 and 9

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
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
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4 - NA	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
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c N/A	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
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 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
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
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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)
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
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
Outcomes and prioritization	13 ☐	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
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
Data synthesis	15a ☐	Describe criteria under which study data will be quantitatively synthesised
	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)
	15c ☐	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d N/A	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)
Confidence in cumulative evidence	17 ☐	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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