BMJ Open

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 randomised 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 randomised 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 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% CI for dichotomous outcomes and as mean difference or standardised 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 summarise the updated evidence on the efficacy and safety of corticosteroids in patients with sepsis.

Trial registration number CRD42017058537.

Strengths and limitations of this study

► Systematic and comprehensive search.
► Multidisciplinary team including oversight and input from semi-independent *BMJ* Rapid Recommendation panel which includes patient and carer representatives.
► The results of this review will directly inform *BMJ* Rapid Recommendation clinical practice guideline recommendation.
► Application of Grading of Recommendations, Assessment, Development and Evaluation methodology to assess certainty in summarised estimates of effect.
► 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 a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] The primary immune mechanisms include hyperstimulation of the inflammatory cascade and upregulation of related cytokines (including tumour necrosis factor-α, interleukin (IL)-1, IL-6). Haemodynamic 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 ≥65 mm Hg and a serum lactate >2 mmol/L in the absence of hypovolaemia.

The incidence of sepsis varies from 900 000 to 3 million cases in the USA 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 downregulates production of inflammatory cytokines through inhibition of nuclear factor-κB.[7] Cortisol also has other physiological 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 regimens 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 mineralocorticoid activity is therefore a promising therapeutic option in patients with sepsis.

Why it is important to do this review

Despite strong physiological 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 randomised 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 Recommendation project, a collaborative effort from the MAGIC research and innovation programme (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 multilayered 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 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 >400 mg/day of

hydrocortisone or equivalent. Similarly, long duration of corticosteroid treatment will be considered ≥3 days. These operational definitions are rationalised 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 maximise 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, intensive care unit (ICU) mortality (whichever is available);
► long-term mortality (closest to 1 year);
► number of participants with shock reversal at day 7 (stable haemodynamic status over 24 hours after withdrawal of vasopressors);
► organ dysfunction at day 7 (using total SOFA score);
► 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 hyperglycaemia;
► 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 online supplementary appendix 1 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, 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

On 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 predesigned 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 randomisation procedure to generate an unpredictable sequence of allocation, including computerised randomisation, 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 judgement for each outcome within each study and categorised 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 V.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 with 95% CI for dichotomous outcomes and as mean difference (MD) or standardised MD 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 MD) with a 95% CI. The risk difference with 95% CI will be derived from pooled risk ratios and its 95% CI using 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 analyse 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 >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 χ^2 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 (hypothesised 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) than adults);
► 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 >10). If not, we will use the χ^2 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 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 summarised 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 summarise 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 characterise 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 regimens and outcome assessments from included studies.

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Provenance and peer review Not commissioned; externally peer reviewed.

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