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Corticosteroids for treating sepsis in children and adults (Review)

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[Intervention Review]

Corticosteroids for treating sepsis in children and adults

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ABSTRACT

Background

Sepsis occurs when an infection is complicated by organ failure. Sepsis may be complicated by impaired corticosteroid metabolism. Thus, providing corticosteroids may benefit patients. The original review was published in 2004 and was updated in 2010 and 2015 prior to this update.

Objectives

To examine the effects of corticosteroids on death in children and adults with sepsis.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS, ClinicalTrials.gov, ISRCTN, and the WHO Clinical Trials Search Portal, on 25 July 2019. In addition, we conducted reference checking and citation searching, and contacted study authors, to identify additional studies as needed.

Selection criteria

We included randomized controlled trials (RCTs) of corticosteroids versus placebo or usual care (antimicrobials, fluid replacement, and vasopressor therapy as needed) in children and adults with sepsis. We also included RCTs of continuous infusion versus intermittent bolus of corticosteroids.

Data collection and analysis

All review authors screened and selected studies for inclusion. One review author extracted data, which was checked by the others, and by the lead author of the primary study when possible. We obtained unpublished data from the authors of some trials. We assessed the methodological quality of trials and applied GRADE to assess the certainty of evidence. Review authors did not contribute to assessment of eligibility and risk of bias, nor to data extraction, for trials they had participated in.

Main results

We included 61 trials (12,192 participants), of which six included only children, two included children and adults, and the remaining trials included only adults. Nine studies are ongoing and will be considered in future versions of this review. We judged 19 trials as being at low risk of bias.

Corticosteroids versus placebo or usual care

Compared to placebo or usual care, corticosteroids probably slightly reduce 28-day mortality (risk ratio (RR) 0.91, 95% confidence interval (CI) 0.84 to 0.99; 11,233 participants; 50 studies; moderate-certainty evidence). Corticosteroids may result in little to no difference in long-term mortality (RR 0.97, 95% CI 0.91 to 1.03; 6236 participants; 7 studies; low-certainty evidence) and probably slightly reduce hospital mortality (RR 0.90, 95% CI 0.82 to 0.99; 8183 participants; 26 trials; moderate-certainty evidence). Corticosteroids reduced length of intensive care unit (ICU) stay for all participants (mean difference (MD) -1.07 days, 95% CI -1.95 to -0.19; 7612 participants; 21 studies; high-certainty evidence) and resulted in a large reduction in length of hospital stay for all participants (MD -1.63 days, 95% CI -2.93 to -0.33; 8795 participants; 22 studies; high-certainty evidence). Corticosteroids increase the risk of muscle weakness (RR 1.21, 95% CI 1.01 to 1.44; 6145 participants; 6 studies; high-certainty evidence). Corticosteroids probably do not increase the risk of superinfection (RR 1.06, 95% CI 0.95 to 1.19; 5356 participants; 25 studies; moderate-certainty evidence). Corticosteroids increase the risk of hypernatraemia (high-certainty evidence) and probably increase the risk of hyperglycaemia (moderate-certainty evidence). Moderate-certainty evidence shows that there is probably little or no difference in gastroduodenal bleeding, stroke, or cardiac events, and low-certainty evidence suggests that corticosteroids may result in little to no difference in neuropsychiatric events.

Continuous infusion of corticosteroids versus intermittent bolus

We are uncertain about the effects of continuous infusion of corticosteroids compared with intermittent bolus administration. Three studies reported data for this comparison, and the certainty of evidence for all outcomes was very low.

Authors' conclusions

Moderate-certainty evidence indicates that corticosteroids probably reduce 28-day and hospital mortality among patients with sepsis. Corticosteroids result in large reductions in ICU and hospital length of stay (high-certainty evidence). There may be little or no difference in the risk of major complications; however, corticosteroids increase the risk of muscle weakness and hypernatraemia, and probably increase the risk of hyperglycaemia. The effects of continuous versus intermittent bolus administration of corticosteroids are uncertain.

PLAIN LANGUAGE SUMMARY

Corticosteroids for treating sepsis

Review question

We reviewed the evidence on the effect on death of using corticosteroids in children and adults with sepsis.

Background

Sepsis is present when an infection is complicated by organ failure. People develop rapid breathing, hypotension (low blood pressure), and mental confusion. Sepsis can interfere with the effectiveness of the body’s corticosteroids, which serve as a key defence against infection. Corticosteroids have been given for decades to people with infection resulting from various causes.

Search date

The evidence provided in this review is current to July 2019.

Study characteristics

This review included 61 trials (12,192 participants). Fifty-eight trials compared corticosteroids to no corticosteroids (placebo or usual care in 48 and nine trials, respectively); three trials also compared continuous versus bolus administration of corticosteroids.

Study funding sources

Three trials were funded by a drug company, 27 by public organizations or through charitable funding, and six by both a drug company and public organizations or charitable funding; 25 did not declare the source of funding.

Key results

We have analysed the following two comparisons.

• Corticosteroids versus placebo/usual care.

Corticosteroids probably reduce the risk of death at 28 days by 9% (50 trials; 11,233 participants), with consistent treatment effects between children and adults. They also probably slightly reduce the risk of dying in hospital. There may be little or no effect of corticosteroids on risk of dying over the long term (longer than three months), but these results are less certain. Corticosteroids result in a large reduction in length of stay in the intensive care unit (ICU) and in hospital. Corticosteroids increase the risk of muscle weakness and hypernatraemia. They probably increase the risk of hyperglycaemia. They probably do not increase the risk of superinfection. There may be little or no effect of corticosteroids on risk of gastroduodenal bleeding, neuropsychiatric events, stroke, or cardiac events.

• Continuous infusion versus intermittent boluses of corticosteroids.

We are uncertain about the effects of continuous infusion of corticosteroids compared with intermittent bolus administration. Three studies reported data for this comparison, and the certainty of evidence for all outcomes was very low.

Certainty of evidence

• Corticosteroids versus placebo/usual care

We judged the certainty of evidence for 28-day mortality as moderate due to some inconsistency related to differences among study populations, types of corticosteroids and how they were given, and use of additional interventions.

• Continuous infusion versus intermittent boluses of corticosteroids

We judged the certainty of evidence for 28-day mortality as very low due to inconsistency and imprecision.

Summary of findings for the main comparison. Corticosteroids compared to placebo or usual care for treating sepsis

Corticosteroids compared to placebo or usual care for treating sepsis

Patient or population: children and adults with sepsis
Setting: hospitalised patients; trials were performed in numerous countries from the 5 continents
Intervention: corticosteroids
Comparison: placebo or usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or usual care	Risk with corticosteroids				
28-Day all-cause mortality[a]	Study population		RR 0.91 (0.84 to 0.99)	11233 (50 RCTs)	⊕⊕⊕⊖ Moderate[b]	Corticosteroids probably slightly reduce 28-day all-cause mortality
	264 per 1000	240 per 1000 (222 to 261)				
Long-term mortality[c]	Study population		RR 0.97 (0.91 to 1.03)	6236 (7 RCTs)	⊕⊕⊖⊖ Low[b,d]	Corticosteroids may result in little to no difference in long-term mortality
	386 per 1000	374 per 1000 (351 to 397)				
Hospital mortality	Study population		RR 0.90 (0.82 to 0.99)	8183 (26 RCTs)	⊕⊕⊕⊖ Moderate[b]	Corticosteroids probably slightly reduce hospital mortality
	323 per 1000	291 per 1000 (265 to 320)				
Length of intensive care unit stay for all participants in days	Mean length of intensive care unit stay for all participants was 14 days	MD 1.07 lower (1.95 lower to 0.19 lower)	-	7612 (21 RCTs)	⊕⊕⊕⊕ High[b,e]	Corticosteroids reduced length of intensive care unit stay for all participants
Length of hospital stay for all participants in days	Mean length of hospital stay for all participants was 21 days	MD 1.63 lower (2.93 lower to 0.33 lower)	-	8795 (22 RCTs)	⊕⊕⊕⊕ High[b,e]	Corticosteroids result in a large reduction in length of hospital stay for all participants
Number of participants with adverse events -	Study population		RR 1.06 (0.95 to 1.19)	5356 (25 RCTs)	⊕⊕⊕⊕ Moderate[d]	Corticosteroids probably do not increase the number of participants with adverse events - superinfection
	169 per 1000	180 per 1000				

superinfection (up to longest follow-up)		(161 to 202)				
Number of participants with adverse events - muscle weakness (up to longest follow-up)	Study population		RR 1.21 (1.01 to 1.44)	6145 (6 RCTs)	⊕⊕⊕⊕ High	Corticosteroids increase the number of participants with adverse events - muscle weakness
	56 per 1000	68 per 1000 (57 to 81)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio.

The unit of measure for length of stay is days.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Sensitivity analysis based on trials judged as being at low risk of bias showed an RR for dying at 28 days of 0.91 (95% CI 0.84 to 0.98; P = 0.01; 7896 participants; 17 studies; I^2 = 0%).
[b]Downgraded one level for inconsistency; there was significant statistical heterogeneity.
[c]Long-term mortality was recorded up to six months for three trials (Annane 2018; Keh 2016; Venkatesh 2018), and up to one year for four trials (Annane 2002; Briegel 1999; Meduri 2007; Sprung 2008).
[d]Large 95% confidence interval overlapping the neutrality line.
[e]Upgraded one level due to large size effects.

BACKGROUND

Description of the condition

Sepsis occurs when the host response to an infection is dysregulated (Singer 2016). The dysregulated host response is usually defined by the presence of a sequential organ failure assessment (SOFA) score of 2 or higher (Singer 2016; Vincent 1996). Septic shock is a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with greater risk of mortality than is sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain mean arterial pressure of 65 mmHg or greater and serum lactate levels greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolaemia. The dysregulated response may result in systemic inflammation and organ damage, or in immune paresis and secondary infection (van der Poll 2017). In 2017, the World Health Organization estimated that around 31 million people develop sepsis each year, and about 10 million die (WHO 2018). According to a recent retrospective cohort study of adult patients admitted to 409 academic, community, and federal hospitals in the USA from 2009 to 2014, sepsis was present in 6% of adult hospitalizations (Rhee 2017). Another study of electronic health records from 27 academic hospitals in the USA reported an annual incidence of septic shock of about 19 per 1000 hospitalizations in 2014 (Kadri 2017). People with sepsis usually die from hypotension or progressive multiple organ failure (Angus 2013; Annane 2003; Annane 2005; Parrillo 1993). There is no current diagnostic test for sepsis. Its standard management includes control of the source of infection with antibiotics and surgery whenever needed, as well as control of tissue oxygenation with fluid replacement, oxygen with or without respiratory support, and vasopressors whenever needed (Rhodes 2017). No specific interventions are yet available to control immune responses to invading pathogens (Rhodes 2017). The financial burden of sepsis on the healthcare system has been calculated to be > 24 billion USD, representing 6.2% of total hospital costs in 2013 (WHO 2018). Studies in Europe and Canada estimated the daily costs of hospital care for a septic patient in 2000 to be between EUR 710 and EUR 1033 (equivalent to about USD 645 and USD 939, respectively) (WHO 2018).

Description of the intervention

Corticosteroids include the natural steroid hormones produced by adrenocortical cells and a broad variety of synthetic analogues. These substances have various effects that may be grossly classified into glucocorticoid and mineralocorticoid effects. Glucocorticoid effects include mainly regulation of carbohydrate, lipid, and protein metabolism, as well as regulation of inflammation. Mineralocorticoid effects include mainly regulation of electrolyte and water metabolism. At molecular levels, glucocorticoids have non-genomic and genomic effects (Annane 2017a; Cain 2017). Rapid (within minutes) non-genomic effects of glucocorticoids include a decrease in platelet aggregation, in cell adhesion, and in intracellular phosphotyrosine kinases, and they include an increase in annexin 1 externalization (Lowenberg 2005). These effects may result from the interaction of glucocorticoids with specific membrane sites (Norman 2004). Glucocorticoids have indirect genomic effects, called trans-repression (Rhen 2005). These occur within a few hours following exposure of cells to glucocorticoids. They result from the physical interaction between the monomeric glucocorticoid-glucocorticoid receptor (G-GR)α complex and various nuclear transcription factors, such as nuclear factor (NF)-κB and activator protein (AP)-1. Subsequently, these nuclear transcription factors are sequestrated in the cytosol and cannot enter the nucleus, preventing the expression of genes encoding for most if not all pro-inflammatory mediators. Glucocorticoids also have direct genomic effects, called transactivation. They require only a few days of cell exposure to glucocorticoids. Indeed, conformational changes (i.e. dimerization of the G-GRα complex) are needed before this complex can migrate to the nucleus to interact with glucocorticoid-responsive elements, that is, parts of genes encoding for regulators of termination of inflammation. Then, key anti-inflammatory factors are up-regulated, leading to phagocytosis, chemokinesis, and anti-oxidative processes. The net effect of glucocorticoids involves reprogramming rather than inhibiting immune cell function (Erschen 2007). Glucocorticoids induce specific activated anti-inflammatory monocyte subtypes that migrate quickly to inflamed tissues (Varga 2008). They prolong survival of this subtype of monocyte via A3 adenosine receptor-triggered anti-apoptotic effects (Barczyk 2010). Overall, these molecular mechanisms of action of glucocorticoids are appropriate for counteracting the uncontrolled inflammation that may characterize sepsis.

How the intervention might work

Researchers have explored the biological mechanisms of sepsis to investigate potential interventions. Corticosteroids have been a topic of particular focus because of their influence on the immune response (Cain 2017). In sepsis, the hypothalamic-pituitary gland hormonal pathway to the adrenal glands stimulates corticosteroid production (Annane 2017a; Chrousos 1995; Cooper 2003; Heming 2018). These hormones affect inflammation through the production of white blood cells, cytokines (proteins that influence the immune response), and nitric oxide. In sepsis, cytokines may suppress adrenocorticotropin hormone synthesis (Annane 2017a; Polito 2011; Sharshar 2003), along with the cortisol response to exogenous adrenocorticotropin hormone (Annane 2017a; Hotta 1986; Jaattela 1991). Likewise, sepsis may be associated with alterations in scavenger receptor B1-mediated cholesterol delivery (Cai 2008). This causes poor adrenal activity in almost half of patients (Annane 2000; Lipiner 2007; Marik 2008; Rothwell 1991), as well as possible resistance of body tissues to corticosteroids due to fewer corticosteroid receptors or receptors with lower affinity (Barnes 1995; Huang 1987; Meduri 1998a; Molijn 1995). Alteration of corticosteroid receptor numbers and in binding capacity may be related at least in part to nitric oxide (Duma 2004; Galigniana 1999). Recent work suggests that immune cells - not steroid-secreting cells - are key regulators of the interaction between the immune system and the adrenals (Kanczkowski 2013). In addition, acute illness such as sepsis may be associated with decreased cortisol clearance from plasma (Boonen 2013; Melby 1958), likely resulting from altered hepatic and renal inactivation of cortisol (Boonen 2013). Early studies showed that a pharmacological dose of corticosteroids prolonged survival among animals with sepsis (Fabian 1982). More recent studies in rodents have demonstrated that lower doses of corticosteroids, for example, 0.1 mg/kg of dexamethasone, improved haemodynamic and organ function, favourably modulated the inflammatory response, and prolonged survival (di Villa Bianca 2003; Heller 2003; Tsao 2004; Vachharajani 2006). Protective effects of these glucocorticoids against sepsis may be mediated in part by the endothelial glucocorticoid receptor (Goodwin 2013). In healthy volunteers challenged with endotoxin,

a low dose of corticosteroids, for example, 10 mg of prednisolone, blocked the release of pro-inflammatory cytokines, prevented endothelial cell and neutrophil activation, and inhibited the acute phase response without altering coagulation and fibrinolysis balance (de Kruif 2007). Studies in patients with septic shock have shown that a short course of corticosteroids may result in a rebound in the systemic inflammatory response (Briegel 1994; Keh 2003). In addition, it is now recognized that increased pro-inflammatory cytokine release can be sustained for longer than a week in patients with sepsis (Kellum 2007). Likewise, the timing of initiation of corticosteroids may be an important factor in the response to treatment. Indeed, in observational studies, short-term mortality increased with delayed initiation of hydrocortisone (Katsenos 2014; Park 2012). For these reasons, we would anticipate that corticosteroid treatment is beneficial for patients with sepsis, and that differences in dose, timing, or duration of corticosteroid treatment may differentially affect patient response to treatment. Finally, several authors have argued that in patients with sepsis, hydrocortisone should be given as a continuous infusion rather than as intermittent boluses to reduce the risk of metabolic complications (Rhodes 2017). In sepsis trials, continuous infusion of hydrocortisone was variably associated with better outcomes or worse outcomes than intermittent intravenous boluses (Loisa 2007; Tilouche 2019).

Why it is important to do this review

Initially, researchers used high doses of corticosteroids, usually given as a single bolus, in an attempt to block potential bursts in pro-inflammatory cytokines. Two systematic reviews and meta-analyses of trials of corticosteroids in sepsis or in septic shock included 10 - Lefering 1995 - and nine - Cronin 1995 - randomized controlled trials (RCTs), respectively. These systematic reviews showed no significant effect on relative risk of death, gastrointestinal bleeding, or superinfection associated with the use of corticosteroids.

Subsequently, most clinicians will not recommend the use of high doses of corticosteroids in sepsis (Annane 2017b; Rhodes 2017). The potential benefits of a lower dose (≤ 400 mg hydrocortisone or equivalent per day) and a longer duration at full dose (≥ 3 days) of treatment have been investigated in numerous RCTs over the past three decades (Annane 2017b; Lamontagne 2018; Rochwerg 2018). In the past two years, clinical practice guidelines about corticosteroid use in sepsis have been released by at least five entities (Annane 2017b; Lamontagne 2018; Nishida 2018; Rhodes 2017; Tavaré 2017). All but one of the guidelines - Lamontagne 2018 - recommended against the use of corticosteroids in sepsis, except in patients with septic shock and a poor response to fluid replacement and vasopressor therapy. Some guidelines suggested that corticosteroids should be given as a continuous infusion rather than in intermittent boluses (Annane 2017b; Rhodes 2017). In the year 2018, five different systematic reviews and meta-analyses addressed the effects of corticosteroids in sepsis (Allen 2018; Fang 2018; Ni 2018; Rochwerg 2018; Rygard 2018). The number of included trials was different in all reviews and ranged from 14 to 42. The risk ratio of death in the short term varied from 0.91 to 0.96, and the upper limit of the 95% confidence interval (CI) varied from 0.98 to 1.03. Another systematic review and meta-analysis of one randomized trial and 17 observational studies examined the risk of acquired muscle weakness associated with exposure to corticosteroids in patients in the intensive care unit (ICU) (Yang 2018). This review found an odds ratio for acquired muscle weakness of 1.84 (95% CI 1.26 to 2.67) with corticosteroids compared to control.

Therefore, we aim to systematically review the effects of corticosteroids in children and adults with sepsis.

OBJECTIVES

To examine the effects of corticosteroids on death in children and adults with sepsis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) with no methodological restrictions. We excluded quasi-randomized trials (i.e. trials assigning patients to treatment arms based on systematic methods, such as alternation, assignment based on date of birth, case record number, and date of presentation).

Types of participants

We included children and adults with sepsis as defined by the Sepsis 3 criteria - Singer 2016 - or by the following criteria (ACCP/SCCM 1992; Vincent 2013).

- Suspected or documented infection defined as culture or Gram stain of blood, sputum, urine, or normally sterile body fluid that is positive for a pathogenic micro-organism; or a focus of infection identified by visual inspection (e.g. ruptured bowel with the presence of free air or bowel contents in the abdomen found at the time of surgery; wound with purulent drainage).
- At least two symptoms of a systemic inflammatory response syndrome, such as fever (body temperature > 38°C) or hypothermia (< 36°C), tachycardia (> 90 beats per minute), tachypnoea (> 20 breaths per minute), or hyperventilation (arterial carbon dioxide tension ($PaCO_2$) < 32 mmHg), and abnormal white blood cell count (> 12,000 cells/mL or < 4000 cells/mL) or more than 10% immature band of neutrophils.
- At least one sign of organ dysfunction, that is, metabolic acidosis, arterial hypoxaemia (arterial oxygen tension (PaO_2):fractional inspired oxygen (FiO_2) < 250 mmHg), oliguria (< 30 mL/h for ≥ 3 hours), coagulopathy, or encephalopathy.

Septic shock is defined by the presence of sepsis and of hypotension (persisting systolic arterial pressure < 90 mmHg) that is refractory to fluid resuscitation and requires vasopressor support (i.e. > 5 µg/kg of body weight per minute of dopamine or any dose of epinephrine or norepinephrine).

We included data from trials of community-acquired pneumonia or acute respiratory distress syndrome (ARDS) when separate data were available for participants with sepsis, or when contact with study authors resulted in provision of the data.

Types of interventions

Corticosteroids versus placebo/usual care

Intervention

Systemic treatment was provided as any type of corticosteroid preparation (e.g. cortisone, hydrocortisone, methylprednisolone, betamethasone, dexamethasone).

Low-dose corticosteroid treatment was defined by a total dose per day of 400 mg or less of hydrocortisone (or equivalent); otherwise, the dose of corticosteroid would be considered high. A long course for the intervention was defined by a full-dose treatment duration of three or more days; otherwise, treatment was considered as a short course.

Control

Standard therapy was provided, which may have included antibiotics, fluid replacement, inotropic or vasopressor therapy, mechanical ventilation, or renal replacement therapy, or placebo.

Continuous infusion versus bolus administration of corticosteroids

Intervention

Continuous infusion was defined by intravenous infusion of corticosteroids with or without an initial loading dose.

Control

Bolus administration was defined by intermittent intravenous injections with duration less than 30 minutes.

Types of outcome measures

Primary outcomes

- 28-Day all-cause mortality

Indeed, this was the primary outcome measure in most of the RCTs on sepsis conducted since 1992 (Annane 2009b). Most studies performed before 1992 looked at 14-day or hospital mortality rates. We used these data to compute the pooled analysis for 28-day mortality, unless we could obtain actual 28-day mortality rates from primary study authors.

Secondary outcomes

- 90-Day all-cause mortality

This was the primary outcome in the two most recent and largest trials on corticosteroids for sepsis.

- Long-term (longest available follow-up beyond three months) all-cause mortality
- ICU all-cause mortality
- Hospital all-cause mortality

In-ICU and in-hospital mortality outcomes provide the location of death, which adds context to the primary outcome.

- Number of participants with shock reversal (as defined by stable haemodynamic status ≥ 24 hours after withdrawal of vasopressor therapy) at day seven and at day 28
- Number of organs affected and severity of organ dysfunction at day seven, in individual patients, as measured by the SOFA score (Vincent 1996). This score scales from 0 (normal function) to 4 (most severe) the dysfunction of six organ systems (Respiration, Coagulation, Liver, Cardiovascular, Central nervous system, Renal). It ranges from 0 (no organ failure) to 24 (most severe organ dysfunction)
- Length of stay in the ICU (for all participants and for survivors only). This outcome is expressed in mean (standard deviation (SD)) number of days, and is calculated by the difference between dates of ICU discharge and ICU admission, with first and last days of ICU stays counted as full ICU days regardless of the time of admission and time of discharge
- Length of hospital stay (for all participants and for survivors only). This outcome is expressed in mean (SD) number of days, and is calculated by the difference between dates of hospital discharge and hospital admission, with first and last days of hospital stays counted as full hospital days regardless of time of admission and time of discharge
- Adverse events (i.e. gastrointestinal bleeding, superinfection, hyperglycaemia, hypernatraemia, muscle weakness, neuropsychiatric events, stroke, cardiac events, or any other adverse effects or complications of corticosteroid treatment). Each adverse event is expressed as the number (%) of patients with at least one episode of this event, as defined in individual studies, except for hyperglycaemia and hypernatraemia. Whenever possible, hyperglycaemia was defined by values > 180 mg/dL, and hypernatraemia by values > 149 mmol/L.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (e.g. published, unpublished, in press, in progress).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2019 Issue 7), in the Cochrane Library, using the search terms 'sepsis', 'septic shock', 'steroids', and 'corticosteroids' (for the detailed search strategy, see Appendix 1).

We also searched (to 25 July 2019) MEDLINE ALL (Ovid SP), Embase (Ovid SP), and Latin American Caribbean Health Sciences Literature (LILACS), using the topic search terms in combination with the search strategy for identifying trials developed by Cochrane (Higgins 2011). (For detailed search strategies, see Appendix 2 (MEDLINE), Appendix 3 (Embase), and Appendix 4 (LILACS).)

Finally, we searched for ongoing RCTs (to 25 July 2019) at ClinicalTrials.gov, International Standard Randomized Controlled Trials Number (ISRCTN), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), using the search terms 'septic shock', 'sepsis', steroids', 'corticosteroids', 'adrenal cortex hormones', and 'glucocorticoids'.

Searching other resources

We checked the reference lists and citations of all trials and relevant systematic reviews identified by the electronic searches, and we contacted study authors to request additional published or unpublished data. We also searched the proceedings of annual meetings of major critical care medicine symposia, that is, Society of Critical Care Medicine, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, American

College of Chest Physicians, and European Society of Intensive Care Medicine (1998 to 2019).

Data collection and analysis

Selection of studies

All review authors checked the titles and abstracts identified during the search. All review authors examined, in full, any trial that potentially met the inclusion criteria. We decided which trials met the inclusion criteria. We resolved disagreements between review authors by discussion until we reached consensus. Review authors did not contribute to the decision for inclusion of trials in which they had participated.

One review author (DA) contacted study authors for clarification, when necessary.

Data extraction and management

One review author (DA) drew up a standard data extraction form, and four other review authors (PEB, JB, DK, YK) amended and validated the design of the form before data abstraction. Review authors (DA, PEB, JB, DK, RP, BR) independently extracted data, except those from trials in which they had participated.

One review author (DA) systematically contacted the authors of trials to request missing data when possible.

One review author (DA) and one member of this author's research staff independently extracted and entered data into the computer. All review authors checked the accuracy of data entered against the original articles.

Assessment of risk of bias in included studies

We assessed risk of bias within individual trials as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We considered the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and any other bias. We judged selection bias on the basis of how the random sequence was generated, and how allocation was concealed. We judged performance bias and detection bias on the basis of who was blinded and how, among participants, caregivers, pharmacists, data collectors, outcome assessors, and data analysts (Devereaux 2001). In judging attrition bias, we considered how many participants were lost to follow-up or were not included in analyses (and the reasons why). When available, we compared outcomes reported in trial protocols versus actual results reported, to identify potential selective reporting bias. We resolved disagreements between review authors by discussion until we reached consensus.

One review author (DA) contacted study authors for clarification, when necessary.

We assessed, independently and in duplicate (two of DA, BR, or RP), for each outcome of individual studies using a modified Cochrane risk of bias tool (Guyatt 2013), which 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 rated the overall risk of bias as the highest risk attributed to any criterion.

Review authors did not contribute to the assessment of risk of bias of any trial in which they had participated.

Measures of treatment effect

- We performed intention-to-treat (ITT) analyses. We performed all statistical calculations using Review Manager 2014 or Stata 2015, as appropriate
- We calculated a weighted treatment effect across trials. We expressed results as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, and as mean differences (MDs, 95% CIs) for continuous outcomes

Unit of analysis issues

In this review, we used data from trials in which the unit of randomization was the individual, and in which parallel groups were designed. For events that may occur repeatedly, such as receiving vasopressor therapy or staying in the ICU, we used only the first occurrence of the event.

When trials included more than two arms (e.g. comparing vs control two different corticosteroids or two different modes of administration of the same corticosteroid), we pooled data from the experimental arms for comparison of steroids versus control.

Dealing with missing data

We systematically tried to contact primary authors of original trials to obtain missing information and unpublished data. We obtained additional data from primary authors of 28 trials, including access to individual patient data for 16 trials (Appendix 5). This information is provided for each trial in the notes section of Characteristics of included studies.

For the primary outcome of this review (28-day all-cause mortality), we systematically contacted trial authors when needed to obtain data for participants who dropped out. When trials did not report 28-day all-cause mortality, and contact with trial authors failed to yield actual 28-day mortality rates, we used available mortality data closest to 28 days.

When trials reported length of stay in the ICU or in hospital only as median and interquartile ratio (IQR), and when contact with trial authors failed to elicit means and SDs, we did not include these trials in the analysis.

Assessment of heterogeneity

We considered that evidence for significant heterogeneity was present when $I^2 > 30\%$.

Assessment of reporting biases

We sought evidence of publication bias by using the funnel plot method. We used Stata 2015 to prepare a contour-enhanced funnel plot (Peters 2008). This graphical analysis used the standard error of the log of the RR. We plotted contours illustrating the statistical significance of study effect estimates by using a two-tailed test.

Data synthesis

We considered methods based on the random-effects model for all analyses, except when we found no evidence for significant heterogeneity in the results (i.e. $I^2 \leq 30\%$). Indeed, we suspected that we would observe heterogeneity across studies, as they

were conducted over a wide period of time (almost half a century between first and last trials) and the rationale on which studies were designed varied greatly over time, with marked differences in treatment strategies and in populations between studies conducted before and after the early 1990s.

Subgroup analysis and investigation of heterogeneity

To identify potential sources of heterogeneity, we sought, a priori, to conduct a subgroup analysis based on 'dose and duration', that is, a long course (≥ 3 days at full dose) of low-dose (≤ 400 mg/d) hydrocortisone or equivalent. This subgroup analysis allowed evaluation of a strategy based on developments in our understanding of the role of corticosteroids in host response to sepsis, as tested in trials performed after 1992. Older trials used most often a short course (one to four bolus doses within 24 hours) of high-dose corticosteroids (> 400 mg of hydrocortisone or equivalent), and trials conducted after 1992 used most often low-dose corticosteroids at full dose over a longer period (≥ 3 days).

We also conducted a subgroup analysis based on the type of corticosteroids, the method of corticosteroid administration, intravenous bolus versus continuous infusion, and termination without versus with tapering off. To further explore the putative interaction between corticosteroid dose and duration and the magnitude of effect, we considered performing a meta-regression analysis using 28-day all-cause mortality as the dependent variable, and dosage and duration of corticosteroids as predictors. We performed meta-regression analyses using Stata 2015. We also tested, a priori, the interaction between baseline severity of illness and magnitude of effect in a meta-regression analysis using mortality rates in controls as predictors. Finally, we conducted a subgroup analysis based on targeted population, sepsis, only septic shock, sepsis with ARDS, community-acquired pneumonia, and sepsis with critical illness-related corticosteroid insufficiency (Annane 2017a).

- We assessed the validity of subgroup analyses on the basis of the following criteria.
  - Subgroup comparisons within rather than between studies.
  - Hypothesis preceding the analysis.
  - One of very few hypotheses.
  - Large and consistent differences across studies.
  - External evidence supporting the results (Guyatt 2008b).

When subgroup analyses met these criteria and were found to be statistically significant, we applied GRADE criteria to evaluate the certainty of evidence (GRADEpro GDT 2015; Guyatt 2008a).

Sensitivity analysis

We conducted sensitivity analyses based on generation of allocation sequence, concealment of allocation, and blinding, and for trials judged at low risk of bias.

'Summary of findings' table and GRADE

For assessment of the overall certainty of evidence for each outcome that included pooled data from RCTs only, we downgraded the evidence from "high certainty" by one level for serious (or by two for very serious) study limitations (according to risk of bias evaluation), indirectness of evidence, serious inconsistency (i.e. when I^2 > 30%), imprecision of effect estimates (large 95% confidence intervals or small treatment effects), or potential publication bias.

We exported data from Review Manager 5 to GRADEpro GDT 2015 to create 'Summary of findings' tables. We included the following patient-centred outcomes in the 'Summary of findings' tables.

- 28-Day all-cause mortality.
- In-hospital all-cause mortality.
- Long-term (longest follow-up beyond three months) all-cause mortality.
- Length of stay in the ICU.
- Length of hospital stay.
- Number of participants with superinfection up to longest follow-up.
- Number of participants with muscle weakness up to longest follow-up.

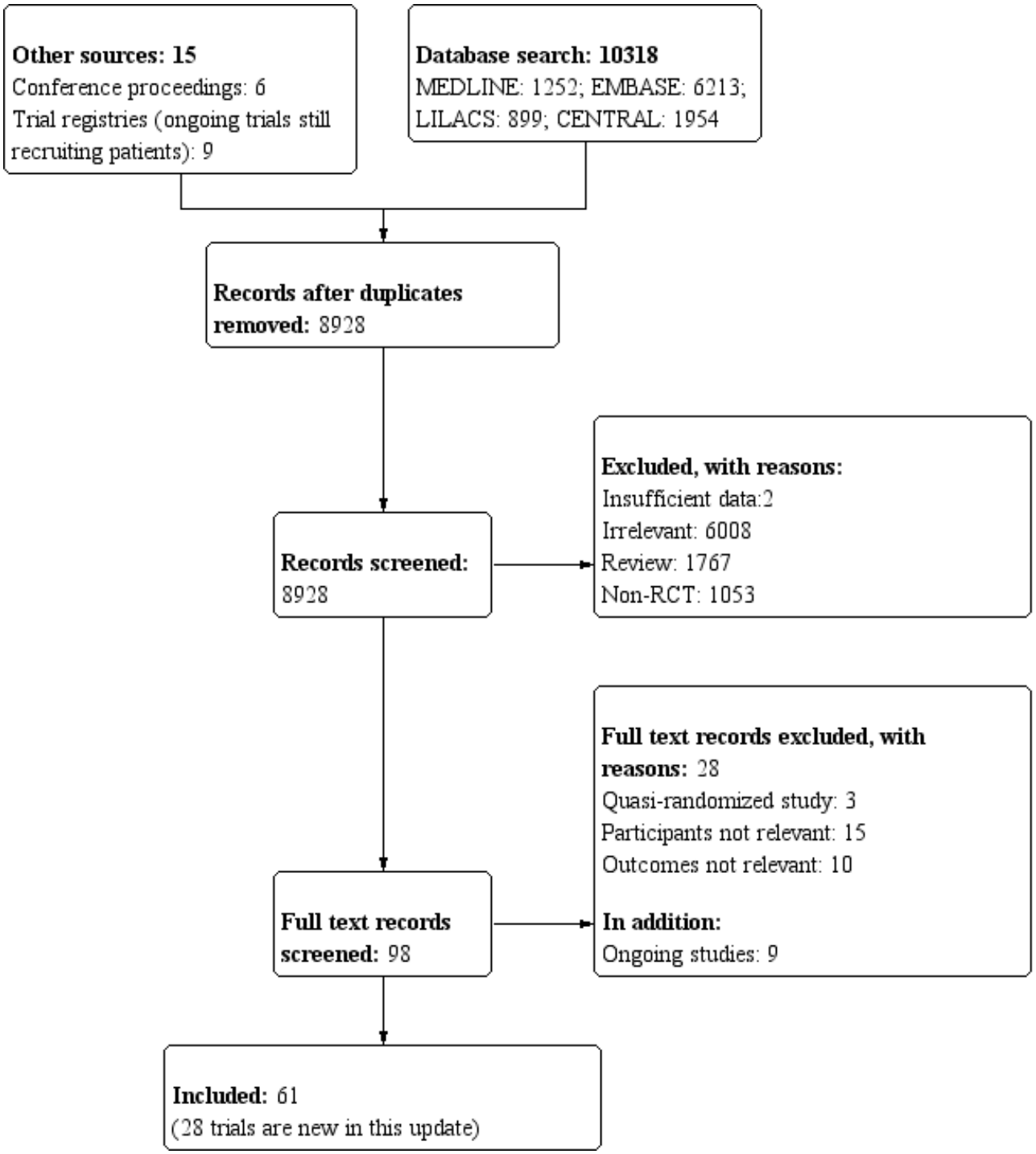
RESULTS

Description of studies

Results of the search

Our search results are detailed in Figure 1.

Figure 1. Study flow diagram.



The search strategy yielded 98 trials that evaluated corticosteroids in sepsis, of which we excluded 28 trials (see Characteristics of excluded studies). Nine trials are still ongoing (see Characteristics of ongoing studies).

Included studies

Since the last update in 2015 (see Published notes), we have included 28 additional trials for a total of 61 trials (n = 12,192 participants); we have described these below (see Characteristics of included studies).

Source of information

In addition to data extracted from these publications, we obtained unpublished information from 28 trials by contacting the primary authors (Appendix 5). We did not contact the authors of 10 trials, mainly because of the absence of contact details (Characteristics of included studies). For the remaining trials, contact with study

authors did not lead to the provision of additional information (Characteristics of included studies).

Trial centres

Twenty trials were multi-centre trials (i.e. > 2 centres) (Characteristics of included studies). Twenty-four trials were conducted in Europe, 11 in North America, 12 in Asia, five in the Middle East, five in Africa, and one in Latin America, and three multi-national trials were conducted in North America and Africa (Slusher 1996), in Europe and the Middle East (Sprung 2008), and in Australia, New Zealand, Europe, and the Middle East (Venkatesh 2018) (Characteristics of included studies).

Age of participants

Two trials enrolled both children and adults (CSG 1963; McHardy 1972). Six trials included only children (El-Nawawy 2017; Menon 2017; Nagy 2013; Slusher 1996; Tagaro 2017; Valoor 2009). All of the remaining trials included only adults.

Description of participants

Eleven trials included both participants with sepsis and individuals with septic shock. Four trials included participants with sepsis without shock (Fernández-Serrano 2011; Keh 2016; Rinaldi 2006; Sabry 2011). Fifteen trials targeted participants with community-acquired pneumonia-related sepsis. Five trials focused on participants with ARDS and sepsis (Liu 2012; Meduri 2007; Rezk 2013; Tongyoo 2016; Zhou 2015). The remaining trials focused on participants with septic shock treated by a vasopressor. Three trials included only participants with septic shock and adrenal insufficiency as defined by a cortisol increment less than 9 µg/dL after a corticotropin bolus (Aboab 2008; Huh 2007; Tandan 2005). In 18 trials, investigators systematically performed a short corticotropin test at baseline.

Control

Comparison of corticosteroids versus placebo or usual care

Nine studies did not use a placebo and compared corticosteroid therapy versus usual care, that is, antibiotics, fluid resuscitation, and vasopressor when needed (El Ghamrawy 2006; Hu 2009; Huang 2014; Li 2016; McHardy 1972; Mirea 2014; Rinaldi 2006; Sui 2013; Zhou 2015). In one study, only one centre used a placebo (Sprung 1984). One trial that compared hydrocortisone versus hydrocortisone plus fludrocortisone did not use a placebo of fludrocortisone for technical reasons (Annane 2010). Another trial compared duration of hydrocortisone treatment (i.e. 3 days vs 7 days) and did not use a placebo (Huh 2007). The remaining trials compared corticosteroid therapy to placebo.

Comparison of continuous infusion versus intermittent intravenous boluses of corticosteroids

Three trials compared continuous infusion versus bolus administration of hydrocortisone (Hyvernat 2016; Loisa 2007; Tilouche 2019). One trial had three parallel arms including continuous infusion of 200 mg hydrocortisone daily for seven days, intravenous bolus of 50 mg hydrocortisone every six hours for seven days, and usual care (Mirea 2014).

Corticosteroid dose and treatment course

Thirty-seven trials tested the effects of a long-course (three or more days at full dose) of low-dose hydrocortisone. In one trial (Huh 2007), investigators compared hydrocortisone 50 mg intravenously every six hours when given for three days versus seven days. One trial had three parallel groups including continuous infusion of 200 mg hydrocortisone per day for seven days, intravenous bolus of 50 mg hydrocortisone every six hours for seven days, and usual care (Mirea 2014). In three trials, investigators compared continuous infusion versus intermittent intravenous boluses of hydrocortisone (Hyvernat 2016; Loisa 2007; Tilouche 2019). Another trial compared seven-day treatment with hydrocortisone versus seven-day treatment with the combination of hydrocortisone plus fludrocortisone (Annane 2010). One trial compared a short course (two days at full dose) of low-dose intravenous hydrocortisone (300 mg on day one and 250 mg on day two) versus placebo (CSG 1963). Another study used a cross-over design to compare a three-day course of low-dose hydrocortisone versus placebo (Keh 2003).

Five trials tested the effects of a long course of low-dose prednisone or prednisolone (Blum 2015; McHardy 1972; Snijders 2010; Yildiz 2002; Yildiz 2011).

Two trials tested the effects of a long course of low-dose dexamethasone (Cicarelli 2007; Meijvis 2011). Two trials tested the effects of a short course (two days at full dose) of low-dose dexamethasone (Slusher 1996; Tagaro 2017).

Eight studies tested the effects of a long course of low-dose intravenous methylprednisolone (Fernández-Serrano 2011; Li 2016; Meduri 2007; Nagy 2013; Rezk 2013; Sui 2013; Torres 2015; Zhou 2015).

Five trials tested the effects of a short course of a large dose of methylprednisolone (Bone 1987; Luce 1988; Schumer 1976; Sprung 1984; VASSCSG 1987), and two tested the effects of a large dose of dexamethasone (Schumer 1976; Sprung 1984).

One trial did not report the type of corticosteroids given (Kurungundla 2008).

Outcomes

Overall, data from 52 trials was used to inform 28-day mortality rates. One trial (Mirea 2014) provided data for both comparison of corticosteroids versus placebo or usual care and comparison of continuous infusion versus bolus administration of corticosteroids. Two trials (Hyvernat 2016;Tilouche 2019) provided data for the comparison of continuous infusion versus bolus administration of corticosteroids. Fifty trials were used in the comparison of corticosteroids versus placebo or usual care. Of these trials, 29 explicitly reported on 28-day mortality and contact with the primary author of three additional trials led to recording of 28-day mortality rates (Meduri 2007; Rinaldi 2006; Sprung 1984). Thus, actual 28-day mortality rates were computed for 32 trials. For 18 additional trials, 28-day mortality rates were extrapolated from hospital mortality rates (Aboab 2008, El Ghamrawy 2006,Fernández-Serrano 2011, Luce 1988, McHardy 1972, Menon 2017,Nafae 2013, Schumer 1976, Slusher 1996, Torres 2015), ICU mortality rates (Hu 2009, Sabry 2011), 14-day mortality rates (Bone 1987, VASSCSG 1987), and short term mortality rates (Kurungundla 2008, Mirea 2014, Nagy 2013, Rezk 2013).

Sixteen trials explicitly reported ICU mortality rates, and the primary authors of three additional trials reported this outcome (Chawla 1999; Rinaldi 2006; Torres 2015).

Hospital mortality rates were available for 26 trials.

Mortality rates at 90 days and in the long term were reported for seven trials.

Rates of shock reversal at day seven and at day 28 were reported in 16 and 13 trials, respectively.

Ten trials reported the numbers of dysfunctional organs, that is, SOFA scores, at day seven.

Twenty-one trials reported length of ICU stay, and 22 reported on length of hospital stay.

Excluded studies

We excluded 28 trials (see Characteristics of excluded studies for details).

Ongoing studies

From trial registries, we identified nine additional RCTs of corticosteroids for sepsis (see Characteristics of ongoing studies). These trials are still recruiting patients, and we will follow the status of these trials to include them in a future update of the review whenever data become publicly available.

Studies awaiting classification

We found no studies awaiting classification

Risk of bias in included studies

We reported the detailed methodological quality of individual trials in the 'Risk of bias' tables in Figure 2 and Appendix 6.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

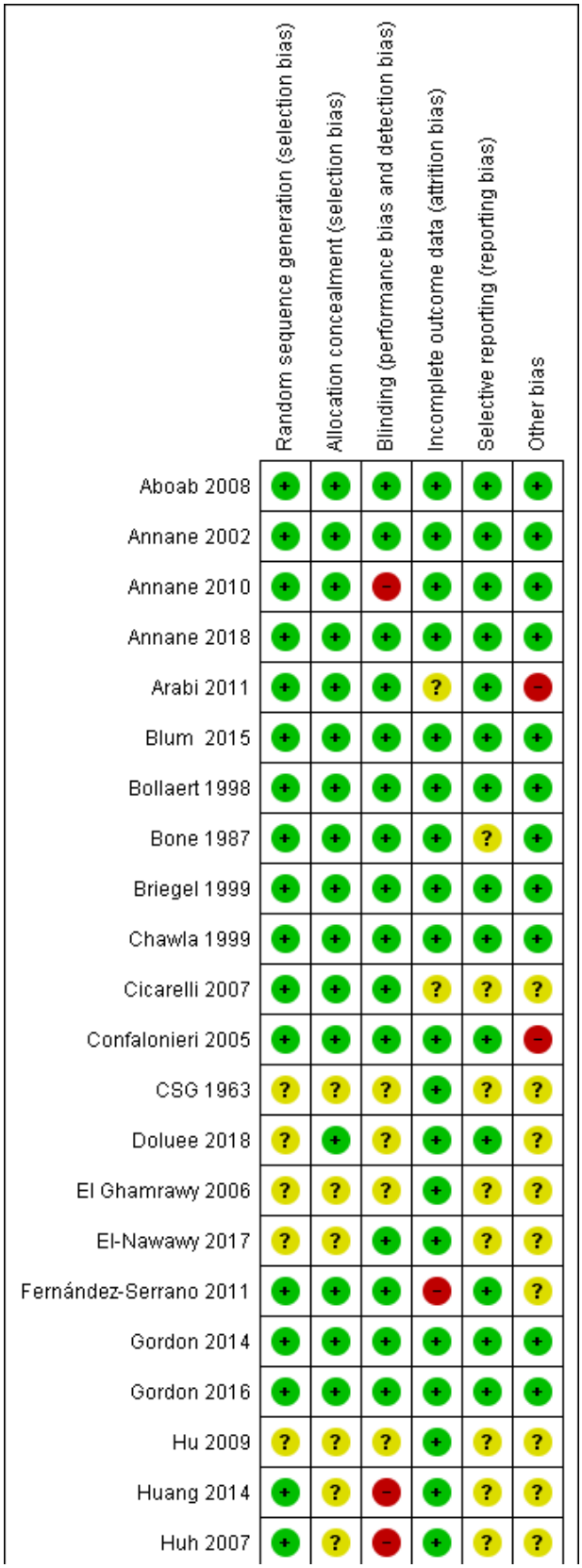


Figure 2. (Continued)

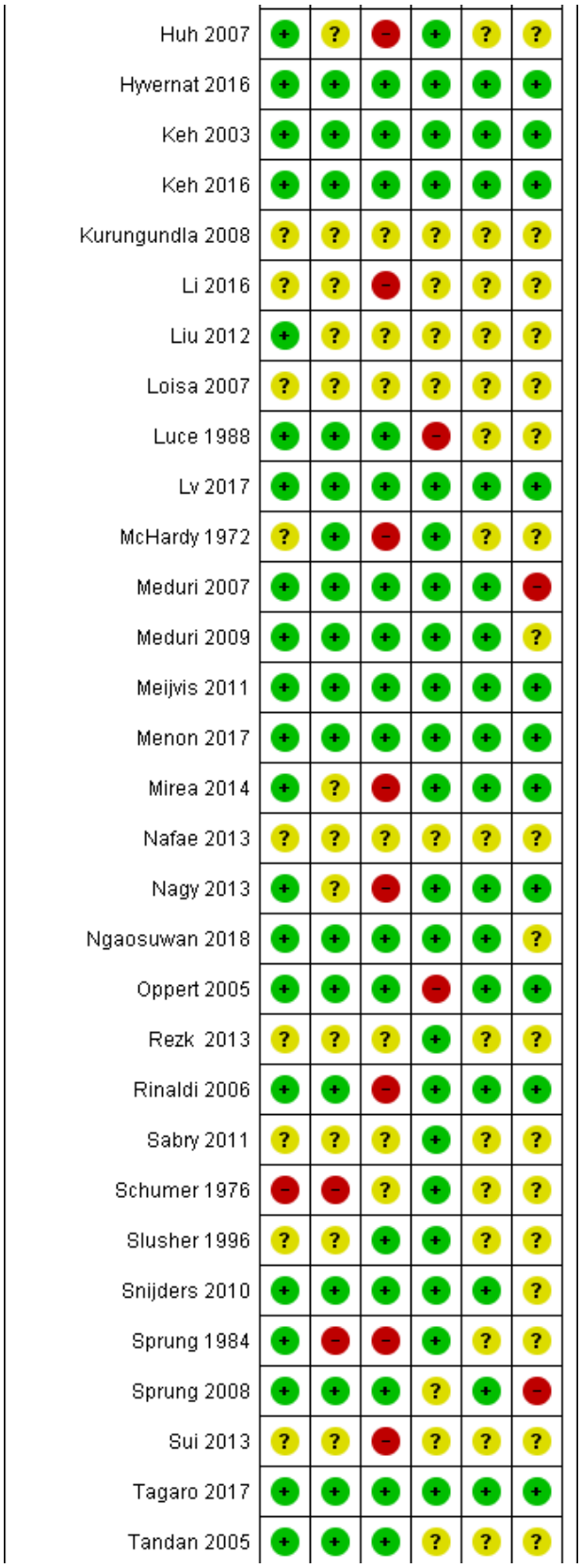
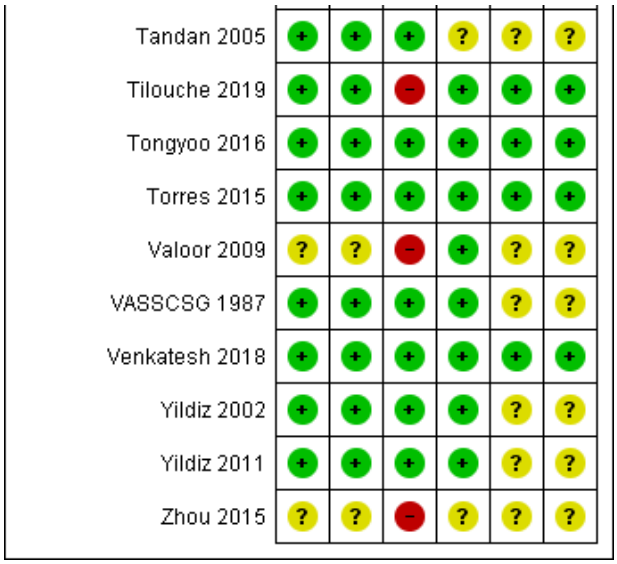


Figure 2. (Continued)



We judged 19 trials as being at low risk of bias, that is, we assessed them as having low risk of bias for the five domains (allocation, blinding, incomplete data, selective reporting, and other potential sources of bias).

Allocation

Random sequence generation

In one trial, the method of generation of allocation sequence was based on a card system (Schumer 1976); we judged this trial to be at high risk of selection bias. For 16 trials, the method was unclear. We judged the remaining trials to have low risk of bias.

Allocation concealment

We judged the method used for allocation concealment to be at low risk of bias in all but 10 trials. One trial assigned treatment using unsealed envelopes (Schumer 1976). In another trial, investigators enrolling participants at one of the two participating centres could have foreseen the upcoming assignment, as the local ethical committee refused to accept concealed allocation (Sprung 1984). In 20 trials, study authors did not report the method used for allocation concealment.

Blinding

Blinding of participants and personnel

For 13 trials, we judged the method used for blinding of participants and personnel as having high risk of bias. Twelve trials used open-label treatments. For one trial (Sprung 1984), the local ethical committee at one of the two centres did not permit double-blind allocation and administration of treatment. Therefore, blinding was not possible for 40 of the 59 participants included in the trial.

Eleven additional trials did not report the method used to ensure blinding.

For the remaining trials, blinding of participants and personnel was deemed appropriate. We judged these trials to be at low risk of bias for this domain.

Blinding of outcomes assessors

In 12 trials, outcome assessors were not blinded to study treatments. We judged these trials to be at high risk of detection bias.

Twelve trials did not report any information that could be used to judge the risk of detection bias.

For the remaining trials, blinding of outcomes assessors was deemed appropriate. We judged these trials to be at low risk of bias for this domain.

Incomplete outcome data

Twenty-eight trials explicitly provided the numbers of and reasons for withdrawals or losses to follow-up.

Nineteen trials explicitly reported the use of intention-to-treat analysis (as the primary analysis) and the numbers of, and reasons for, non-adherence to the protocol. One trial reported only use of intention-to-treat analysis (Luce 1988). The remaining trials provided no information about these criteria. However, the number of analysed participants matched the number of randomly assigned participants, except for 16 trials. One trial did not include one of 191 participants in the placebo group in the mortality analysis (Bone 1987). In four trials (Annane 2002; Lv 2017; Sprung 2008; Tongyoo 2016), participants withdrew their consent, and study authors did not include in the analyses one of 300, two of 120, one of 500, and nine of 206 randomly assigned participants, respectively. For two trials, contact with the primary author allowed us to obtain information on participants who were dropped out from the analysis (Oppert 2005; Rinaldi 2006). In the first study, seven randomly assigned participants (five in the corticosteroid group and two in the placebo group) were not analysed (Oppert 2005). Four of these participants (two in the corticosteroid group and two in the placebo group) were discharged alive from the ICU and then were lost to follow-up. The three remaining participants (in the corticosteroid group) died: two before receiving hydrocortisone, and the last at study day 17. In the

second study, 12 of 52 participants dropped out of the study: six in the control group and six in the corticosteroid group (Rinaldi 2006). Nine participants (four in the control group) were excluded, as they developed renal failure. Two control participants died in the ICU at day five and at day seven, respectively. Three of the corticosteroid-treated participants died, at days 5, 6, and 28, respectively. Three other participants (two in the control group) were excluded, as they developed septic shock. All died at days 3, 5, and 6, respectively.

Two trials gave additional open-label corticosteroids to some participants (Gordon 2014; Snijders 2010). In the first trial, five (23.3%) participants in the placebo arm were given rescue corticosteroids for treatment of life-threatening hypotension and were considered as cross-overs (Gordon 2014). In the second trial, 37 (17.4%) participants did not complete the full course of study treatment as a consequence of premature death of 10 participants, consent withdrawal for five participants, post-randomization exclusion for eight participants, and additional open-label corticosteroid treatment for 14 participants (Snijders 2010). In seven trials, from 4% to 20% were withdrawn from the primary analysis for various reasons that were explained in the trial report (Blum 2015; Fernández-Serrano 2011; Keh 2016; Gordon 2016; Menon 2017; Tilouche 2019; Venkatesh 2018).

Selective reporting

For 34 trials, we could rule out selective reporting bias after contact with authors, full access to trial protocols, or access to individual participant data. We judged these trials to be at low risk of bias for this domain.

Seventeen trials were published before it was mandatory to register trials in an open access repository, and we have had no access to trial protocols. We judged these trials as having unclear risk of selective reporting bias. For the remaining trials, we could not obtain access to protocols, we could not find trials on an open access registry, and our attempts to contact trial authors failed.

Other potential sources of bias

One trial recruited only 500 of the 800 expected participants, mainly as the result of loss of equipoise among investigators (Sprung 2008). Another trial was halted prematurely for futility after enrolment of 75 of 150 foreseen participants (Arabi 2011).

No trials used the Sepsis 3 definition as all were designed before publication of the new definition for sepsis (Singer 2016). Thirty trials provided an explicit definition of sepsis (as defined in the Methods section of this review). Seven trials provided a definition of septic shock without referring to the need for vasopressor agents (Bone 1987; Luce 1988; Rinaldi 2006; Schumer 1976; Slusher 1996; VASSCSG 1987; Yildiz 2002). One study did not explicitly provide the definition used for sepsis (CSG 1963). Eleven trials explicitly defined sepsis due to community-acquired pneumonia. Two trials randomly assigned participants on the basis of the presence of ARDS, and data provided in these papers confirmed the presence of sepsis (Liu 2012; Rezk 2013). In another trial on early ARDS, contact with the primary author confirmed that explicit definitions of sepsis were used (Meduri 2007).

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids compared to placebo or usual care for treating sepsis

We did not pool the data from one trial that included both children and adults (CSG 1963), one cross-over trial (Keh 2003), one trial that compared two durations of hydrocortisone treatment (Huh 2007), and one trial that compared hydrocortisone versus the combination of hydrocortisone plus fludrocortisone (Annane 2010).

In this update, we introduced a new comparison (i.e. continuous infusion vs intermittent boluses of steroids).

Corticosteroids versus placebo or usual care

We have summarized the main results in Summary of findings for the main comparison.

Primary outcome

28-Day all-cause mortality

Data for 28-day mortality were available for 32 trials. In addition, we used data on 14-day mortality (two trials), hospital mortality (10 trials), or ICU mortality (2 trials), or data on short-term mortality (four trials). Thus, we computed data from 50 trials that accounted for 11,233 participants. In the treated group, 1388 of 5667 participants died by day 28 compared with 1469 of 5566 participants in the control group. Some heterogeneity was evident in the results (Chi^2 test = 68.06; P = 0.03; I^2 = 29%). The risk ratio (RR) of dying at 28 days was 0.91 (95% confidence interval (CI) 0.84 to 0.99; P = 0.04; random-effects model; Analysis 1.1). We downgraded the certainty of evidence for this outcome from high to moderate for inconsistency (significant heterogeneity across trial results).

Differences in methodological quality across trials may have accounted for observed heterogeneity in the results. A sensitivity analysis based on trials judged as being at low risk of bias showed an RR for dying at 28 days of 0.91 (95% CI 0.84 to 0.98; P = 0.01; 7896 participants; 17 studies; I^2 = 0%; Analysis 1.2).

Heterogeneity across trials also may have been the result of different therapeutic regimens. Subgroup analyses based on types of corticosteroids did not suggest that this may influence the response to treatment (test for subgroup differences: Chi^2 = 1.48; df = 3; P = 0.69; I^2 = 0%; Analysis 1.3). Likewise there was no evidence that dose/duration (test for subgroup differences: Chi^2 = 0.29; df = 1; P = 0.59; I^2 = 0%; Analysis 1.4) or mode (continuous vs intermittent bolus) of corticosteroid administration (test for subgroup differences: Chi^2 = 0.41; df = 1; P = 0.52; I^2 = 0%; Analysis 1.5) influences the response to treatment. Meta-regression analyses showed no evidence of interaction between the RR for dying at 28 days and the dose given at day 1 (P = 0.14; Figure 3), total dose (P = 0.12; Figure 4), or duration of treatment (P = 0.86). One trial of a large dose of corticosteroids was a statistical outlier and was excluded from the meta-regression analysis (Schumer 1976).

Figure 3. Figure represents the results from meta-regression of log of risk ratio of dying and the dose of corticosteroids given at day 1 and expressed as equivalent milligrams of hydrocortisone. Estimates from each study are represented by circles. Circle sizes depend on the precision of each estimate (the inverse of its within-study variance), which is the weight given to each study in the fixed-effect model. Meta-regression included 53 trials.
REML estimate of between-study variance: tau^2 = .008551.
% residual variation due to heterogeneity: I^2 res = 28.86%.
Proportion of between-study variance explained: Adj R^2 = 43.76%.

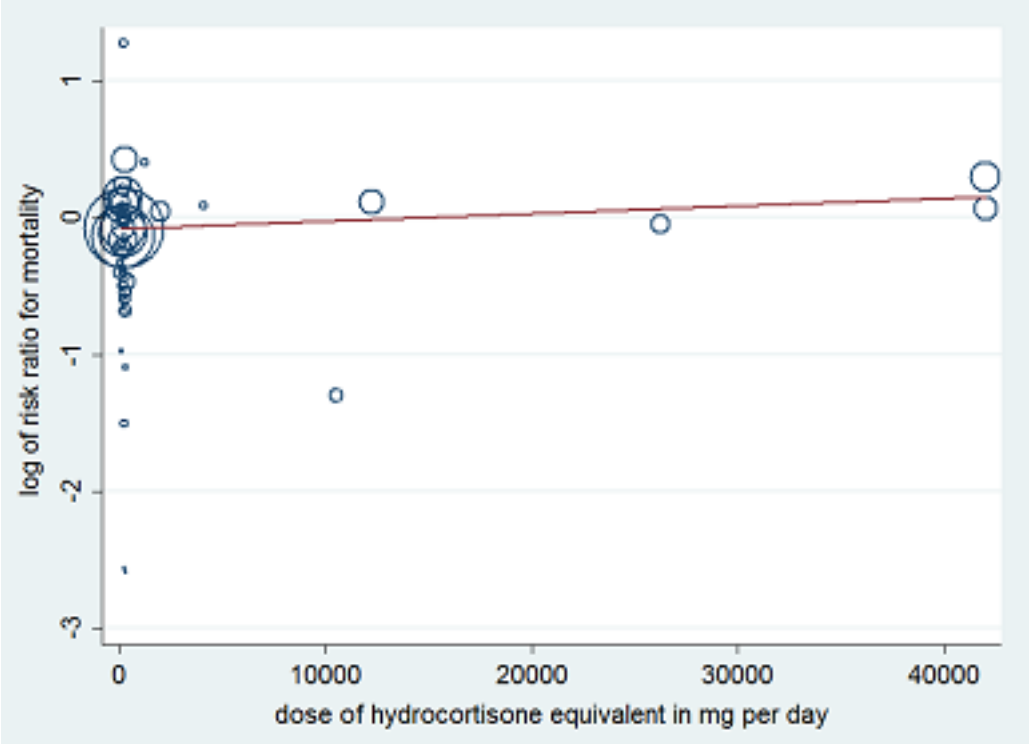
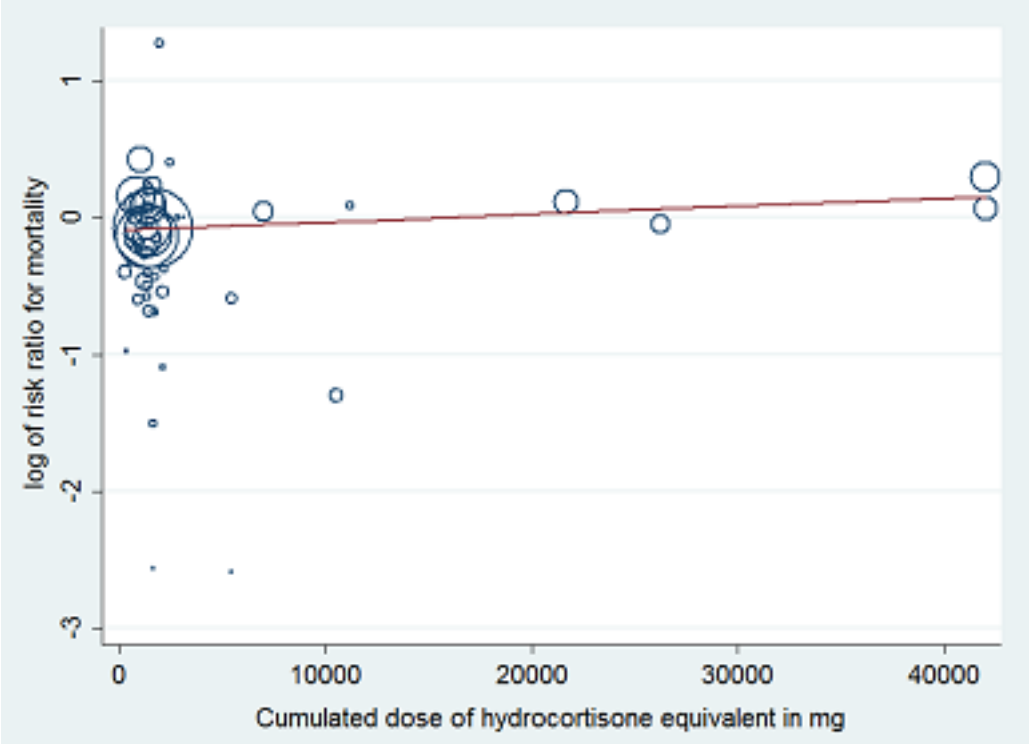


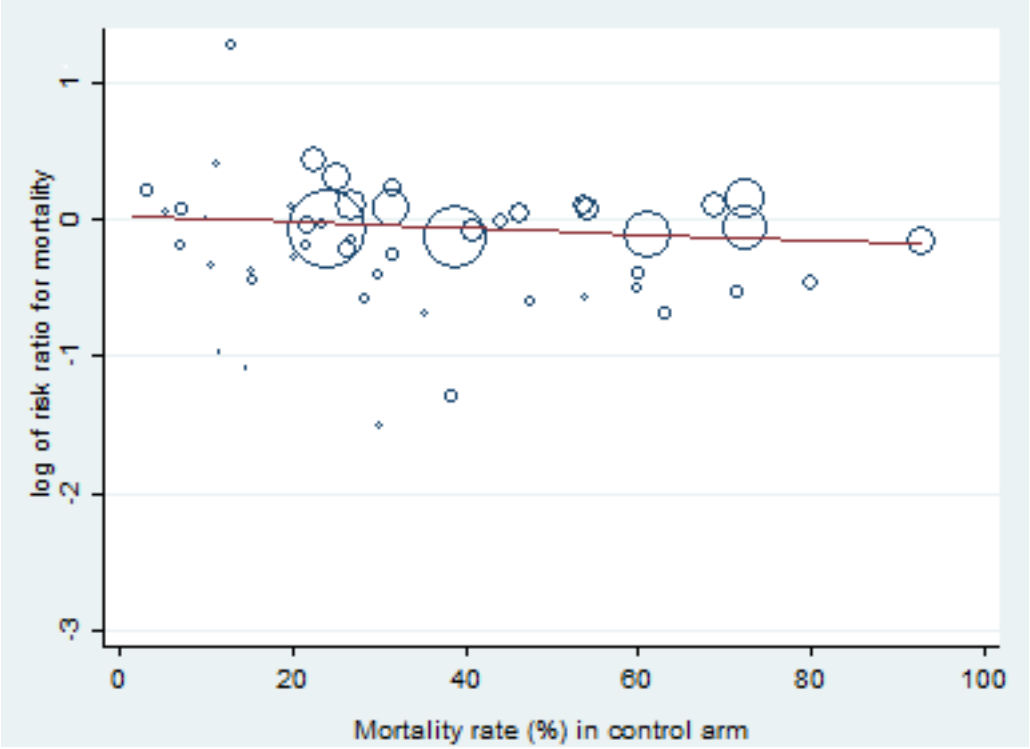
Figure 4. Figure represents results from meta-regression of log of risk ratio of dying and log of cumulated dose of corticosteroids expressed as equivalent milligrams of hydrocortisone. Estimates from each study are represented by circles. Circle sizes depend on the precision of each estimate (the inverse of its within-study variance), which is the weight given to each study in the fixed-effect model. Meta-regression included 53 trials. REML estimate of between-study variance: tau² = .008628.
% residual variation due to heterogeneity: I^2 res = 28.68%.
Proportion of between-study variance explained: Adj R^2 = 43.25%.



By contrast, trials in which corticosteroids were not tapered off found an RR of dying at 28 days of 0.87 (95% CI 0.78 to 0.98; 8770 participants; 30 studies; I^2 = 42%; random-effects model) in favour of corticosteroids, whereas trials in which corticosteroids were tapered off found no evidence of mortality differences between groups (RR 1.04, 95% CI 0.92 to 1.18; P = 0.54; 2136 participants; 17 studies; I^2 = 0%) (test for subgroup differences: Chi^2 = 3.94; df = 1; P = 0.05; I^2 = 74.6%; Analysis 1.6).

Heterogeneity across trials may have resulted from factors related to participants. There was no evidence of differences in response to treatment between children and adults (test for subgroup differences: Chi^2 = 0.29; df = 1; P = 0.62; I^2 = 0%; Analysis 1.7). Subgroup analysis based on targeted populations showed non-significant subgroup differences (test for subgroup differences: Chi^2 = 7.60; df = 3; P = 0.06; I^2 = 60.5%; Analysis 1.8). In studies of heterogeneous populations of participants with sepsis, the RR for dying at 28 days was 1.17 (95% CI 0.98 to 1.39; P = 0.09; 1358 participants; 10 studies; I^2 = 25%; fixed-effect model). In studies of only participants with septic shock, the RR for dying at 28 days was 0.91 (95% CI 0.83 to 1.00; P = 0.06; 7428 participants; 23 studies; I^2 = 32%; random-effects model). In studies of participants with sepsis and ARDS, the RR was 0.66 (95% CI 0.46 to 0.94; P = 0.02; 411 participants; 4 studies; I^2 = 8%; fixed-effect model), and in studies of participants with sepsis and community-acquired pneumonia, the RR was 0.69 (95% CI 0.50 to 0.96; P = 0.03; 2038 participants; 13 studies; I^2 = 0%; fixed-effect model). Likewise, meta-regression showed no evidence of interaction between the RR of dying at 28 days and severity of illness as assessed by crude mortality in the control arm (P = 0.29; Figure 5). Subgroup analysis of participants with adrenal insufficiency showed no heterogeneity in the results. Investigators reported 251 deaths among 525 participants in the treated group and 291 deaths among 554 in the placebo group. The RR for dying was 0.92 (95% CI 0.82 to 1.03; P = 0.16; 1079 participants; 12 studies; I^2 = 0%; fixed-effect model; Analysis 1.9).

Figure 5. Meta-regression of the log of the risk ratio for 28-day mortality against actual mortality at 28 days in the control arm.



Funnel plot analysis, including all trials, suggested some asymmetry (Figure 6). Contour-enhanced funnel plot analysis including trials of a long course of low-dose corticosteroids suggested no significant asymmetry (Figure 7).

Figure 6. Funnel plot of comparison: 1 Steroids vs control, outcome: 1.1 28-Day all-cause mortality.

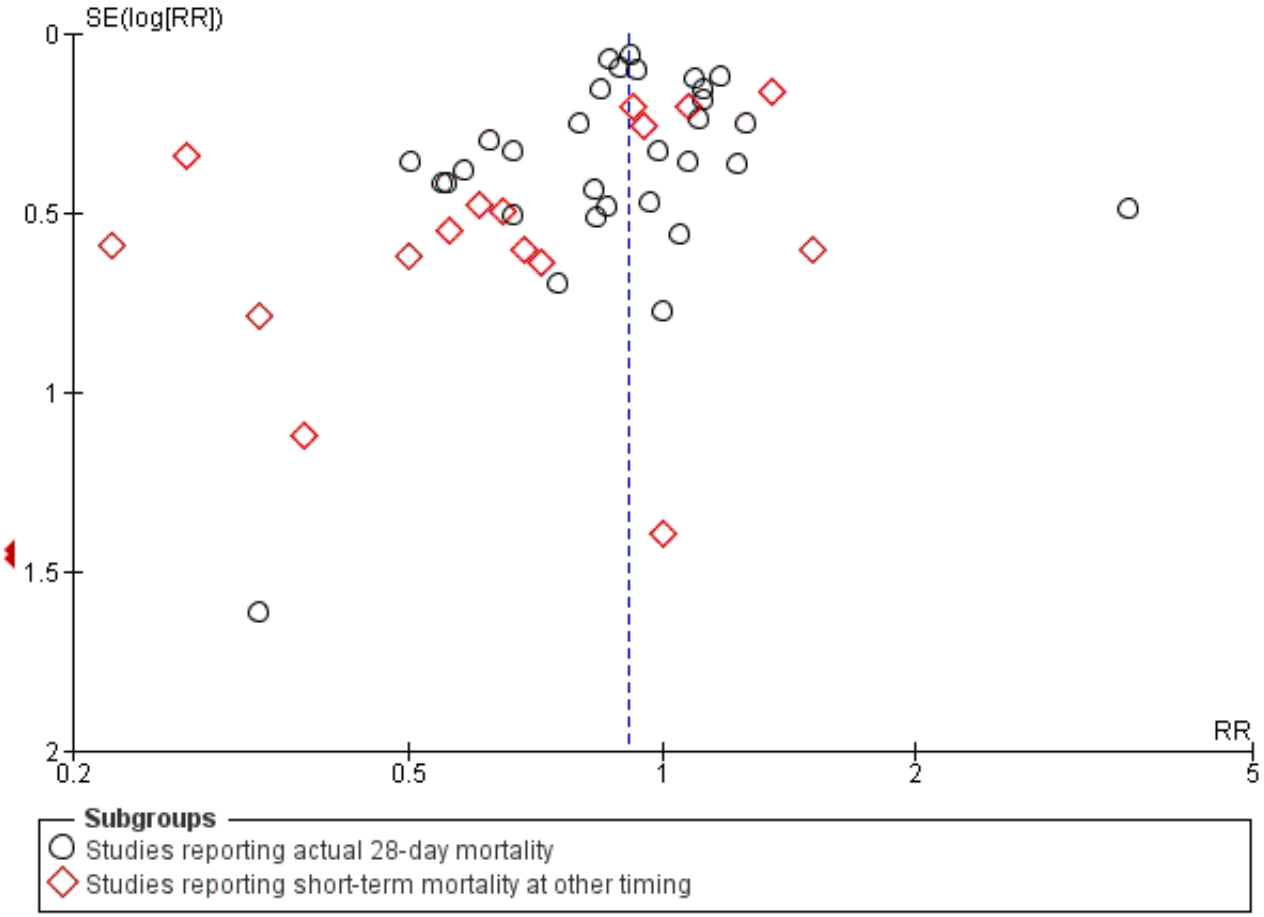
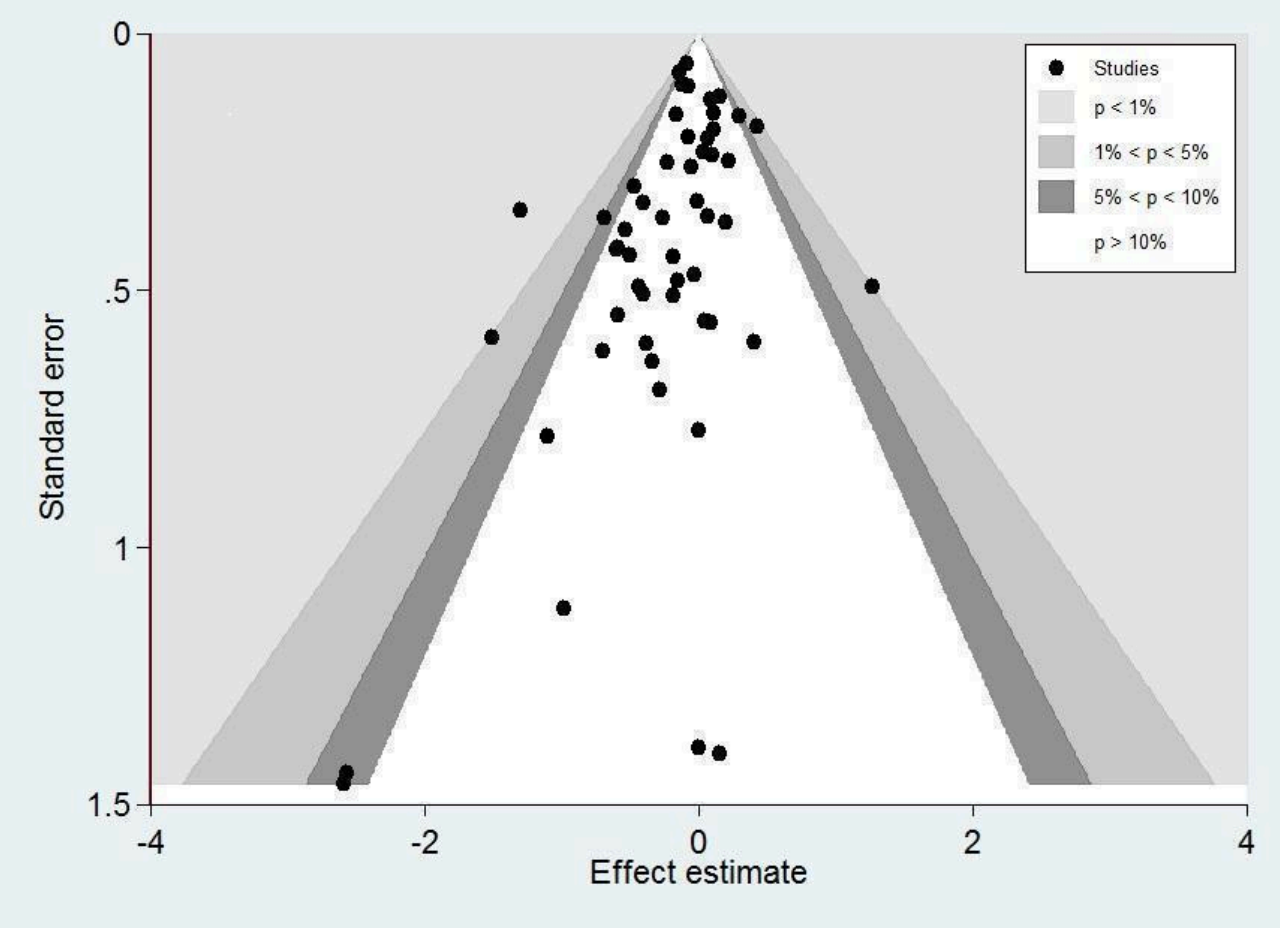


Figure 7. Contour-enhanced funnel plot. Log of risk ratio for 28-day mortality is plotted against its standard error.



In one trial comparing hydrocortisone alone versus hydrocortisone plus fludrocortisone, the hazard ratio of death was 0.94 (95% CI 0.73 to 1.21; Annane 2010).

Secondary outcomes

90-Day all-cause mortality

We could extract data on 90-day mortality from seven trials. A total of 961 of 2975 participants in the treated group and 1026 of 2959 in the control group died within 90 days. The RR of dying within 90 days was 0.93 (95% CI 0.87 to 1.00; P = 0.05; 5934 participants; 7 studies; I^2 = 0%; fixed-effect model; Analysis 1.10) in favour of the corticosteroid group. This was based on moderate-certainty evidence (lowered for imprecision).

Long-term mortality

We could extract data on mortality beyond three months for seven trials. The RR of dying was 0.97 (95% CI 0.91 to 1.03; P = 0.29; 6236 participants; 7 studies; I^2 = 28%; Analysis 1.11). We downgraded the certainty of evidence to low owing to inconsistency in results and imprecision.

Intensive care unit (ICU) mortality

Data were available from 18 trials, accounting for 7267 participants. All of these trials investigated a long course of low-dose corticosteroids. A total of 908 of 3636 participants in the treated group and 1015 of 3631 participants in the control group died in the ICU. There was little heterogeneity in the results (Chi^2 = 19.18; df = 17; P = 0.32; I^2 = 11%). The RR for dying in the ICU was 0.89 (95% CI 0.83 to 0.96; fixed -effect model; Analysis 1.12). This was based on high-certainty evidence.

Hospital mortality

We could extract data on hospital mortality from 26 trials that accounted for 8183 participants. A total of 1223 of 4109 participants in the treated group compared with 1315 of 4074 in the control group died in hospital. Heterogeneity in the results was significant (Chi^2 = 39.58; df = 25; P = 0.03; I^2 = 37%). The RR for dying in hospital was 0.90 (95% CI 0.82 to 0.99; P = 0.03; random-effects model; Analysis 1.13). We downgraded the certainty of evidence for this outcome from high to moderate for inconsistency.

Number of participants with shock reversal (as defined by stable haemodynamic status ≥ 24 hours after withdrawal of vasopressor therapy) at day 7

We could extract data from 16 trials that accounted for 6711 participants. A total of 2642 of 3361 participants in the treated group and 2168 of 3350 in the control group had shock reversed at day 7. Significant heterogeneity was evident in the results (Chi^2 = 43.87; df = 15; P = 0.0001; I^2 = 66%). The RR for having shock reversed at day 7 was 1.23 (95% CI 1.13 to 1.34; P < 0.0001; random-effects model)

in favour of the corticosteroid group (Analysis 1.14). This was based on moderate-certainty evidence (lowered for inconsistency).

Sensitivity analysis excluding the two trials that evaluated a short course of high-dose corticosteroids did not reduce heterogeneity in the results (RR 1.26, 95% CI 1.16 to 1.37; 6408 participants; 16 studies; I^2 = 59%) (Bone 1987; Sprung 1984).

In one cross-over trial, hydrocortisone was given for three days at a dose of 240 mg per day (Keh 2003). Although this trial could not provide information on shock reversal at day 7, investigators showed that at day 3, fewer hydrocortisone patients than placebo-treated patients required norepinephrine treatment (6/20 vs 14/20; P = 0.025).

Number of participants with shock reversal (as defined by stable haemodynamic status ≥ 24 hours after withdrawal of vasopressor therapy) at day 28

We could extract data from 13 trials, accounting for 6753 participants. A total of 2767 of 3382 participants in the treated group had shock reversed at day 28, as did 2629 of 3397 in the placebo group. No heterogeneity was evident in the results (I^2 = 0%). The RR for having shock reversed was 1.06 (95% CI 1.03 to 1.08; P < 0.00001) in favour of the corticosteroid group (Analysis 1.15). This was based on high-certainty evidence.

Number of organs affected and severity of organ dysfunction at day 7, as measured by the sequential organ failure assessment (SOFA) score

Ten studies (2157 participants) reported the SOFA score at seven days post randomization. The mean difference (MD) in the SOFA score at day 7 was -1.37 (95% CI -1.84 to -0.90; P < 0.00001; random-effects model) in favour of corticosteroids. Moderate heterogeneity across studies was noted (Chi^2 = 17.03; df = 9; P = 0.05; I^2 = 47%; Analysis 1.16). This was based on moderate-certainty evidence (lowered for inconsistency).

In one study (Briegel 1999), corticosteroid treatment was associated with a non-significant (P = 0.18) trend toward earlier resolution of organ dysfunction.

Length of stay in the intensive care unit

For all participants

In 21 trials (7612 participants), the MD for ICU length of stay for all participants was -1.07 days (95% CI -1.95 to -0.19; P = 0.02; random-effects model) in favour of the corticosteroid group, with some heterogeneity evident across studies (Chi^2 = 31.49; df = 20; P = 0.05; I^2 = 36%; Analysis 1.17). We judged the certainty of evidence for this outcome as high. There was some heterogeneity in the results. However, the treatment effect was large.

For survivors only

We could extract data from 10 trials on 778 ICU survivors. The MD for ICU length of stay among these survivors was -2.19 days (95% CI -3.93 to -0.46; P = 0.01; fixed-effect model). No heterogeneity was evident across studies (Chi^2 test = 8.63; P= 0.47; I^2 = 0%; Analysis 1.18).

Length of hospital stay

For all participants

From 22 trials (8795 participants), we could extract data on all participants. We noted heterogeneity in the results (heterogeneity: Chi^2 = 51.44; df = 201; P = 0.0002; I^2 = 59%). The MD for length of hospital stay for all participants was -1.63 days (95% CI -2.93 to -0.33 ; P = 0.01; random-effects model; Analysis 1.19). We judged the certainty of evidence for this outcome as high. There was some heterogeneity in the results. However, the treatment effect was large.

For survivors only

We could extract data for hospital survivors from nine studies (710 participants). We noted some heterogeneity in the results (I^2 = 43%). No evidence suggested a difference between the two groups (MD -4.11 days, 95% CI -8.50 to 0.28; P = 0.07; random-effects model; Analysis 1.20).

Adverse events

Gastroduodenal bleeding

We could extract data from 25 trials (5171 participants). A total of 131 of 2607 participants in the treated group and 120 of 2564 in the control group had an episode of gastroduodenal bleeding. We noted no heterogeneity in the results (I^2 = 0%). The RR for having gastroduodenal bleeding was 1.07 (95% CI 0.85 to 1.35; P = 0.55; fixed-effect model; Analysis 1.21). We judged this to be based on moderate-certainty evidence (lowered due to imprecision).

Superinfection

We could extract data from 25 trials (5356 participants). A total of 487 of 2695 participants in the treated group and 451 of 2661 participants in the control group had an episode of nosocomial infection. We noted no heterogeneity in the results (Chi^2 = 20.66; df = 21; P = 0.48; I^2 = 0%). The RR for superinfection was 1.06 (95% CI 0.95 to 1.19; P = 0.27; fixed-effect model; Analysis 1.21). We judged the certainty of evidence as moderate for this outcome (lowered for imprecision).

Hyperglycaemia

The number of participants who presented with hyperglycaemia was reported for 20 trials (8594 participants). There was heterogeneity in the results (Chi^2 = 35.96; df = 17; P = 0.005; I^2 = 53%). The RR for hyperglycaemia was 1.20 (95% CI 1.10 to 1.31; P < 0.00001; random-effects model; Analysis 1.21). This was based on moderate-certainty evidence (lowered for inconsistency).

One trial comparing tight glucose control versus standard care found no benefit in normalizing blood glucose levels among corticosteroid-treated septic shock participants (Annane 2010).

Hypernatraemia

The number of participants who presented with hypernatraemia was reported for six trials (5069 participants). We noted no heterogeneity in the results (Chi^2 = 4.45; df = 5; P = 0.49; I^2 = 0%). The RR for hypernatraemia was 1.66 (95% CI 1.34 to 2.06; P < 0.00001; fixed-effect model; Analysis 1.21). This was based on high-certainty evidence.

Muscle weakness

The number of participants who presented with muscle weakness was reported for six trials (6145 participants). There was little to no heterogeneity in the results (Chi^2 = 5.42; df = 5; P = 0.37; I^2 = 8%). The RR for muscle weakness was 1.21 (95% CI 1.01 to 1.44; P = 0.04;

fixed-effect model; Analysis 1.21) in favour of the control group. We judged the certainty of evidence as high for this outcome.

Neuropsychiatric events

The number of participants who presented with neuropsychiatric events was reported for eight trials (6941 participants). There was some heterogeneity in the results (Chi^2 = 9.93; df = 7; P = 0.19; I^2 = 30%). The RR for neuropsychiatric events was 1.15 (95% CI 0.52 to 2.57; P = 0.73; random-effects model; Analysis 1.21). This was based on low-certainty evidence (lowered for imprecision and inconsistency).

Stroke

The number of participants who presented with stroke was reported for four trials (2842 participants). There was no heterogeneity in the results (Chi^2 = 1.66; df = 3; P = 0.64; I^2 = 0%). The RR for stroke was 0.83 (95% CI 0.41 to 1.68; P = 0.73; fixed-effect model; Analysis 1.21). This was based on moderate-certainty evidence (lowered for imprecision).

Cardiac events

The number of participants who presented with cardiac events was reported for six trials (3567 participants). There was no heterogeneity in the results (Chi^2 = 3.51; df = 5; P = 0.62; I^2 = 0%). The RR for acute coronary events was 1.12 (95% CI 0.66 to 1.88; P = 0.68; fixed-effect model; Analysis 1.21). This was based on moderate-certainty evidence (lowered for imprecision).

Continuous infusion versus intermittent bolus of corticosteroids

We have summarized the main results in Table 1.

Primary outcome

28-Day all-cause mortality

Data for 28-day mortality were available for three trials accounting for 310 participants. There was no heterogeneity in the results (Chi^2 = 1.94; df = 2; P = 0.38; I^2 = 0%). A total of 73 of 159 participants in the continuous infusion group and 67 of 151 participants in the intermittent bolus group died at 28 days. The RR of dying at 28 days was 1.03 (95% CI 0.81 to 1.31; P = 0.82; fixed-effect model; Analysis 2.1) in favour of the intermittent bolus group. We downgraded the certainty of evidence to very low due to high risk of bias in all except one trial and due to imprecision.

Secondary outcomes

90-Day all-cause mortality

Data for 90-day mortality were available for only one trial (Hyvernat 2016). This trial provided no evidence of a difference between groups for 90-day all-cause mortality (RR 0.87, 95% CI 0.61 to 1.22; Analysis 2.2). We judged this to be very low-certainty evidence (with very high risk of bias and imprecision).

Long-term mortality

In one trial that reported mortality at one year, the RR of dying was 1.36 (95% CI 1.02 to 1.81; 70 participants; Analysis 2.3) (Tilouche 2019). We downgraded the certainty of evidence to very low owing to the fact that data were available from only one small trial that was at high risk of performance and detection bias.

Intensive care unit mortality

We could extract data from four trials. We found no evidence of a difference between the two groups (RR 1.02, 95% CI 0.80 to 1.29; 358 participants; I^2 = 0%; fixed-effect model; Analysis 2.4). This was based on very low-certainty evidence (with very high risk of bias and imprecision).

In-hospital mortality

We could extract data from two trials. We found no evidence of a difference between the two groups (RR 0.95, 95% CI 0.72 to 1.25; P = 0.70; 240 participants; 4 studies; I^2 = 0%; fixed-effect model; Analysis 2.5). We downgraded the certainty of evidence to very low owing to imprecision and risk of bias in one study.

Number of participants with shock reversal (as defined by stable haemodynamic status ≥ 24 hours after withdrawal of vasopressor therapy) at day 7

We could extract data about shock reversal from four trials (358 participants). The results showed heterogeneity (Chi^2 = 10.09; df = 3; P = 0.02; I^2 = 70%). A total of 104 of 183 participants in the continuous infusion group and 118 of 175 participants in the intermittent bolus group had shock reversal. The RR of shock reversal was 0.80 (95% CI 0.59 to 1.10; P = 0.17; random-effects model; Analysis 2.6). This was based on very low-certainty evidence (due to risk of bias, imprecision, and inconsistency).

Number of participants with shock reversal (as defined by stable haemodynamic status ≥ 24 hours after withdrawal of vasopressor therapy) at 28 days

Data were available from one trial (Tilouche 2019). The RR of having shock reversed by 28 days was 0.78 (95% CI 0.45 to 1.34; 70 participants; Analysis 2.7). This was based on very low-certainty evidence (due to risk of bias and very severe imprecision).

Number of organs affected and severity of organ dysfunction at day 7, as measured by the sequential organ failure assessment (SOFA) score

The SOFA score at day 7 was available for three trials. The mean difference between groups for the SOFA score was 1.00 (95% CI -0.25 to 2.26; 260 participants; I^2 = 7%; fixed-effect model; Analysis 2.8). This was based on very low-certainty evidence (due to risk of bias and very severe imprecision).

Length of stay in the intensive care unit

For all participants

We could extract data about length of stay in the ICU for three trials. We found no evidence of a difference between groups (MD -1.05 days, 95% CI -4.54 to 2.45; P = .56; 310 participants; I^2 = 67%; random-effects model; Analysis 2.9). We downgraded the certainty of evidence to very low owing to inconsistency, imprecision, and high risk of bias in two studies.

For survivors only

No trial provided data for length of ICU stay among survivors only.

Length of stay in the hospital

For all participants

We could extract data about length of stay in the hospital from three trials. We found no evidence of a difference between groups (MD 0.01 days, 95% CI -5.05 to 5.07; P = 1.00; 310 participants; I^2 = 70%; random-effects model; Analysis 2.10). We downgraded

the certainty of evidence to very low owing to inconsistency, imprecision, and high risk of bias in two studies.

For survivors only

No trial provided data for length of hospital stay among survivors only.

Adverse events

Gastroduodenal bleeding

Data from two trials suggest no evidence of a difference between groups in the risk of gastroduodenal bleeding (RR 0.79, 95% CI 0.10 to 6.37; P = 0.83; 193 participants; I^2 = 67%; random-effects model; Analysis 2.11). This was based on very low-certainty evidence (due to risk of bias, inconsistency, and very severe imprecision).

Superinfection

Data from two trials suggest no evidence of a difference between groups in the risk of superinfection (RR 1.12, 95% CI 0.37 to 3.33; P = 0.84; 193 participants; I^2 = 74%; random-effects model; Analysis 2.11). We downgraded the certainty of evidence to very low owing to inconsistency, imprecision, and high risk of bias in one of the studies.

Hyperglycaemia

Data from three trials suggest no evidence of a difference between groups in the number of patients with at least one episode of hyperglycaemia (RR 0.89, 95% CI 0.47 to 1.71; P = 0.74; 310 participants; I^2 = 80%; random-effects model; Analysis 2.11). This was based on very low-certainty evidence (due to risk of bias, inconsistency, and imprecision).

Two trials reported mean blood glucose levels. One trial found slightly lower mean blood glucose levels in the continuous infusion group when compared to the intermittent boluses group (6.4 ± 0.7 mmol/L vs 6.2 ± 0.7; P = 0.04) (Loisa 2007). Another trial found no statistically significant difference between these groups (9.± 2.5 mmol/L vs 8.5 ± 6.0; P = 0.55) (Hyvernat 2016). In addition, three trials found that managing hyperglycaemia required higher doses of insulin in continuous infusion versus bolus administration. The MDs for insulin dose were 12.92 (95% CI -15.43 to 41.27) (Hyvernat 2016), -5.00 (95% CI -28.50 to 18.50) (Loisa 2007), and 7.57 (95% CI 4.07 to 11.07) (Tilouche 2019).

Hypernatremia

Data from two trials suggest no evidence of a difference between groups (RR 0.74, 95% CI 0.34 to 1.61; P = 0.45; 187 participants; I^2 = 47%; random-effects model; Analysis 2.11). This was based on very low-certainty evidence (due to risk of bias, inconsistency, and imprecision).

Muscle weakness

Only one trial reported data about muscle weakness (Tilouche 2019). This trial provided no evidence of a difference in this outcome between groups (RR 0.89, 95% CI 0.13 to 5.98). We downgraded the certainty of evidence to very low as this outcome was available from only one trial that was at high risk of performance and detection bias.

Neuropsychiatric events

Only one trial reported data about neuropsychiatric events (Tilouche 2019). This trial provided no evidence of a difference in this outcome between groups (RR 1.56, 95% CI 0.50 to 4.86). This was based on very low-certainty evidence (due to risk of bias, inconsistency, and very severe imprecision).

Stroke

One trial reported that this outcome did not occur during patient follow-up (Tilouche 2019). The other trials did not report information about this outcome.

Cardiac events

One trial reported that this outcome did not occur during patient follow-up (Analysis 2.11) (Tilouche 2019). The other trials did not report information about this outcome.

DISCUSSION

Summary of main results

Effects of corticosteroids on mortality

Overall, this review suggests that in sepsis, corticosteroids reduce all-cause mortality at 28 days and at 90 days, as well as mortality at intensive care unit (ICU) and hospital discharge. For these outcomes, results show some heterogeneity.

Sensitivity analysis based on trials judged as being at low risk of bias found a significant reduction in 28-day all-cause mortality with corticosteroids.

Subgroup analysis based on the specific study drug used did not find significant subgroup differences, although treatment effects on 28-day mortality might be greater with the combination of hydrocortisone and fludrocortisone. Only one trial directly compared hydrocortisone alone to hydrocortisone and fludrocortisone and found a non-statistically significant 3% absolute reduction in in-hospital mortality in favour of the combination (Annane 2010). Meta-regression and subgroup analyses based on treatment modalities show that dose and duration did not influence response to corticosteroids. Nevertheless, most trials published in the past two decades provided a long course (> 72 hours at full dose) of low-dose (< 400 mg per day of hydrocortisone equivalent) corticosteroids. Researchers provided no evidence of subgroup differences based on continuous infusion versus intermittent bolus administration of corticosteroids. Likewise, trials that directly compared continuous infusion versus intermittent bolus of corticosteroids reported no evidence of a difference between groups in mortality at 28 days, at 90 days, in the long term, and at ICU and hospital discharge. Subgroup analysis based on modalities for stopping corticosteroids suggests that survival benefit from corticosteroids was greater without versus with tapering off.

Subgroup analyses based on factors related to participants suggest that age (children vs adults) did not influence patients' response to corticosteroids. Patients with septic shock, those with acute respiratory distress syndrome (ARDS), and those with community-acquired pneumonia may be more likely to derive a survival benefit from corticosteroids than patients with less severe sepsis, although subgroup differences were barely statistically significant. Analysis of trials including patients with critical illness-related

corticosteroid insufficiency (CIRCI) did not show a significant reduction in the risk of death at 28 days. However, studies did not use the same definition for adrenal insufficiency. Additional studies are needed to determine the best diagnostic tool for CIRCI (Annane 2017b).

Effects of corticosteroids on morbidity outcomes

The beneficial effects of corticosteroids on mortality may be related to favourable effects of this treatment on the duration of shock. Indeed, this review shows that treatment with corticosteroids resulted in a substantial reduction in shock duration, with fewer patients remaining on vasopressor therapy by day 7 and by day 28. Treatment with corticosteroids may attenuate the severity of inflammation (Confalonieri 2005; Keh 2003; Mikami 2007; Oppert 2005; Rinaldi 2006), as well as the intensity and duration of organ system failure (Briegel 1999; Confalonieri 2005; Keh 2003; Oppert 2005; Sprung 2008), as shown in this review by a marked decrease in sequential organ failure assessment (SOFA) score at day 7. In addition, subsequent to favourable effects on cardiovascular and other organ functions, corticosteroid therapy resulted in substantial shortening of ICU and hospital length of stay.

These favourable effects of corticosteroids on sepsis-related morbidity were not influenced by modalities of treatment administration, as was found in trials that directly compared continuous infusion versus intermittent boluses of corticosteroids.

Tolerance of corticosteroids

Finally, this review also found no evidence of an effect of corticosteroids on rates of gastroduodenal bleeding or superinfection, nor on the proportion of patients with neuropsychiatric events, stroke, or cardiac events. Corticosteroids were associated with increased risk for developing hyperglycaemia and hypernatraemia, and for developing acquired muscle weakness.

Evidence from four trials that compared continuous infusion versus intermittent bolus of corticosteroids does not show significant differences in rates of hyperglycaemia, mean blood glucose levels, or the need for higher insulin doses when corticosteroids were administered as continuous infusion. One trial including 509 corticosteroid-treated patients with septic shock reported no benefit for normalizing blood glucose levels (Annane 2010). The rates of any other serious adverse events were not significantly different between continuous infusion and intermittent bolus administration of corticosteroids.

Overall completeness and applicability of evidence

We identified 61 trials addressing the question of corticosteroids versus control for sepsis. These trials accounted for a large population (i.e. 12,192 participants). Most of the eligible trials contributed to the primary outcome for this review. In addition, four trials provided information on direct comparison of continuous infusion versus intermittent bolus administration of corticosteroids. We found no evidence of publication bias.

Owing to the large number of trials, and to the large size of some individual trials, we could investigate all foreseen outcomes. We found mild heterogeneity in results for the primary outcome, which we explored through sensitivity analyses, subgroup analyses, and meta-regression analyses. Although subgroup analyses represent a between-study - not a within-study - hypothesis, we thought its validity was acceptable according to proposed criteria (Guyatt 2008b). First, we defined the hypothesis for an interaction between practical modalities of administration and effects of corticosteroids on mortality a priori. Second, we conducted subgroup analyses based on only two factors (i.e. modalities of drug administration and population). Third, findings show that the treatment effect was consistent in terms of 28-day, ICU, hospital, 90-day, and long-term mortality (risk ratios (RRs) 0.91, 0.89, 0.90, 0.93, and 0.97, respectively). Fourth, strong external evidence supports these results. Experimental and human studies have shown that a dose of 400 mg or less of hydrocortisone or equivalent can reverse the systemic inflammatory response, endothelial activation, and coagulation disorders secondary to infection (Annane 2005; Heming 2018), thus arguing against the use of higher doses. Moreover, at these low doses, corticosteroids have been shown to improve rather than suppress innate immunity in patients with septic shock (Kaufman 2008). It is now established that sepsis results in a sustained pro-inflammatory state, arguing against a short course of treatment (Angus 2013; Kellum 2007; van der Poll 2017).

Review authors noted some variation in the routine use of corticosteroids in sepsis. A survey of 542 US critical care physicians found that 83% do not routinely use corticosteroids in adults with sepsis, contrasting with 81% reporting common use of corticosteroids for septic shock (Bruno 2012). The findings of this review suggest that treatment effects on mortality may be greater in sepsis with versus without shock. Roughly one out of three respondents to the survey believed that corticosteroids reduce mortality in septic shock, whereas 27% did not and 45% were unsure. Hydrocortisone was the most common corticosteroid prescribed (93%), with a median dosage of 200 mg/d and administration via intermittent intravenous injection.

Quality of the evidence

We judged the certainty of evidence for 28-day mortality as moderate rather than high because of some inconsistency across trials that was related in part to differences in study populations and to differences in the types of corticosteroids used and the ways in which corticosteroids were given.

Potential biases in the review process

For this review, we performed a comprehensive search of the literature with no restriction on language, so we can assume that the risk of missing important trials was very limited. Slight asymmetry in the funnel plot for the primary outcome of this review may suggest some publication bias. However, potential sources of an asymmetrical funnel plot also include selection biases, poor methodological quality of smaller studies, true heterogeneity, artefacts, and chance (Egger 1997). Visual inspection of the funnel plot suggests a small-study effect (i.e. among small studies, the positive ones are more likely to be published). Nevertheless, our thorough search strategy and the need to enrol studies in public clinical trial registries may have decreased the risk of missing any randomized controlled trials. True heterogeneity seems to be a more plausible explanation for the observed asymmetrical funnel plot. Indeed, the effects of corticosteroids on mortality may be proportionate to the basal risk of death, and the two large trials that did not find survival benefit - Sprung 2008 and Venkatesh 2018 - included patients at lower risk of death than was seen in the two

large trials that found a survival benefit - Annane 2002 and Annane 2018. Finally, the asymmetrical funnel plot may have been due to chance.

One trial used a cross-over design (Keh 2003), and we could obtain none of the foreseen outcomes for this review. This trial concluded that prolonged treatment with a low dose of hydrocortisone improved haemodynamic and immune outcomes. Another trial compared three days versus seven days of hydrocortisone therapy and provided no evidence of differences in outcomes between patients treated for three days or seven days (Huh 2007). However, this trial had some limitations, including lack of blinding and small sample size. We considered that pooling the results of remaining trials in a meta-analysis was acceptable.

Three trials were published only as an abstract (Chawla 1999; Mirea 2014; Tandan 2005). Nevertheless, the primary investigators for these studies provided sufficient unpublished data for review authors to compute the primary outcome and several secondary outcomes for this review, allowing us to include these trials in the meta-analysis. Both published and unpublished data were available for 28 trials (Appendix 5), and the primary author for each trial validated the data extraction form. For four studies, contact with the primary investigator yielded no additional data (Luce 1988; Meijvis 2011; Rezk 2013; Snijders 2010).

We chose to convert outcome measures that correspond to censored data into dichotomous variables, that is, the proportion of participants with a particular event after one week and after four weeks, or at ICU or hospital discharge.

Agreements and disagreements with other studies or reviews

Findings in this review that a short course of high-dose corticosteroids provides no benefit for patients with sepsis are in line with reports from previous systematic reviews (Cronin 1995; Lefering 1995), as well as with current international guidelines (Annane 2017b; Rhodes 2017).

We found scarce data that could not allow conclusions on the effects of corticosteroids in children with sepsis, in keeping with a recent systematic review (Menon 2013). Nevertheless, we found no evidence of a difference in response to corticosteroids between children and adults.

The beneficial effects of corticosteroids on shock reversal in patients with septic shock are consistent across recent systematic reviews (Allen 2018; Fang 2018; Kalil 2011; Moran 2010; Ni 2018; Rochwerg 2018; Rygard 2018; Sherwin 2012). The survival benefit derived from corticosteroids for patients with sepsis was suggested by some previous authors (Allen 2018; Fang 2018; Moran 2010; Ni 2018; Rochwerg 2018), but not by others (Table 2) (Kalil 2011; Rygard 2018; Sherwin 2012). Nevertheless, this systematic review included trials that were not included in previous systematic reviews, as they were published only recently or were published in a non-English language. The current review included non-published information for a large number of trials after contact was made with original study authors, resulting in inclusion of qualitatively and quantitatively better data than were provided previously.

A recent network meta-analysis suggests that hydrocortisone was more likely than methylprednisolone to achieve shock reversal (Gibbison 2017).

AUTHORS' CONCLUSIONS

Implications for practice

Moderate-certainty evidence indicates that corticosteroids probably reduce 28-day, 90-day, and hospital mortality among patients with sepsis. Corticosteroids result in a large reduction in ICU and hospital length of stay (high-certainty evidence). There may be little or no difference in the risk of major complications; however, corticosteroids increase the risk of muscle weakness and hypernatraemia (high-certainty evidence), and probably increase the risk of hyperglycaemia (moderate-certainty evidence). The effects of continuous versus intermittent bolus administration of corticosteroids are uncertain.

Implications for research

The criteria for critical illness-related corticosteroid insufficiency in septic shock remain to be defined.

Subgroup analyses suggest that additional studies are needed to address these topics related to the use of corticosteroids in patients with sepsis.

- The role of a long course of low-dose corticosteroids for treatment of septic shock in children.
- The role of a long course of low-dose corticosteroids for treatment of patients with sepsis without shock, or with a mild form of septic shock; patients with ARDS; and patients with sepsis related to community-acquired pneumonia.
- The role of mineralocorticoid replacement.
- Optimal timing of initiation of treatment.
- Optimal dose and duration of hydrocortisone (or equivalent).
- Optimal modality to administer treatment that is continuous versus intermittent bolus.
- Optimal modality to stop treatment with or without taper off.
- The role of a long course of low-dose corticosteroids for treatment of sepsis caused by different types of infections.
- Long-term neuromuscular effects of steroids.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aboab 2008

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: not reported
Participants	Adults (n = 23) with septic shock and adrenal insufficiency as defined by a cortisol response to 250 µg synacthene (delta cortisol) ≤ 9 µg/dL

Aboab 2008 *(Continued)*

	Setting: intensive care unit Study location: France
Interventions	• Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) plus fludrocortisone (50 µg taken orally every 24 hours for 7 days) • Respective placebos
Outcomes	• Short-term improvement in autonomic failure as assessed by changes in the components of spectral analysis of cardiac and vascular signal variability between baseline and day 3 • In-hospital mortality
Notes	We contacted study authors and they could not provide missing data Funding source: authors' institution (public source) Data were extracted by BR Risk of bias was assessed by EB and BR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

Annane 2002

Methods	Randomized controlled trial with 2 parallel groups 19 centres Dates study was conducted: from October 1995 to February 1999
Participants	Adults (n = 300) with vasopressor- and ventilator-dependent septic shock

Annane 2002 *(Continued)*

	Stratification according to cortisol response to 250 µg synacthene for non-responders (delta cortisol ≤ 9 µg/dL) and responders (> 9 µg/dL) Setting: intensive care unit Study location: France
Interventions	• Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) plus fludrocortisone (50 µg taken orally every 24 hours for 7 days) • Respective placebos Treatments have to be initiated within 8 hours from shock onset
Outcomes	**Primary** • 28-Day mortality in non-responders **Secondary** • 28-Day mortality in responders and in all participants • Intensive care unit (ICU) mortality rate • Hospital mortality rate • 1-Year mortality rate • Shock reversal • Organ system failure-free days • Length of stay in ICU and at hospital • Safety
Notes	We contacted study authors and obtained access to individual patient data Funding source: French Ministry of Health Data were extracted by JB Risk of bias were assessed by RP and BR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none

Annane 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

Annane 2010

Methods	Randomized controlled trial with 2 × 2 factorial design 11 centres Dates study was conducted: from July 2014 to October 2014
Participants	Adults (n = 509) with vasopressor-dependent septic shock Subgroups based on adrenal status assess by a 250-µg ACTH test Setting: intensive care unit Study location: France
Interventions	• Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) plus fludrocortisone (50 µg taken orally every 24 hours for 7 days) and intravenous insulin to maintain blood glucose between 80 and 110 mg/dL • Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) and intravenous insulin to maintain blood glucose between 80 and 110 mg/dL • Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) plus fludrocortisone (50 µg taken orally every 24 hours for 7 days) and conventional control of blood glucose levels • Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) and conventional control of blood glucose levels Treatments have to be initiated within 24 hours from shock onset
Outcomes	**Primary** • Hospital mortality in non-responders **Secondary** • Mortality rates at 28 days, 90 days, and 180 days and at ICU discharge • Vasopressor-free days • Organ failure-free days • ICU and hospital length of stay • Safety
Notes	We contacted study authors and obtained access to individual patient data Funding source: French Ministry of Health Data were extracted by EB Risk of bias was assessed by EB and BR

Risk of bias

Bias	Authors' judgement	Support for judgement

Annane 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization through a secured website
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

Annane 2018

Methods	Randomized controlled trial with 2 × 2 factorial design 34 centres Dates study was conducted: from July 2014 to October 2014
Participants	Adults (n = 1241) with vasopressor-dependent septic shock Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit Study location: France
Interventions	• Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) plus fludrocortisone (50 µg taken orally every 24 hours for 7 days) and drotrecogin alfa (activated) at a dose of 24 µg/24 h • Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) plus fludrocortisone (50 µg taken orally every 24 hours for 7 days) and placebo of drotrecogin alfa (activated) • Placebo of hydrocortisone plus placebo of fludrocortisone (50 µg taken orally every 24 hours for 7 days) and drotrecogin alfa (activated) at a dose of 24 µg/24 h • Placebo of hydrocortisone plus placebo of fludrocortisone (50 µg taken orally every 24 hours for 7 days) and placebo of drotrecogin alfa (activated) Treatments have to be initiated within 24 hours from shock onset
Outcomes	**Primary** • 90-Day all-cause mortality **Secondary** • All-Cause mortality at ICU discharge, hospital discharge, day 28, and day 180

Annane 2018 *(Continued)*

- Percentage of participants from whom care was withheld or withdrawn
- Percentage of participants weaned from vasopressors at day 28 and at day 90
- Time to weaning from vasopressors
- Number of days that participants were alive and free of vasopressors (vasopressor-free days) up to day 28 and day 90 (patients who died before day 28 or day 90 were assigned zero free days)
- Percentage of participants weaned from mechanical ventilation at day 28 and at day 90
- Time to weaning from mechanical ventilation - ventilator-free days up to day 28 and day 90
- Percentage of participants with a total SOFA score < 6 (organ failure–free) at day 28 and at day 90
- Time to reaching a SOFA score < 6 organ failure–free days up to day 28 and day 90
- Percentage of participants discharged from the ICU and hospital up to day 28 and day 90
- Time to discharge from ICU and hospital and ICU-free and hospital-free days up to day 28 and day 90

Safety outcomes included

- Superinfection up to day 180
- Gastrointestinal bleeding up to day 28
- Episodes of hyperglycaemia up to day 7
- Neurological sequelae (cognitive impairment and muscle weakness) at time of ICU and hospital discharge, at day 90, and at day 18

Notes	We contacted study authors and obtained access to individual patient data Funding source: French Ministry of Health Data were extracted by BR Risk of bias was assessed by BR and RP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

Arabi 2011

Methods	Randomized controlled trial 1 centre Dates study was conducted: from April 2004 to October 2007
Participants	Adults (n = 75) with liver cirrhosis and septic shock Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit Study location: Saudi Arabia
Interventions	• Hydrocortisone (50 mg intravenous bolus every 6 hours until shock resolution, then treatment tapered off by 1 mL every 2 days until discontinuation) • Placebo (normal saline)
Outcomes	**Primary** • 28-Day all-cause mortality **Secondary** • ICU and hospital mortality • Shock reversal • Mechanical ventilation-free days • Renal replacement therapy-free days • Length of stay • SOFA score at day 7 • Adverse events Outcomes were also analysed in relation to adrenal insufficiency
Notes	We contacted authors and obtained access to individual patient data Funding source: King Abdulaziz City for Science and Technology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Use of sealed envelopes by pharmacists
Blinding (performance bias and detection bias) All outcomes	Low risk	Pharmacists: no Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes

Arabi 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unexplained discrepancy between reported K-M curves and number of deaths at 28 days in placebo arm
Selective reporting (reporting bias)	Low risk	Access to unpublished data
Other bias	High risk	Trial terminated prematurely after enrolment of 75 participants; planned sample size was 150

Blum 2015

Methods	Multi-centre. randomized, placebo-controlled, 2-parallel-group study Dates study was conducted: from December 2009 to May 2014
Participants	Adults (n = 800) patients hospitalized with community-acquired pneumonia Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: emergency and medical wards Study location: Switzerland
Interventions	• Prednisone 50 mg per day for 7 days • Placebo
Outcomes	**Primary** • Clinical stability **Secondary** • All-cause mortality within 30 and 180 days post randomization • ICU admission and length of stay • Duration of antibiotic treatment • Disease activity scores • Adverse events
Notes	We contacted study authors and obtained access to trial protocol and some missing data Funding source: Swiss National Science Foundation, Viollier AG, Nora van Meeuwen Haefliger Stiftung, Julia und Gottfried Bangerter-Rhyner Stiftung

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Randomization was centralized Generator and executor of randomization were separated Variable block sizes of 4 to 6

Blum 2015 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Outcomes reported matched outcomes planned by trial protocol, which was publicly released before the end of the recruitment period
Other bias	Low risk	Contact with trial authors; access to trial protocol but could not identify areas of bias

Bollaert 1998

Methods	Randomized controlled trial with 2 parallel groups 2 centres Dates the study was conducted: not reported
Participants	Adults (n = 41) with vasopressor- and ventilator-dependent septic shock Stratification according to cortisol response to 250 µg synacthene for non-responders (delta cortisol ≤ 6 µg/dL) and responders (> 6 µg/dL) Setting: intensive care unit Study location: France
Interventions	• Hydrocortisone (100 mg intravenous bolus every 8 hours for 5 days, then tapered over 6 days) • Placebo Treatments have to be initiated after 48 hours or longer from shock onset
Outcomes	**Primary** • Shock reversal **Secondary** • 28-Day mortality • ICU mortality • Hospital mortality • Improvement in haemodynamics • Length of stay in ICU and at hospital • Safety
Notes	We contacted study authors and obtained access to individual patient data Funding source: Nancy University Hospital.

Bollaert 1998 *(Continued)*

	Data were extracted by DA Risk of bias was assessed by DA and EB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

Bone 1987

Methods	Randomized controlled trial with 2 parallel groups 19 centres Dates study was conducted: from November 1982 to December 1985
Participants	Adults (n = 382) with sepsis (n = 234) or septic shock (n = 148) Setting: intensive care unit Study location: USA
Interventions	• Methylprednisolone (30 mg/kg 20-minute intravenous infusion, every 6 hours for 24 hours) • Placebo Treatments have to be initiated 2 hours from time entry criteria were met
Outcomes	**Primary** • 14-Day development of shock for sepsis • Shock reversal for septic shock • 14-Day death and safety

Bone 1987 *(Continued)*

Notes	We did not contact study authors Funding source: Upjohn Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No access to study protocol to exclude reporting bias
Other bias	Low risk	No access to full data including screening log to exclude selection bias

Briegel 1999

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: from November 1993 to September 1996
Participants	Adults (n = 40) with vasopressor- and ventilator-dependent septic shock Setting: intensive care unit Study location: Germany
Interventions	• Hydrocortisone (100-mg 30-minute intravenous infusion followed by 0.18 mg/kg/h continuous infusion until shock reversal, then tapered off) • Placebo Treatments have to be initiated within 72 hours from shock onset
Outcomes	**Primary** • Shock reversal **Secondary**

Briegel 1999 *(Continued)*

- 28-Day mortality
- ICU mortality
- Hospital mortality
- Improvement in haemodynamics
- Organ system failure (SOFA at day 7)
- Length of stay in ICU
- Safety

Notes	We contacted study authors and obtained access to individual patient data Funding source: Friedrich-Baur-Stiftung, Germany, by departmental funds Data were extracted by DA Risk of bias was assessed by DA and EB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Adequate randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Access to full data including screening log

Chawla 1999

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: not reported
Participants	Adults (n = 44) with vasopressor-dependent septic shock Setting: intensive care unit Study location: USA

Chawla 1999 *(Continued)*

Interventions	• Hydrocortisone (100 mg intravenous bolus every 8 hours for 3 days, then tapered over 4 days) • Placebo Treatments have to be initiated after 72 hours or longer from shock onset
Outcomes	**Primary** • Shock reversal **Secondary** • 28-Day mortality • Hospital mortality • Improvement in haemodynamics • Length of stay in ICU • Safety
Notes	We contacted study authors and obtained access to trial protocol and some missing data Funding source: not declared Data were extracted by DA Risk of bias was assessed by DA and EB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list was kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Access to full data including screening log

Cicarelli 2007

Methods	Randomized controlled trial with 2 parallel groups

Cicarelli 2007 *(Continued)*

	1 centre Dates study was conducted: from November 2004 through December 2005
Participants	Adults (n = 29) with vasopressor-dependent septic shock Setting: intensive care unit Study location: Brazil
Interventions	• Dexamethasone (0.2 mg/kg intravenous, 3 doses at intervals of 36 hours) • Placebo (normal saline)
Outcomes	• Duration of vasopressor support (SOFA score for cardiovascular system ≥ 2) • Duration of mechanical ventilation • 28-Day mortality
Notes	We contacted study authors and obtained information on study design but no additional unpublished data Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up: none; 3 participants were withdrawn after next of kin refused to consent
Selective reporting (reporting bias)	Unclear risk	No access to study protocol to rule out reporting bias
Other bias	Unclear risk	No access to data to rule out selection bias

Confalonieri 2005

Methods	Randomized controlled trial with 2 parallel groups 6 centres Dates study was conducted: from July 2000 through March 2003

Confalonieri 2005 *(Continued)*

Participants	Adults (n = 46) with severe community-acquired pneumonia Setting: intensive care unit Study location: Italy
Interventions	• Hydrocortisone (200 mg intravenous loading bolus followed by a continuous infusion at a rate of 10 mg/h for 7 days, then tapered over 4 days) • Placebo
Outcomes	**Primary** • Improvement in PaO_2:FiO_2 and in multiple organ dysfunction syndrome score by study day 8 **Secondary** • Duration of mechanical ventilation • Length of stay • 60-Day mortality • ICU mortality • Hospital mortality • Safety
Notes	We contacted study authors and obtained access to individual patient data Funding source: Assisi Foundation of Memphis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: 2 at 60 days after randomization, all in the placebo group
Selective reporting (reporting bias)	Low risk	Access to full data including screening log
Other bias	High risk	Study was stopped prematurely for apparent benefit; no sample size was defined a priori, but study authors used the triangular test as a stopping rule, analysing the primary outcome after each 20 participants

CSG 1963

Methods	Randomized controlled trial with 2 parallel groups 5 centres
Participants	Adults (n = 194), and children (n = 135) with vasopressor-dependent septic shock Setting: intensive care unit Study location: USA
Interventions	• Hydrocortisone (intravenous infusion of 300 mg for 24 hours, then 250 mg for 24 hours, followed by 200 mg orally on day 3, then tapered off in steps of 50 mg per day, i.e. total duration of treatment - 6 days) • Placebo
Outcomes	**Primary** • Hospital mortality **Secondary** • Safety
Notes	We did not contact study authors Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not given
Allocation concealment (selection bias)	Unclear risk	Not given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants: yes Caregivers: yes Data collectors: unclear Outcome assessors: unclear Data analysts: unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No access to study protocol to exclude reporting bias
Other bias	Unclear risk	No access to data to exclude selection bias

Doluee 2018

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: from August 2014 to April 2015
Participants	Adults (n = 160) that did not respond to vasopressor therapy for longer than 60 minutes Subgroup based on adrenal status as assessed by 250-µg ACTH given intramuscularly Setting: intensive care unit Study location: Iran
Interventions	• Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) • Placebo
Outcomes	**Primary** • 28-Day all-cause mortality **Secondary** • Shock termination as defined by full withdrawal of vasopressor for at least 6 consecutive hours
Notes	Study authors contacted but did not reply Funding source: Mashhad University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information was provided on method for generating the randomization list
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information was provided on who was blinded to study drug, albeit it is stated that hydrocortisone was compared to placebo (serum saline)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Reported outcomes in the publication matched those planned in the protocol as recorded in the Iranian Registry of Clinical Trials (https://en.irct.ir/trial/12131?revision=12131; accessed 7 April 2019)
Other bias	Unclear risk	No access to data to exclude selection bias

El Ghamrawy 2006

Methods	Randomized trial on 2 parallel groups Single centre

El Ghamrawy 2006 *(Continued)*

	Dates study was conducted: not reported
Participants	Adults (n= 34) with severe community-acquired pneumonia Setting: intensive care unit Study location: Saudi Arabia
Interventions	Hydrocortisone 200 mg intravenous bolus followed by infusion at 10 mg/h for 7 days
Outcomes	• In-hospital mortality • Serious adverse events
Notes	Study authors contacted but did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported
Other bias	Unclear risk	Insufficient information reported

El-Nawawy 2017

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: not reported
Participants	Children (n = 96) aged 1 month to 4 years with septic shock Subgroups based on adrenal status assess by a 250-µg ACTH test Setting: intensive care unit Study location: Egypt
Interventions	• Standard management without any study-specific intervention (n = 32) • ACTH test, diagnosed positive when maximal cortisol increment < 9 µg/dL (n = 32)

El-Nawawy 2017 *(Continued)*

	• Hydrocortisone continuous infusion of 50 mg/m^2/24 h for 5 days, then weaned off over 5 days (n = 32)
Outcomes	• Pediatric logistic organ dysfunction (PELOD) score • Shock reversal time • Length of stay in the paediatric intensive care unit • Survival time • Safety
Notes	Study authors contacted but did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information was provided on the method used for generating the randomization list
Allocation concealment (selection bias)	Unclear risk	No information was provided on the method used for randomization concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: yes
Selective reporting (reporting bias)	Unclear risk	No access to study protocol to exclude reporting bias
Other bias	Unclear risk	No access to data to exclude selection bias

Fernández-Serrano 2011

Methods	Randomized trial on 2 parallel groups Single centre Dates study was conducted: not reported
Participants	Adults (n = 56) with severe community-acquired pneumonia without shock and spontaneously breathing Setting: respiratory medicine department Study location: Spain

Fernández-Serrano 2011 *(Continued)*

Interventions	• Methylprednisolone as an intravenous bolus of 200 mg administered 30 minutes before the start of antibiotic treatment, followed by 29 mg every 6 hours for 3 days, then 20 mg every 12 hours for 3 days, and finally 20 mg/d for another 3 days • Placebo
Outcomes	**Primary** • Need for mechanical ventilation **Secondary** • Time to resolution of morbidity score • Time course of PaO_2/FiO_2 • Time for radiological clearance • ICU length of stay • Hospital length of stay • Short-term mortality • Time course of serum levels of various inflammatory biomarkers • Adverse events
Notes	Study authors contacted but did not reply Funding source: Fondo de Investigaciones Sanitarias (FIS) and partial funding from ISCIII RTIC (Red Respira)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Generator and executor of randomization were separated
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% of participants not analysed
Selective reporting (reporting bias)	Low risk	Outcomes reported in the publication matched those planned in the protocol as released on ISRCTN registry
Other bias	Unclear risk	Insufficient information

Gordon 2014

Methods	Randomized controlled trial with 2 parallel groups

Gordon 2014 *(Continued)*

	4 centres Dates study was conducted: from October 2010 through March 2012
Participants	Adults (n = 61) with septic shock on a maximal dose of vasopressin up to 0.06 U/min Setting: intensive care unit Study location: UK
Interventions	• Hydrocortisone phosphate (50 mg IV bolus 6-hourly for 5 days, 12-hourly for 3 days, then once daily for 3 days) • Placebo (0.5 mL of 0.9% saline)
Outcomes	**Primary** • Difference in plasma vasopressin concentrations between treatment groups **Secondary** • Difference in vasopressin requirements • 28-Day mortality • ICU mortality • Hospital mortality • Organ failure-free days to 28 days post randomization • Shock reversal • Length of stay in ICU and at hospital • Safety
Notes	We contacted study authors and obtained access to individual patient data Funding source: National Institute for Health Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers prepared by an independent statistician
Allocation concealment (selection bias)	Low risk	Randomization done via an online system
Blinding (performance bias and detection bias) All outcomes	Low risk	Hydrocortisone and its placebo presented in indiscernible forms
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Reported information matched published statistical plan
Other bias	Low risk	Accessed unpublished information to exclude other risk of bias

Gordon 2016

Methods	Randomized controlled trial with 2 × 2 factorial design 18 centres Dates study was conducted: from February 2013 through May 2015
Participants	Adults (n = 409) with septic shock requiring vasopressors despite fluid resuscitation within a maximum of 6 hours after onset of shock Setting: intensive care unit Study location: UK
Interventions	• Vasopressin (titrated up to 0.06 U/min) and hydrocortisone intravenous bolus every 6 hours for 5 days, every 12 hours for 3 days, and then once daily for 3 days (n = 101) • Vasopressin (titrated up to 0.06 U/min) and placebo of hydrocortisone (n = 104) • Norepinephrine (titrated up to 12 µg/min) and hydrocortisone intravenous bolus every 6 hours for 5 days, every 12 hours for 3 days, and then once daily for 3 days (n = 101) • Norepinephrine (titrated up to 12 µg/min) and placebo (n = 103) Hydrocortisone or its placebo was started only when maximum dose for vasopressin or norepinephrine was reached to maintain the target mean arterial pressure of 65 to 75 mmHg
Outcomes	**Primary** • Kidney failure–free days (i.e. number of days alive and free of kidney failure), defined by the Acute Kidney Injury Network (AKIN) group stage 3 definition during the 28 days after randomization, with no additional penalty for death **Secondary** • Rate and duration of renal replacement therapy • Length of kidney failure in survivors and non-survivors • 28-Day, ICU, and hospital mortality rates • Organ failure–free days in the first 28 days, assessed via the SOFA score
Notes	We contacted study authors and obtained access to individual patient data Funding source: National Institute for Health Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes

Gordon 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

Hu 2009

Methods	Randomized controlled trial 1 centre Dates study was conducted: not reported
Participants	Adults (n = 77) with septic shock Setting: intensive care unit Study location: China
Interventions	• Hydrocortisone (50 mg intravenous bolus 6-hourly for 7 days, then 50 mg 8-hourly for 3 days, then 50 mg 12-hourly for 2 days and 50 mg once daily for 2 days) • Control group: no mention of placebo
Outcomes	**Primary** • Time on norepinephrine and lactate clearance **Secondary** • ICU mortality • ICU length of stay • Shock reversal
Notes	We contacted study authors, who did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated in the manuscript
Allocation concealment (selection bias)	Unclear risk	Not stated in the manuscript
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated in the manuscript
Incomplete outcome data (attrition bias)	Low risk	Lost to follow-up: none

Hu 2009 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Huang 2014

Methods	Randomized controlled trial with 3 parallel groups Single centre Dates study was conducted: not reported
Participants	Adults (n = 60) with sepsis Setting: intensive care unit Study location: China
Interventions	• Hydrocortisone 200 mg as continuous infusion for 7 days • Chinese herb (Sini decoction) 100 mL per day enterally for 7 days • Standard therapy
Outcomes	**Primary** • Hypothalamic-pituitary-adrenal function assessed by levels of cortisol and ACTH and cortisol increment post ACTH injection at day 3 and day 14 **Secondary** • 3-Day shock reversal • 28-Day all-cause mortality
Notes	We contacted study authors, who did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: yes Caregivers: no Data collectors: no Outcome assessors: no Data analysts: no

Huang 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Huh 2007

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: from July 2005 through June 2006
Participants	Adults (n = 82) with septic shock and adrenal insufficiency Setting: intensive care unit Study location: South Korea
Interventions	• Hydrocortisone (50 mg intravenous bolus every 6 hours for 7 days) • Hydrocortisone (50 mg intravenous bolus every 6 hours for 3 days)
Outcomes	**Primary** • 28-Day mortality **Secondary** • Shock reversal • Duration of mechanical ventilation • Length of stay • Safety
Notes	We contacted study authors, who did not reply Fundig source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Unclear risk	Not given
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: no

Huh 2007 *(Continued)*

		Data analysts: no
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No explicit information on plan analysis
Other bias	Unclear risk	No information

Hyvernat 2016

Methods	Randomized controlled trial with 2 parallel groups 4 centres Dates study was conducted: from November 2008 through June 2010
Participants	Adults (n = 120) with septic shock Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit Study location: France
Interventions	• Hydrocortisone 50 mg intravenous bolus every 6 hours for 5 days without tapering • Hydrocortisone as an initial bolus of 100 mg followed by continuous infusion of 300 mg per day for 5 days without tapering
Outcomes	**Primary** • 28-Day all-cause mortality **Secondary** • Time • Days free of vasopressor (with zero days assigned to participants dying before being weaned off) • Days free of mechanical ventilation (with zero days assigned to participants dying before being weaned off) • Days free of renal replacement therapy (with zero days assigned to participants dying before being weaned off) • Safety
Notes	We contacted study authors and obtained access to individual patient data Fundng source: Association Niçoise de Réanimation Médicale

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme

Hyvernat 2016 *(Continued)*

Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	No evidence of other bias

Keh 2003

Methods	Randomized controlled trial with cross-over design 1 centre Dates study was conducted: from March 1997 through September 2000
Participants	Adults (n = 40) with vasopressor-dependent septic shock Setting: intensive care unit Study location: Germany
Interventions	• Hydrocortisone (100-mg 30-minute intravenous infusion followed by 10 mg/h continuous infusion for 3 days) • Placebo All participants received hydrocortisone for 3 days preceded or followed by placebo for 3 days
Outcomes	**Primary** • Immune response **Secondary** • Improvement in haemodynamics and organ system failure • Safety
Notes	We contacted study authors and obtained access to individual patient data Funding sources: Deutsche Forschungsgemeinschaft (expenses for analytes) and Pharmacia/Upjohn (expenses for patients' insurance) Data were extracted by DA Risk of bias was assessed by DA and BR

Keh 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol
Other bias	Low risk	Full access to data including screening log

Keh 2016

Methods	Randomized controlled trial with 2 parallel groups 34 centres Dates study was conducted: from January 2009 to August 2013
Participants	Adults (n = 380) with severe sepsis who were not in septic shock Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit Study location: Germany
Interventions	• Hydrocortisone as continuous infusion of 200 mg per day for 5 days followed by dose tapering until day 11 • Placebo
Outcomes	**Primary** • Proportion of participants who developed septic shock within 14 days **Secondary** • Time until septic shock • Mortality in the intensive care unit or hospital • Survival up to 180 days

Keh 2016 *(Continued)*

	• Safety • Secondary infection • Mechanical ventilation weaning failure • Muscle weakness • Hyperglycaemia (blood glucose level > 150 mg/dL)
Notes	We contacted study authors and obtained access to individual patient data Funding sources: Charité–Universitätsmedizin Berlin and grant from the German Federal Ministry of Education and Research Data were extracted by DA Risk of bias was assessed by DA and BR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

Kurungundla 2008

Methods	Randomized trial with 2 parallel groups Single centre
Participants	Adults (n = 21) with sepsis Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit Study location: USA

Kurungundla 2008 *(Continued)*

Interventions	• Corticosteroids at stress dose (molecule, exact dose, and duration not reported) • Placebo
Outcomes	• Short-term mortality • ICU length of stay
Notes	We contacted the study authors, who did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Li 2016

Methods	Randomized trial with 2 parallel groups Single centre Dates study was conducted: from May 2014 to February 2016
Participants	Adults (n = 58) with community-acquired pneumonia and septic shock Setting: intensive care unit Study location: China
Interventions	• Methylprednisolone 80 mg intravenously once a day for 7 days • Standard therapy
Outcomes	• 28-Day mortality • Hospital length of stay • Time on mechanical ventilation • Time on vasopressor • Time course of PaO_2/FiO_2 and C-reactive protein levels

Li 2016 *(Continued)*

	• Adverse events
Notes	We contacted the study authors, who did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: no Data analysts: no
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information reported
Selective reporting (reporting bias)	Unclear risk	No access to trial protocol
Other bias	Unclear risk	Insufficient information reported

Liu 2012

Methods	Randomized controlled trial with parallel groups 1 centre Dates the study was conducted: not reported
Participants	Adults (n = 26) with ARDS and sepsis, including septic shock (n = 12), and with critical illness-associated corticosteroid insufficiency Setting: intensive care unit Study location: China
Interventions	• Hydrocortisone (100 mg intravenous bolus 8-hourly for 7 consecutive days) • Placebo (normal saline)
Outcomes	**Primary** • Unclear **Secondary**

Liu 2012 *(Continued)*

- 28-Day mortality
- Prevalence of shock within 28 days
- SOFA score (information for SOFA score at day 7 not available)
- ICU length of stay
- Safety

Notes	We contacted the study authors and obtained access to individual patient data Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Unclear risk	No explicit information in the manuscript
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No explicit information in the manuscript
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No explicit information in the manuscript
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Loisa 2007

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: from July 2005 through April 2006
Participants	Adults (n = 48) with septic shock Setting: intensive care unit Study location: Finland
Interventions	• Hydrocortisone intravenous bolus of 50 mg every 6 hours for 5 days • Hydrocortisone as continuous infusion of 200 mg per day for 5 days
Outcomes	**Primary** • Difference in mean blood glucose levels between study groups and occurrence of hyperglycaemic and hypoglycaemic episodes **Secondary**

Loisa 2007 *(Continued)*

	• Reversal of shock • Extent of nursing workload required to maintain strict normoglycaemia
Notes	We contacted the study authors, who did not reply Fuding source: Medical Research Fund of Tampere University Hospital and Medical Research Fund of Päijät-Häme Central Hospital, Lahti

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated by study authors
Allocation concealment (selection bias)	Unclear risk	Not stated by study authors
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated by study authors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated by study authors
Selective reporting (reporting bias)	Unclear risk	Not stated by study authors
Other bias	Unclear risk	Not stated by study authors

Luce 1988

Methods	Randomized controlled trial 1 centre
Participants	Adults (n = 75) with sepsis and septic shock Setting: intensive care unit Study location: USA
Interventions	• Methylprednisolone (30-mg/kg 15-minute intravenous infusion every 6 hours for 24 hours) • Placebo
Outcomes	**Primary** • Prevention of ARDS **Secondary** • Hospital mortality
Notes	We contacted study authors and their data were no longer available Funding source: National Heart, Lung and Blood Institute, and Upjohn Company

Luce 1988 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	High risk	12 out of 87 randomly assigned participants were not analysed, and follow-up was not provided
Selective reporting (reporting bias)	Unclear risk	No access to study protocol
Other bias	Unclear risk	No access to data to exclude selection bias

Lv 2017

Methods	Randomized controlled trial with parallel groups 1 centre Dates study was conducted: from September 2015 to September 2016
Participants	Adults (n = 118) with septic shock that has developed within 6 hours before randomization Setting: intensive care unit Study location: China
Interventions	• Hydrocortisone administered at a dose of 200 mg/d as a continuous infusion for 6 days, and then tapered off. Once all vasopressors were discontinued, the taper protocol was initiated (half dose for 3 days, then quarter dose for 3 days, then stopped) • Placebo (normal saline)
Outcomes	**Primary** • 28-Day all-cause mortality **Secondary** • Reversal of shock • In-hospital mortality • Length of stay at ICU and at hospital

Lv 2017 *(Continued)*

Notes	We contacted study authors and obtained access to individual patient data Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

McHardy 1972

Methods	Randomized trial on 4 parallel groups Single centre Dates study was conducted: not reported
Participants	Children age > 12 years and adults (n = 126) with severe community-acquired pneumonia Setting: respiratory wards Study location: Scotland
Interventions	• Ampicillin 1 g per day orally for 7 to 14 days according to clinical response • Ampicillin 1 g per day orally for 7 to 14 days according to clinical response plus prednisolone 5 mg orally every 6 hours for 7 days • Ampicillin 2 g per day orally for 7 to 14 days according to clinical response • Ampicillin 2 g per day orally for 7 to 14 days according to clinical response plus prednisolone 5 mg orally every 6 hours for 7 days
Outcomes	• In-hospital death • Duration of antibiotic therapy • Need to change antibiotic therapy

McHardy 1972 *(Continued)*

- Time to resolution of fever
- Time to pathogen clearance
- Time to radiological clearance

Notes	We did not contact study authors Funding source: anonymous gift to the Department of Respiratory Diseases, University of Edinburgh

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: no Data analysts: no
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Meduri 2007

Methods	Randomized controlled trial (2:1 scheme) 5 centres Dates the study was conducted: from April 1997 through April 2002
Participants	Adults (n = 91) with early ARDS (≤ 72 hours from diagnosis of ARDS); 61 (67%) had sepsis or septic shock, and the primary author provided separate data for these participants Stratification according to cortisol response to 250 µg synacthene for non-responders (delta cortisol ≤ 9 µg/dL) and responders (> 9 µg/dL) Setting: intensive care unit Study location: USA
Interventions	• Methylprednisolone loading dose of 1 mg/kg followed by continuous infusion of 1 mg/kg/d from day 1 to day 14, then 0.5 mg/kg/d from day 15 to day 21, then 0.25 mg/kg/d from day 22 to day 25, then 0.125 mg/kg/d from day 26 to day 28. If participant was extubated before day 14, he/she was advanced

Meduri 2007 *(Continued)*

	to day 15 of drug therapy. Treatment was given intravenously until enteral intake was restored, then was given as a single oral dose • Placebo
Outcomes	**Primary** • Improvement in Lung Injury Score (LIS) at day 7. This improvement was defined as a reduction in score ≥ 1 point and a day 7 score ≤ 2 (if randomization LIS score < 3) or ≤ 2.5 (if randomization LIS score < 3) **Secondary** • Mechanical ventilation-free days • Multiple organ dysfunction (MOD) score at study day 7 • 28-Day mortality • ICU mortality • Hospital mortality • Length of stay in ICU and at hospital • C-reactive protein levels at study day 7 • Safety
Notes	If participant failed to improve on LIS between day 7 and day 9, he/she received open-label methylprednisolone at 2 mg/kg/d for unresolving ARDS We contacted study authors, who provided separate data for patients with sepsis Funding source: Baptist Memorial Health Care Foundation and the Assisi Foundation of Memphis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full access to data excluding any attrition bias
Selective reporting (reporting bias)	Low risk	Full access to data including screening log - reported outcomes matched those planned in protocol
Other bias	High risk	Study was stopped prematurely for efficacy

Meduri 2009

Methods	Randomized controlled trial with 2 parallel groups, stratified according to absence of shock and a multiple organ dysfunction score (MODS) < 3 (strata A), or presence of shock and MODS ≥ 3 (strata B) 1 centre Dates study was conducted: not reported
Participants	Adults (n = 80) with sepsis with or without septic shock Setting: intensive care unit Study location: USA
Interventions	• Hydrocortisone as a bolus of 300 mg followed by continuous infusion at 10 mg per hour for 7 days without tapering • Placebo
Outcomes	**Primary** • In strata A: improvement in MODS by day 7 • In strata B: resolution of shock by day 7 **Secondary** • Mortality at day 7 and at day 28 • Time to wean off vasopressors • New onset of shock • New onset of ARDS • MODS at day 7
Notes	Study was published as an abstract only. We contacted study authors and obtained access to individual patient data Funding source: Baptist Memorial Health Care Foundation and Assisi Foundation of Memphis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full access to data excluding any attrition bias

Meduri 2009 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study was stopped prematurely for efficacy
Other bias	Unclear risk	Full access to data including screening log Some imbalance in numbers allocated to hydrocortisone versus placebo

Meijvis 2011

Methods	Randomized controlled trial with 2 parallel groups 2 centres Dates the study was conducted: from November 2007 to September 2010
Participants	Adults (n = 304) with confirmed community-acquired pneumonia Setting: emergency departments and medical wards Study location: The Netherlands
Interventions	• Dexamethasone (5 mg intravenous bolus once a day for 4 days) • Placebo (normal saline)
Outcomes	**Primary** • Length of hospital stay **Secondary** • 30-Day mortality • Hospital mortality • Duration of treatment with intravenous antibiotics • Admission to ICU • Inflammation markers and health performance • Lung function • Safety
Notes	We contacted study authors and obtained separate data for patients with sepsis Funding source: no funding source identified for this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Pharmacist: no Participants: yes Caregivers: yes

Meijvis 2011 *(Continued)*

		Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	All outcomes reported in the study protocol are reported in the final analysis
Other bias	Low risk	Full access to study protocol

Menon 2017

Methods	Randomized controlled trial with 2 parallel groups 7 centres Dates study was conducted: from July 2014 through March 2016
Participants	Children (n = 57) newborn to 17 years old inclusive with suspected septic shock on vasopressor therapy from 1 to 6 hours before randomization Setting: intensive care unit Study location: Canada
Interventions	• Hydrocortisone initial IV bolus of 2 mg/kg followed by 1 mg/kg of hydrocortisone every 6 hours until patient met stability criteria (defined as no increase in vasoactive infusions and no administration of a fluid bolus) for at least 12 hours • Placebo
Outcomes	**Primary** • Patient accrual rate **Secondary** • Agreement between clinical diagnosis of septic shock with either the International Pediatric Sepsis Consensus Conference definition of septic shock (24) or the International Classification of Diseases, 10th edition (ICD-10), diagnostic codes • Number of eligible patients who were randomized within 6 hours from identification • Rate of protocol adherence (percentage of study drug doses correctly administered) • Frequency of corticosteroid use outside of the protocol (prescreening and post randomization) • PICU length of stay • Hospital length of stay • Time on vasopressors • Duration of mechanical ventilation
Notes	We did not contact study authors Funding source: Canadian Institutes of Health Research (CIHR)

Risk of bias

Menon 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization through a secured website
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Access to study protocol with no evidence of other bias

Mirea 2014

Methods	Randomized controlled trial with 3 parallel groups 1 centre Dates study was conducted: not reported
Participants	Adults (n = 171) with septic shock Setting: intensive care unit Study location: Romania
Interventions	• Hydrocortisone 50 mg intravenous bolus every 6 hours for a maximum of 7 days • Hydrocortisone 200 mg per day as a continuous infusion for a maximum of 7 days • Usual care
Outcomes	**Primary** • Mean serum sodium values over 7 days **Secondary** • Number of hyperglycaemia episodes, number of severe hyperglycaemia episodes (> 150 mg/dL) during 7-day study period • Short-term mortality
Notes	We contacted study authors and obtained access to individual patient data Funding source: not declared

Mirea 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: no Data analysts: no
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol and to raw data of individual patients excluding reporting bias
Other bias	Low risk	Full access to raw data of individual patients including screening log

Nafae 2013

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: not reported
Participants	Adults (n = 80) with severe community-acquired pneumonia Setting: chest department, respiratory, intensive care unit, general medicine department, and general medicine intensive care unit Study location: Egypt
Interventions	• Hydrocortisone 200 mg as intravenous bolus followed by infusion at 10 mg/h for 7 days • Placebo
Outcomes	• In-hospital mortality • Serious adverse events
Notes	We contacted study authors, who did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement

Nafae 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported
Other bias	Unclear risk	Insufficient information reported

Nagy 2013

Methods	Randomized controlled trial performed on 2 parallel groups Single centre Dates study was conducted: from June 2007 through September 2009
Participants	Children (n = 59) with severe community-acquired pneumonia Setting: Department of Paediatric Medical Health Study location: Hungary
Interventions	• Intravenous methylprednisolone 20 mg (0.5 to 2.0 mg/kg body weight in different ages) for 5 days • Intravenous 5% dextrose for 5 days
Outcomes	**Primary** • Clinical improvement at 7 days defined as decrease in coughing and respiratory distress, ≤ 4 days to defervescence (i.e. temperature < 37.58°C), improved levels of white blood cell count and CRP **Secondary** • Length of hospital stay • Complications including worsening of radiological findings such as pleural effusion, abscess formation, empyema, and pneumothorax
Notes	We did not contact study authors Funding source: New Hungary Development Plan, co-financed by the European Social Fund and the European Regional Development Fund

Risk of bias

Bias	Authors' judgement	Support for judgement

Nagy 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Sequence of random numbers for parallel groups was computer generated without block randomization
Allocation concealment (selection bias)	Unclear risk	No information given on how people were blinded to randomization list
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: unclear Data analysts: unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up
Selective reporting (reporting bias)	Low risk	Reported outcomes matched outcomes released on EudraCT registry
Other bias	Low risk	No evidence of other source of bias. Trial was completed with planned number of participants

Ngaosuwan 2018

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates the study was conducted: from October 2014 to October 2016
Participants	Adults (n = 80) with septic shock Setting: intensive care unit Study location: Thailand
Interventions	• Hydrocortisone 100 mg per day • Hydrocortisone 200 mg per day
Outcomes	• Hyperglycaemic rate • 28-Day mortality • Time to shock reversal • Superinfection • Gastrointestinal bleeding
Notes	We contacted study authors, who did not provide additional information Funding source: Srinakharinwirot University

Risk of bias

Bias	Authors' judgement	Support for judgement

Ngaosuwan 2018 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Reported outcomes in publication matched planned outcomes as released on clinicaltrial.gov registry
Other bias	Unclear risk	Study authors did not reply, and we could not access full protocol

Oppert 2005

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: not reported
Participants	Adults (n = 40) with vasopressor-dependent septic shock Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit Study location: Germany
Interventions	• Hydrocortisone (50 mg intravenous bolus followed by 0.18 mg/kg/h continuous infusion up to cessation of vasopressor for ≥ 1 hour, reduced to a dose of 0.02 mg/kg/h for 24 hours, then reduced by 0.02 mg/kg/h every day) • Placebo
Outcomes	**Primary** • Time to cessation of vasopressor support **Secondary** • Cytokine response • 28-Day survival • Sequential organ failure assessment (SOFA) score
Notes	We contacted study authors and obtained details for randomization and blinding procedures, along with additional information for mortality, for outcomes of participants randomized and not analysed, for shock reversal, and for adverse events

Oppert 2005 *(Continued)*

	Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	High risk	7 of 48 randomly assigned participants were not analysed: 5 in the corticosteroid group and 2 in the placebo group. 4 of these 7 participants were lost to follow-up, and 3 died (all in the steroid group)
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data including screening log

Rezk 2013

Methods	Randomized controlled trial (2:1 scheme) with 2 parallel groups 1 centre Dates study was conducted: from October 2011 through October 2012
Participants	Adults (n = 27) with ARDS and hospital- or community-acquired pneumonia Setting: intensive care unit Study location: Egypt
Interventions	• Methylprednisolone (loading dose of 1 mg/kg followed by infusion of 1 mg/kg/d from day 1 to day 14, 0.5 mg/kg/d from day 15 to day 21, 0.25 mg/kg/d from day 22 to day 25, and 0.125 mg/kg/d from day 26 to day 28) • Placebo (normal saline)
Outcomes	**Primary** • Unclear **Secondary** • Short-term mortality (time point unclear) • Time on mechanical ventilation • Vital signs

Rezk 2013 *(Continued)*

	• Safety
Notes	We contacted study authors, who did not provide additional information Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No explicit information in the manuscript
Allocation concealment (selection bias)	Unclear risk	No explicit information in the manuscript
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No explicit information in the manuscript
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Rinaldi 2006

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: not reported
Participants	Adults (n = 40) with sepsis and not receiving vasopressor support Setting: intensive care unit Study location: Italy
Interventions	• Hydrocortisone (300 mg per day as a continuous infusion for 6 days, then tapered off) • Standard therapy
Outcomes	**Primary** • Not explicitly stated **Secondary** • Markers of inflammation: microalbuminuria-to-creatinine ratio, serum levels of C-reactive protein and procalcitonin • Duration of mechanical ventilation • Sequential organ failure assessment (SOFA) score • Length of stay

Rinaldi 2006 *(Continued)*

	• Hospital mortality
Notes	We contacted study authors and obtained details for randomization and blinding procedures, along with additional information for mortality, for outcomes of participants randomized and not analysed, and for adverse events Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: no Data analysts: no
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 of 52 participants dropped out of the study: 6 in the control group and 6 in the corticosteroid group; contact with the primary author permitted completion of follow-up for all 12 participants
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding any reporting bias
Other bias	Low risk	Full access to data including screening log

Sabry 2011

Methods	Randomized controlled trial 3 centres Dates the study was conducted:from July 2010 through January 2011
Participants	Adults (n = 80) admitted to ICU with community-acquired pneumonia and sepsis Setting: intensive care unit Study location: Egypt
Interventions	• Hydrocortisone (intravenous loading dose of 200 mg over 30 minutes, followed by 300 mg in 500 mL 0.9% saline at a rate of 12.5 mg/h) for 7 days • Placebo (normal saline)
Outcomes	**Primary** • Improvement in PaO_2:FiO_2 (PaO_2:FiO_2 > 300 or ≥ 100 increase from study entry)

Sabry 2011 *(Continued)*

	Secondary • SOFA score by day 8 • Development of delayed septic shock • ICU mortality rate
Notes	We contacted study authors, who did not provide additional information Funding source: authors' institution (public)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information in the manuscript
Allocation concealment (selection bias)	Unclear risk	No information in the manuscript
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information in the manuscript
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No information in the manuscript
Other bias	Unclear risk	No information in the manuscript

Schumer 1976

Methods	Randomized controlled trial with 3 parallel groups 1 centre Dates the study was conducted: from 1967 through 1975
Participants	Adults (n = 172) with septic shock with positive blood culture Setting: surgical department Study location: USA
Interventions	• Dexamethasone (3 mg/kg as a single intravenous bolus) • Methylprednisolone (30 mg/kg as a single intravenous bolus) • Placebo Treatments might have been repeated once after 4 hours and had to be initiated at the time of diagnosis
Outcomes	**Primary** • Hospital mortality

Schumer 1976 *(Continued)*

	Secondary • Complication rates
Notes	We did not contact study authors Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomized card system
Allocation concealment (selection bias)	High risk	Unsealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants: yes Caregivers: unclear Data collectors: unclear Outcome assessors: unclear Data analysts: unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No access to study protocol
Other bias	Unclear risk	No data to exclude selection bias

Slusher 1996

Methods	Randomized controlled trial 2 centres Dates the study was conducted: from September 1991 through October 1992
Participants	African children (n = 72; 1 to 16 years of age) with sepsis or septic shock Setting: 2 rural hospitals in Africa Study location: USA, Kenya, and Nigeria
Interventions	• Dexamethasone (0.20 mg/kg every 8 hours for 2 days) • Placebo Treatments had to be initiated 5 to 10 minutes before first dose of antibiotic
Outcomes	**Primary** • Hospital mortality (unclear)

Slusher 1996 *(Continued)*

	Secondary • Haemodynamic stability at 48 hours • Complications
Notes	We did not contact study authors Funding source: Roche Pharmaceuticals donated ceftriaxone and provided partial financial support for the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not given
Allocation concealment (selection bias)	Unclear risk	Unclear; not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No access to study protocol
Other bias	Unclear risk	No data to exclude selection bias

Snijders 2010

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates the study was conducted: from August 2005 through July 2008
Participants	Adults (n = 213) with severe community-acquired pneumonia Setting: medical wards Study location: The Netherlands
Interventions	• Prednisolone (40 mg intravenously once per day for 7 days) • Placebo
Outcomes	**Primary**

Snijders 2010 *(Continued)*

	• Day 7 and day 30 rates of treatment failure, defined by persistence or progression of all signs and symptoms that developed during acute disease episode after randomization, or development of new pulmonary or extrapulmonary respiratory tract infection, or deterioration of chest radiography after randomization or death due to pneumonia, or inability to complete the study due to adverse events **Secondary** • Time to clinical stability • Length of hospital stay • 30-Day mortality • Inflammatory markers • Safety
Notes	We contacted study authors and did not obtain additional information Funding source: unrestricted grant by Astra Zeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Pharmacist: no Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	All outcomes reported in study protocol are reported in final analysis
Other bias	Unclear risk	No access to full protocol

Sprung 1984

Methods	Randomized controlled trial with 3 parallel groups 2 centres Dates the study was conducted: from August 1979 to February 1982
Participants	Adults (n = 59) with vasopressor-dependent septic shock

Sprung 1984 *(Continued)*

	Setting: intensive care unit Study location: USA
Interventions	• Dexamethasone (6 mg/kg as a single intravenous 10- to 15-minute infusion) • Methylprednisolone (30 mg/kg as a single intravenous 10- to 15-minute infusion) • No treatment • Placebo Treatments might have been repeated once after 4 hours if shock persisted, and they had to be initiated at time of diagnosis
Outcomes	**Primary** • Hospital mortality • Shock reversal **Secondary** • Complications of septic shock • Safety
Notes	We contacted study authors and obtained additional data (i.e. 28-day all-cause mortality) Funding source: Veterans Administration and Upjohn Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	High risk	At 1 centre, not clear how randomization list was kept confidential
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: yes at 1 centre, no at the other Caregivers: yes at 1 centre, no at the other Data collectors: yes at 1 centre, no at the other Outcome assessors: yes at 1 centre, no at the other Data analysts: unclear University of Miami Research Committee did not allow study to be performed in a double-blind manner, nor for participants to receive placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No access to study protocol
Other bias	Unclear risk	No data to exclude selection bias

Sprung 2008

Methods	Randomized controlled trial with 2 parallel groups 52 centres Dates the study was conducted: from March 2002 to November 2005
Participants	Adults (n = 499) with septic shock Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit Study locations: Europe and Israel
Interventions	• Hydrocortisone (50 mg every 6 hours for 5 days, then 50 mg every 12 hours for 3 days, then 50 mg once a day for 3 days) • Placebo
Outcomes	**Primary** • 28-Day mortality in non-responders **Secondary** • 28-Day mortality in responders and in all participants • ICU mortality rate • Hospital mortality rate • 1-Year mortality rate • Shock reversal • Organ system failure-free days • Safety
Notes	We contacted study authors and obtained access to individual patient data Funding sources: contract (QLK2-CT-2000-00589) from the European Commission, the European Society of Intensive Care Medicine, the European Critical Care Research Network, the International Sepsis Forum, and the Gorham Foundation. Roche Diagnostics provided the Elecsys cortisol immunoassay Data were extracted by EB Risk of bias was assessed by EB and BR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes

Sprung 2008 *(Continued)*

		Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up: none; 1 participant withdrew his consent Data for serious adverse events reported for only 466 of 499 participants, and analysis of these outcomes performed per-protocol, not by intent-to-treat
Selective reporting (reporting bias)	Low risk	Access to study protocol and to raw data of individual participants to confirm absence of reporting bias
Other bias	High risk	Only 500 participants included; expected sample size 800 participants

Sui 2013

Methods	Randomized controlled trial with 2 parallel groups Single centre Dates the study was conducted: not reported
Participants	Adults (n = 60) with severe community-acquired pneumonia Setting: medical wards Study location: China
Interventions	• Methylprednisolone intravenously 80 mg per day for 3 days, then 16 mg per day for 4 days • Standard therapy
Outcomes	• 7-Day clinical efficacy • Time course of C-reactive protein levels in plasma • Hospital length of stay • Reinfection rate • Serious adverse event
Notes	We contacted study authors, who did not reply Funding source: not declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information reported
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: no

Sui 2013 *(Continued)*

		Data analysts: no
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information reported
Other bias	Unclear risk	Insufficient information reported

Tagaro 2017

Methods	Randomized trial performed on 2 parallel groups 9 centres Dates the study was conducted: 1 January 2011, and 31 May 2015
Participants	Children (n = 60), ranging in age from 1 month to 14 years, with community-acquired pneumonia and pleural effusion Setting: intensive care unit Study location: Spain
Interventions	• Intravenous bolus of dexamethasone, 0.25 mg/kg every 6 hours for 48 hours • Intravenous bolus of placebo (0.9% sodium chloride) every 6 hours for 48 hours
Outcomes	**Primary** • Time to recovery, measured in hours. Recovery criteria were ambient oxygen saturation (SaO_2) > 92%, and temperature < 37°C, no respiratory distress, end of invasive procedures, pneumonia in resolution, and oral feeding. Time to recovery was calculated from the first dose of trial treatment until the time when all recovery criteria were fulfilled; for fever, this was the first hour of absence of fever **Secondary** • Complications of disease from time of hospitalization to day 30 after discharge, including all-cause mortality, pneumothorax, necrotizing pneumonia, initial uncomplicated effusion eventually needing drainage or surgery • Progression of simple effusion to complicated effusion requiring chest drainage • Decreased CRP level • Decreased effusion during days 1 to 3 • Adverse events including hyperglycaemia (up to study day 3), gastroduodenal bleeding, anaemia, oropharyngeal candidiasis, allergic reaction, rash
Notes	Source of funding: Spanish Ministry of Health and Sociedad de Pediatría de Madrid y Castilla La Mancha. Kern Pharma, Inc, Barcelona, Spain, supplied the drugs (dexamethasone and saline) and randomization. We did not contact trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme performed by manufacturer of the study drug (Kern Pharma, Barcelona, Spain)

Tagaro 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Use of prepackaged boxes provided by manufacturer of the study drug (Kern Pharma, Barcelona, Spain). The boxes were numbered consecutively for each hospital, severity stratum, and patient, according to the randomization scheme. They contained 15 transparent ampoules of dexamethasone or placebo, which were indiscernible from each other
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: no Data analysts: no
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up
Selective reporting (reporting bias)	Low risk	No difference between planned outcomes as released on ClinicalTrial.gov registry and reported outcomes in the main publication
Other bias	Low risk	No evidence for other bias - trial was completed with planned sample size

Tandan 2005

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates the study was conducted: not reported
Participants	Adults (n = 28) with septic shock and adrenal insufficiency Setting: intensive care unit Study location: India
Interventions	• Hydrocortisone (stated low dose but actual dose and duration not reported) • Placebo
Outcomes	**Primary** • 28-Day mortality or survival to hospital discharge **Secondary** • Shock reversal • Improvement in APACHE II score • Safety
Notes	We contacted study authors and obtained information on study design but no additional data Funding source: not declared
Risk of bias	

Tandan 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the local pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up: unknown; data reported only as an abstract with minimal information to allow accurate assessment of bias
Selective reporting (reporting bias)	Unclear risk	No access to study protocol; data reported only as an abstract with minimal information to allow accurate assessment of bias
Other bias	Unclear risk	Data reported only as an abstract with minimal information to allow accurate assessment of bias

Tilouche 2019

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: from April 2013 through June 2016
Participants	Adults (n = 70) with septic shock Setting: intensive care unit Study location: Tunisia
Interventions	• Hydrocortisone 200 mg/d by continuous infusion for 7 days • Hydrocortisone 50 mg intravenously every 6 hours for 7 days
Outcomes	**Primary** • Shock reversal on day 7 **Secondary** • 28-Day mortality • Number of days under vasopressors • Vasopressor free-days • ICU and hospital length of stay • Duration of mechanical ventilation • Occurrence of superinfection • New episode of septic shock

Tilouche 2019 *(Continued)*

- Episodes of hyperglycaemia
- Dose of insulin administered
- Occurrence of side effects to corticosteroids

Notes	We contacted study authors and obtained additional information and unpublished data Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Participants: no Caregivers: no Data collectors: no Outcome assessors: no Data analysts: no
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Reported outcomes matched those mentioned in trial protocol
Other bias	Low risk	No evidence for other risk of bias

Tongyoo 2016

Methods	Randomized controlled trial with 2 parallel groups 1 centre Dates study was conducted: from December 2010 through December 2014
Participants	Adults (n = 197) with septic shock and ARDS Setting: intensive care unit Study location: Thailand
Interventions	• Hydrocortisone 50 mg intravenous bolus every 6 hours for 7 days • Placebo (normal saline)
Outcomes	**Primary** • 28-Day all-cause mortality

Tongyoo 2016 *(Continued)*

	Secondary • Shock reversal • Number of organ support-free days to 28 days • Lung injury score at day 3 • PaO_2/FiO_2 at day 3 • Safety
Notes	We contacted study authors and obtained access to individual patient data Funding source: Siriraj critical care research funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	Full access to data excluding selection bias

Torres 2015

Methods	Randomized controlled trial with 2 parallel groups 3 centres Dates the study was conducted: from June 2004 through February 2012
Participants	Adults (n = 61) with both severe CAP and high inflammatory response, defined as levels of C-reactive protein > 15 mg/dL on admission Setting: intensive care unit Study location: Spain
Interventions	• Methylprednisolone (intravenous bolus of 0.5 mg/kg/12 h for 5 days started within 36 hours of hospital admission)

Torres 2015 *(Continued)*

	• Placebo (normal saline)
Outcomes	**Primary** • Rate of treatment failure, which includes early and/or late treatment failure. Early treatment failure was defined as clinical deterioration within 72 hours of treatment, as indicated by development of shock or need for invasive mechanical ventilation not present at baseline, or death. Late treatment failure was defined as radiographic progression (increase ≥ 50% of pulmonary infiltrates compared with baseline), persistence of severe respiratory failure (PaO_2/FiO_2 < 200, with respiratory rate ≥ 30 min^{-1} in non-intubated participants), development of shock or need for invasive mechanical ventilation not present at baseline or death between 72 and 120 hours after treatment initiation **Secondary** • Time to clinical stability • Length of ICU and hospital stay • In-hospital mortality • Inflammatory markers • Safety
Notes	We contacted study authors and obtained details for randomization and blinding procedures, along with additional information for mortality, shock reversal, SOFA, length of stay, and adverse events Funding source: SEPAR, SOCAP, FUCAP, SGR-2011, Fondo de Investigación Sanitaria, IDIBAPS, CIBERES

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to full protocol and unpublished information
Other bias	Low risk	Access to full protocol and unpublished information

Valoor 2009

Methods	Randomized controlled trial on 2 parallel groups

Valoor 2009 *(Continued)*

	1 centre Dates the study was conducted: not reported
Participants	Children (n = 38; 2 months to 12 years of age) with septic shock unresponsive to fluid therapy alone Setting: intensive care unit Study location: India
Interventions	• Hydrocortisone (intravenous dose of 5 mg/kg/d in 4 divided doses followed by half the dose for a total duration of 7 days) • Placebo (normal saline)
Outcomes	**Primary** • Time to shock reversal **Secondary** • Vasopressor doses • Mortality (unclear time point) • Safety
Notes	We did not contact study authors Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No explicit information in the manuscript
Allocation concealment (selection bias)	Unclear risk	No explicit information in the manuscript
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

VASSCSG 1987

Methods	Randomized controlled trial 10 centres
Participants	Adults (n = 223) with sepsis or septic shock (n = 100)

VASSCSG 1987 *(Continued)*

	Setting: intensive care unit Study location: USA
Interventions	• Methylprednisolone (30 mg/kg as a single intravenous 10- to 15-minute infusion, followed by a constant infusion of 5 mg/kg/h for 9 hours) • Placebo Treatment had to be initiated within 2 hours
Outcomes	**Primary** • 14-Day mortality **Secondary** • Complications
Notes	We did not contact study authors Funding source: Veterans Administration Cooperative Studies Program, Medical Research Service, Veterans Administration Central Office, Washington, DC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No access to study protocol
Other bias	Unclear risk	No data to exclude selection bias

Venkatesh 2018

Methods	Randomized controlled trial with 2 parallel groups 69 centres Dates the study was conducted: from March 2013 to April 2017

Venkatesh 2018 *(Continued)*

Participants	Adults (n = 3800) with vasopressor- and ventilator-dependent septic shock Setting: intensive care unit Study locations: Australia, Denmark, New Zeland, Saudi Arabia, UK
Interventions	• Hydrocortisone continuous intravenous infusion over a period of 24 hours for a maximum of 7 days or until ICU discharge or death, whichever occurred first. • Placebo
Outcomes	**Primary** • 90-Day all-cause mortality **Secondary** • 28-Day all-cause mortality • Time to resolution of shock • Recurrence of shock • Frequency and duration of mechanical ventilation • Frequency and duration of treatment with renal replacement therapy • Organ system failure-free days • Length of stay in ICU and at hospital • Safety
Notes	We contacted study authors and did not obtain additional data Funding source: National Health and Medical Research Council of Australia; Pfizer (which supplied hydrocortisone); Radpharm Scientific (which supplied placebo)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Low risk	Access to study protocol excluding reporting bias
Other bias	Low risk	No evidence for other bias

Yildiz 2002

Methods	Randomized controlled trial 1 centre Dates study was conducted: May 1997 to April 1999
Participants	Adults (n = 40) with sepsis (n = 14), severe sepsis (n = 17), and septic shock (n = 9) Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit and infectious disease department Study location: Turkey
Interventions	• Prednisolone (2 intravenous boluses: 5 mg at 06:00 and 2.5 mg at 18:00 for 10 days) • Placebo
Outcomes	**Primary** • 28-Day mortality **Secondary** • Hospital mortality • Safety
Notes	We contacted study authors and obtained details for randomization and blinding procedures, along with additional information for mortality, hospital length of stay, and adverse events Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Low risk	Randomization list kept confidential by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No access to protocol

Yildiz 2002 *(Continued)*

Other bias	Unclear risk	No data to exclude selection bias

Yildiz 2011

Methods	Randomized controlled trial on 2 parallel groups 1 centre Dates the study was conducted: April 2005 and May 2008
Participants	Adults (n = 55) with sepsis or septic shock Subgroups based on adrenal status assessed by a 250-µg ACTH test Setting: intensive care unit and infectious disease department Study location: Turkey
Interventions	• Prednisolone (intravenous 3 times a day at 06:00 (10 mg), 14:00 (5 mg), and 22:00 (5 mg) for 10 days) • Placebo (normal saline)
Outcomes	**Primary** • 28-Day mortality from all causes **Secondary** • Reversal of organ failure • Length of stay • Safety Outcomes were also assessed in relation to adrenal insufficiency
Notes	We contacted study authors, who did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers used
Allocation concealment (selection bias)	Low risk	Randomization list kept by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Pharmacist: no Participants: yes Caregivers: yes Data collectors: yes Outcome assessors: yes Data analysts: yes

Yildiz 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up: none
Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

Zhou 2015

Methods	Randomized controlled trial on 2 parallel groups 1 centre Dates the study was conducted: January 2008 to January 2013
Participants	Adults (n = 46) with community-acquired pneumonia and ARDS Setting: intensive care unit Study location: China
Interventions	• Methylprednisolone, 120 mg intravenously per day for 7 days • Standard therapy
Outcomes	• Duration of mechanical ventilation • Hospital length of stay
Notes	We contacted study authors, who did not reply Funding source: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	High risk	Pharmacist: no Participants: no Caregivers: no Data collectors: no Outcome assessors: no Data analysts: no
Incomplete outcome data (attrition bias)	Unclear risk	No information

Zhou 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No information
Other bias	Unclear risk	No information

ACTH: adrenocorticotrophin hormone.
AKIN: Acute Kidney Injury Network.
APACHE II: Acute Physiology and Chronic Health Evaluation II.
ARDS: acute respiratory distress syndrome.
CAP: community-acquired pneumonia.
CRP: C-reactive protein.
FiO_2: fractional inspired oxygen.
ICD-10: International Classification of Disease - version 10.
ICU: intensive care unit.
K-M curves: Kaplan-Meier curves.
LIS: Lung Injury Scale score.
MOD: multiple organ dysfunction.
PaO_2: arterial oxygen tension.
PELOD: paediatric logistic organ dysfunction score.
PICU: paediatric intensive care unit.
SaO_2: saturated oxygen.
SOFA: sequential organ failure assessment.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Asehnoune 2014	This study has compared hydrocortisone plus fludrocortisone vs placebo in patients with traumatic brain injury and not in sepsis
Bernard 1987	Mixed population of patients with refractory hypoxia; separate data on patients with sepsis not available
Cicarelli 2006	Mixed population of critically ill patients; separate data on patients with sepsis not available
Hahn 1951	Patients with acute streptococcal infection This trial investigated effects of hydrocortisone on fever, anti-streptolysin titers, and onset of rheumatic fever. No data are reported for analysis of the various outcomes considered in this systematic review
Huang 2014a	This study has compared in adults with community-acquired *Mycoplasma pneumoniae* pneumonia early (within 12 hours) vs late (at 72 hours) administration of methylprednisolone on clinical course
Huang 2015	This study included severely burned patients without sepsis
Hughes 1984	Only acute effects (within 1 hour) of methylprednisolone and/or naloxone on haemodynamic data were available; no data for any of the outcomes considered in this systematic review were reported
Kaufman 2008	In this study, participants were randomly assigned to receive hydrocortisone or its placebo for 24 hours only. Then, treatment with open-labelled hydrocortisone was given at physicians' discretion. This study was aimed at exploring effects of hydrocortisone on immune cell function
Klastersky 1971	This study was not a randomized trial. Investigators did not describe how participants were allocated to experimental treatment

Study	Reason for exclusion
Lan 2015	This study focused on methylprednisolone effects on cytokines levels in the bronchoalveolar lavage fluid in children with Mycoplasma pneumoniae pneumonia without providing information about outcomes relevant for this review
Lucas 1984	This study was not a randomized trial. Participants were allocated to experimental treatment according to their hospital number
Luo 2014	This study compared prednisolone as an adjunct therapy to antibiotics vs antibiotics alone in children with refractory *Mycoplasma pneumoniae* pneumonia. Researchers focused on short-term improvement in clinical symptoms and on variations in serum ferritin and LDH levels. None of the outcomes relevant for this review were assessed in this study
Marik 1993	This study compared effects of a short course (single bolus) of high-dose (10 mg/kg) hydrocortisone given before antibiotics to adults with community-acquired pneumonia. The trial focused on treatment effects on circulating levels of tumour necrosis factor and on short-term clinical course without providing information about outcomes relevant for this review
McKee 1983	Mixed population of critically ill patients; separate data on septic shock not available
Meduri 1998b	This trial included participants with late acute respiratory distress syndrome phase - not those with sepsis
Mikami 2007	This study included participants with community-acquired pneumonia and explicitly excluded patients with sepsis, those needing admission to the intensive care unit, and those requiring mechanical ventilation
Newberry 2017	This study assessed the effects of adjuvant prednisolone treatment in HIV-exposed infants aged 2-6 months. Thus study suggested that corticosteroids significantly reduced mortality at hospital discharge and at 6 months.
Peeters 2018	This trial compared ACTH responses to 100 µg IV CRH and placebo in 3 cohorts of 40 matched patients in the acute (ICU-day 3-6), subacute (ICU-day 7-16) or prolonged phase (ICU-day 17-28) of critical illness, with 20 demographically matched healthy subjects. CRH or placebo was injected in random order on two consecutive days
Rogers 1970	Study published only as an abstract; no contact with study authors was possible; incomplete information on primary and secondary outcomes
Roquilly 2011	This study has assessed the effects of hydrocortisone on the onset of ventilator-associated pneumonia in adults with multiple trauma and not in sepsis
Schwingshackl 2016	This trial included children within 72 hours of onset of acute respiratory distress syndrome of various etiologies. Separate data on children with sepsis were not available. The trial focused on methylprednisolone effects on circulating levels of several cytokines without providing information on outcomes that are relevant for this review
Steinberg 2006	This trial included participants with late acute respiratory distress syndrome phase - not those with sepsis
Tam 2012	This study assessed effects of oral prednisolone on viraemia in patients with dengue
Thompson 1976	Study published only as an abstract; no contact with study authors was possible; incomplete information on primary and secondary outcomes

Study	Reason for exclusion
van Woensel 2003	This study evaluated a short course (48 hours) of dexamethasone in children with viral pneumonia requiring mechanical ventilation. Viral pneumonia is a condition that is different in many aspects from bacterial sepsis
Venet 2015	This study included severely burned patients without sepsis
Wagner 1955	This study was not a randomized trial. Participants were allocated to experimental treatment according to hospital numbers
Weigelt 1985	Mixed population of critically ill patients; separate data on septic shock not available

LDH: lactate dehydrogenase.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02517489

Trial name or title	Community-acquired pneumonia: evaluation of corticosteroids (CAPE_COD)
Methods	Randomized double-blind trial on 2 parallel groups
Participants	Adults (n = 1200), admitted to the ICU or intermediate care unit, with community-acquired pneumonia
Interventions	• Hydrocortisone intravenously for 8 or 14 full days. Treatment course will include 4 or 7 days of full dose (200 mg/d by continuous infusion), 2 or 4 days of half dose (100 mg/d by continuous infusion), and 2 or 3 days of tapering dose (50 mg/d by continuous infusion). Duration of treatment is chosen upon patient initial improvement • Placebo
Outcomes	**Primary** • Day 28 all-cause mortality (time frame: at day 28) **Secondary** • In patients non-invasively ventilated at inclusion, proportion of participants needing endotracheal intubation (time frame: participants will be followed for duration of hospital stay, for maximum of 28 days) • In patients non-ventilated at inclusion, proportion of participants requiring non-invasive ventilation (time frame: participants will be followed for duration of hospital stay, for maximum of 28 days) • In patients non-ventilated at inclusion, proportion of participants needing endotracheal intubation (time frame: participants will be followed for duration of hospital stay, for maximum of 28 days) • Day 28 ventilator-free days (time frame: between 0 and day 28) • Number of participants with vasopressor therapy initiation from inclusion to day 28 (time frame: between 0 and day 28) • Day 28 vasopressor-free days (time frame: between 0 and day 28) • ICU and/or intermediate care unit LOS (time frame: participants will be followed for duration of hospital stay, for maximum of 28 days) • All-cause mortality at day 90 (time frame: at day 90) • SF-36 Health Survey at day 90 (time frame: at day 90) • Biomarkers: procalcitonin at baseline, day 3, and day 7 (time frame: at inclusion, day 3, and day 7) • Biomarkers: C-reactive protein at baseline, day 3, and day 7 (time frame: at inclusion, day 3, and day 7)

NCT02517489 *(Continued)*

	• Biomarkers: plasmatic concentration of pro-inflammatory cytokines (IL-6, IL-20, IL-22, IL-22BP, HBD2, TNF) at baseline, day 3, and day 7 (time frame: at inclusion, day 3, and day 7) • P/F ratio measured daily from baseline to day 7, at end of treatment, at end of ICU stay, and/or at day 28 (time frame: measured daily from baseline to day 7, at end of treatment, i.e. 14 days after start of treatment, at end of ICU stay (for maximum of 28 days), and/or at day 28) • SOFA calculated daily from baseline to day 7, at end of treatment, at end of ICU stay, and/or at day 28 (time frame: calculated daily from baseline to day 7, at end of treatment (i.e. 14 days after start of treatment), at end of ICU stay (for maximum of 28 days), and/or at day 28) • Proportion of participants experiencing secondary infection during their ICU stay (time frame: participants will be followed for the duration of hospital stay, for maximum of 28 days) • Proportion of participants experiencing gastrointestinal bleeding during their ICU stay (time frame: participants will be followed for the duration of hospital stay, for maximum of 28 days) • Daily amount of insulin administered to the patient from day 1 to day 7 (time frame: patients will be followed from day 1 to day 7) • Weight gain at baseline and at day 7 (time frame: patients will be followed at baseline and at day 7)
Starting date	October 2015
Contact information	Pierre-François DEQUIN; pierre-françois.dequin@univ-tours.fr
Notes	

NCT02602210

Trial name or title	Supplemental corticosteroids in cirrhotic hypotensive patients with suspicion of sepsis (SCOTCH)
Methods	Randomized double-blind trial on 2 parallel groups
Participants	Adults (n = 346), with liver cirrhosis and sepsis
Interventions	• Hydrocortisone IV bolus of 100 mg hydrocortisone in 50 mL NaCl 0.9% (sodium chloride), followed by continuous IV infusion of 200 mg hydrocortisone in 50 mL NaCl 0.9% at a rate of 2 mL/h until the start of day 4. Reduction in infusion rate with 0.5 mL/h/d • Placebo
Outcomes	**Primary** • 28-Day all-cause mortality **Secondary** • Patient survival at 90 days analysed from day of randomization (time frame: 90 days): survival status • ICU and hospital mortality (time frame: from date of randomization until ICU discharge or hospital mortality, whichever came first, up to day 90): mortality • Reversal of shock (time frame: up to day 90) time in days from start of placebo or active medication to resolution of shock defined as cessation of continuous vasopressor medication (for > 24 hours) • Reversal of organ failure (time frame: up to 90 days) measured with SOFA-score and CLIF-SOFA score • Vasopressor doses (time frame: up to 90 days): administration of vasopressor • Vasopressor-free days (time frame: up to 90 days): days without vasopressor • Mechanical ventilation-free days (time frame: up to 90 days): days without mechanical ventilation • Need for, and duration of, renal replacement therapy (time frame: up to 90 days): days of renal replacement therapy • ICU and hospital length of stay (time frame: up to 90 days): days of ICU stay, days of hospital stay

NCT02602210 *(Continued)*

	• Acquiring new infections (time frame: up to 90 days), bacterial or fungal, or both: defined according to CDC criteria (pneumonia, bacteraemia, spontaneous bacterial peritonitis, catheter-related bloodstream infection, skin infection, and others) • Shock relapse (time frame: during tapering period until 3 days after end of study drug) defined as hypotension recurrence during the tapering period or within 3 days of total discontinuation of study drug • Clinically important bleeding (time frame: up to 90 days) defined as new melena, new hematemesis, or unexplained fall in haemoglobin > 2 g/dL (not related to volume expansion). The presence of 'coffee ground' aspirate from nasogastric aspirate will not be considered active GI bleeding • Glycaemic control (time frame: during ICU stay, up to 10 days) measured as units of insulin required to attain glycaemic levels between 80 and 140 mg/dL • Episode of hyperglycaemia (> 180 mg/dL) or hypoglycaemia (< 60 mg/dL) (time frame: during study treatment period, up to 10 days): number of episodes of hypoglycaemia/hyperglycaemia • New shock episode (time frame: during study treatment period, up to 13 days): hypotension recurrence with need for vasopressor therapy after 3 days of total discontinuation of study drug • Impact of coagulopathy (time frame: during ICU stay up to 10 days) assessed by disseminated intravascular coagulopathy (DIC) score • Incidence of ICU-acquired weakness (time frame: during ICU stay, up to 90 days): occurrence of IC-acquired weakness
Starting date	January 2015
Contact information	Philippe Meersseman, MD; philippe.meersseman@uzleuven.be
Notes	

NCT03258684

Trial name or title	Hydrocortisone, vitamin C, and thiamine for treatment of sepsis and septic shock (HYVCTTSSS)
Methods	Randomized trial on 2 parallel groups
Participants	Adults (n = 140) with sepsis or septic shock
Interventions	• Intravenous vitamin C (1.5 g every 6 hours for 4 days or until ICU discharge) + hydrocortisone (50 mg every 6 hours for 7 days or until ICU discharge followed by a taper over 3 days) + intravenous thiamine (200 mg every 12 hours for 4 days or until ICU discharge) • Placebo
Outcomes	**Primary** • Hospital survival **Secondary** • Duration of vasopressor therapy (time frame: up to hour 72) • Requirement for renal replacement therapy in participants with acute kidney injury (AKI) (time frame: up to day 14) • ICU LOS (time frame: up to day 14) • Change in serum procalcitonin (PCT) (time frame: up to hour 72) • SOFA score (time frame: up to hour 96)
Starting date	September 2017
Contact information	Yuping Liao

NCT03258684 *(Continued)*

Notes	

NCT03333278

Trial name or title	The vitamin C, hydrocortisone, and thiamine in patients with septic shock trial (VITAMINS)
Methods	Multi-centre, randomized, open-label controlled trial
Participants	Adults (n = 216) with septic shock
Interventions	• Intravenous: ascorbic acid (vitamin C: 1.5 g every 6 hours), thiamine (vitamin B1: 200 mg every 12 hours), hydrocortisone (50 mg every 6 hours) • Hydrocortisone (50 mg every 6 hours)
Outcomes	**Primary** • Time alive and free of vasopressors at day 7 (168 hours) after randomization **Secondary** • ICU mortality (time frame: 90 days after randomization): participant died during ICU admission • Alive and ICU-free days at day 28 calculated as number of days alive and out of the ICU to day 28 (time frame: 28 days after randomization): alive and ICU-free days calculated as the number of days alive and out of ICU to day 28 • Hospital mortality (time frame: 90 days after randomization): participant died during hospital admission • 28-Day mortality (time frame: 28 days after randomization): participant died within 28 days after randomization • 90-Day mortality (time frame: 90 days after randomization): participant died within 90 days after randomization • Delta of sequential organ failure assessment (SOFA) score at 72 hours (time frame: 72 hours after randomization): defined as initial total SOFA* score minus day 3 at 72 hours): SOFA score* total SOFA. Sequential organ failure assessment = sum of each organ system point score. Score is based on 6 different scores, 1 each for respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. Organ scores are ranging from 0 to 4, with the best score being 0 and the worst being 4. The maximal (and worst) total SOFA score is 24 points • Hospital length of stay (time frame: 90 days after randomization): duration participant stayed in the hospital • 28-Day cumulative vasopressor-free hours (time frame: 28 days after randomization): cumulative vasopressor-free hours from shock resolution to day 28 post randomization • 28-Day cumulative invasive mechanical ventilation-free hours (time frame: 28 days after randomization): cumulative invasive mechanical ventilation-free hours during the 28-day period post randomization • RRT duration (time frame: 28 days after randomization): length of renal replacement therapy dependency during 28-day period post randomization
Starting date	May 2018
Contact information	R Bellomo; rinaldo.bellomo@austin.org.au
Notes	

NCT03335124

Trial name or title	The effect of vitamin C, thiamine, and hydrocortisone on clinical course and outcome in patients with severe sepsis and septic shock
Methods	Randomized double-blind placebo-controlled trial
Participants	Adults (n = 30) with sepsis or septic shock
Interventions	• Vitamin C: 1500 mg vitamin C infused over 30 minutes to 1 hour every 6 hours for 4 days or until discharge from the ICU + Hydrocortisone 50 mg IV every 6 hourly for 4 days or until ICU discharge + Intravenous thiamine at a dose of 200 mg every 12 hourly for 4 days or until ICU discharge • Placebo
Outcomes	**Primary** • Hospital mortality **Secondary** • 60-Day mortality (time frame: 60 days from inclusion in the study): we will compare mortality between treatment and placebo groups 60 days after inclusion in the study • 28-Day mortality (time frame: 28 days from inclusion in the study): we will compare mortality between treatment and placebo groups 28 days after inclusion in the study • Time to vasopressor independence (time frame: defined as time from start of active treatment or placebo to discontinuation of all pressors, until discharge from ICU, assessed in the first month): defined as time from start of active treatment or placebo to discontinuation of all pressors • PCT clearance (time frame: first 4 days in ICU): clearance of calculated procalcitonin using the following formula: initial PCT minus PCT at 96 hours, divided by initial PCT multiplied by 100 • Delta SOFA score (time frame: first 4 days in ICU): delta SOFA score, defined as initial SOFA score minus day 4 SOFA score. SOFA is a morbidity severity score and a mortality estimation tool developed from a large sample of ICU patients throughout the world. The higher the value, the higher the mortality. Maximum score is 24, lowest is 0 • ICU length of stay (LOS) and ICU-free days (time frame: ICU-free days is calculated as the number of days alive and out of the ICU to day 28): ICU-free days is calculated as the number of days alive and out of the ICU to day 28 • Hospital LOS (time frame: hospital LOS through study completion, assessed up to 12 months): LOS in the hospital
Starting date	December 2018
Contact information	S Stefanovic; sebastian.stefanovic@gmail.com
Notes	

NCT03389555

Trial name or title	Ascorbic acid, corticosteroids, and thiamine in sepsis (ACTS) trial
Methods	Randomized trial on parallel groups
Participants	n = 200 adults with septic shock
Interventions	• Vitamin C (ascorbic acid) 1.5 g every 6 hours × 4 days + vitamin B1 (thiamine) 100 mg every 6 hours × 4 days + hydrocortisone 50 mg every 6 hours × 4 days • Placebo

NCT03389555 *(Continued)*

Outcomes	**Primary** • SOFA score change (time frame: enrolment to 72 hours): change in degree of organ dysfunction as defined by SOFA score **Secondary** • Renal failure (time frame: enrolment until discharge from ICU): development of renal failure as defined by a kidney disease improving global outcomes (KDIGO) grade 3 or higher • 30-Day mortality • Ventilator-free days • Vasopressor-free days • Length of ICU stay • Length of hospital stay • Rate of delirium • Quality of life
Starting date	February 2018
Contact information	Michael W Donnino, MD; mdonnino@bidmc.harvard.edu
Notes	

NCT03422159

Trial name or title	Metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in sepsis (ORANGES)
Methods	Randomized double-blind placebo-controlled trial
Participants	Adults (n = 140) with sepsis or septic shock
Interventions	• Ascorbic acid 1.5 g IV piggyback every 6 hours for 4 days (or discharge from ICU if before 4 days) + Thiamine 200 mg IV piggyback every 12 hours for 4 days (or discharge from ICU if before 4 days) + Hydrocortisone 50 mg IV push every 6 hours for 4 days (or discharge from ICU if before 4 days) • Placebo
Outcomes	**Primary** • In-hospital mortality rate **Secondary** • 28-Day mortality (time frame: 28 days post randomization): 28-day mortality rate • Time to vasopressor independence (hours) (time frame: through study completion): defined as time from start of active treatment or placebo to discontinuation of all pressors • Procalcitonin (PCT) clearance (time frame: 4 days post randomization) PCT at 96 hours minus initial PCT, divided by initial PCT multiplied by 100 • Change in SOFA score (time frame: 4 days post randomization): defined as day 4 post randomization SOFA score minus initial SOFA score. SOFA score ranges from 0 (no organ dysfunction) to 24 (highest possible score or organ dysfunction) • ICU mortality (time frame: through study completion): ICU mortality rate • ICU length of stay (time frame: through study completion): time from admitting to ICU to discharge • ICU-free days (time frame: 28 days post randomization): number of days alive and out of the ICU at day 28

NCT03422159 *(Continued)*

	• Hospital LOS (time frame: through study completion): time from admitting to discharge of hospital stay
Starting date	February 2018
Contact information	A Vassallo; Andrew.Vassallo@rwjbh.org
Notes	

NCT03509350

Trial name or title	Vitamin C, thiamine, and steroids in sepsis (VICTAS)
Methods	Multi-centre, randomized, placebo-controlled, double-blind, adaptive clinical trial
Participants	Adults (n = 2000) with sepsis
Interventions	• Vitamin C intravenous vitamin C (1.5 grams every 6 hours) will be administered for 4 days or until ICU discharge + Intravenous thiamine (100 mg every 6 hours) will be administered for 4 days or until ICU discharge + Intravenous hydrocortisone (50 mg every 6 hours) will be administered for 4 days or until ICU discharge • Placebo
Outcomes	**Primary** • VVFD at 30 days (± 3 days) after randomization. Vasopressor and ventilator-free days will be determined by recording all start and stop days of these measures **Secondary** • Mortality at 30 days (time frame: day 30): numbers of participants who did not survive until day 30 will be compared between study arms • Delirium-free and coma-free days (DCFD) (time frame: day 14): DCFD is defined as number of days between enrolment and day 14 the participant has a Richmond Agitation-Sedation Scale (RASS) 3 or higher and confusion assessment method for ICU (CAM-ICU) negative (or Brief Confusion Assessment Method (bCAM) negative if in the ED) among survivors at that time point (day 14). The RASS categorizes patient sedation level on a scale from -5 (non-responsive sedation) to +4 (combative), where 0 indicates alert and calm. Delirium is diagnosed with the CAM when the patient exhibits an acute change in mental status and inattention plus either disorganized thinking or an altered level of consciousness
Starting date	August 2018
Contact information	J Sevranski; jonathan.sevransky@emoryhealthcare.org
Notes	

NCT03592693

Trial name or title	Vitamin C, hydrocortisone, and thiamine for septic shock (CORVICTES)
Methods	Randomized, multicenter, parallel-group, placebo-controlled
Participants	Adults (n = 400) with septic shock

NCT03592693 *(Continued)*

Interventions	• 1500 mg vitamin C every 6 hours for 4 days after randomization and stress-dose hydrocortisone for 4 days (250 mg on day 1; and 200 mg on days 2, 3, and 4) after randomization • Placebo
Outcomes	**Primary** • Hospital mortality **Secondary** • 60-Day mortality (time frame: 60 days): death before day 60 post randomization • 28-Day mortality (time frame: 28 days): death before day 28 post randomization • Procalcitonin (PCT) clearance (time frame: 4 days) will be defined as baseline PCT minus PCT at 96 hours post randomization, divided by initial PCT and multiplied by 100 • Delta SOFA score (time frame: 4 days) will be defined as initial SOFA score minus day 4 post randomization SOFA score. The SOFA score is the sum of 6 subscores that range from 0 to 4 and provide an assessment of the function of the following organs or systems: respiratory, nervous, cardiovascular, liver, coagulation, and renal. Increasing SOFA subscore (from 0 to 1, 2, 3, and 4) indicates worsening function culminating into failure of the corresponding organ or system. Maximum possible total SOFA score equals 24. SOFA score ≥ 15 has been previously associated with mortality rate > 90% • Neurological failure-free days (defined as daily follow-up Glasgow Coma Score > 9) within first 28 days of follow-up (time frame: 28 days) will be defined as the number of days with a (daily) follow-up Glasgow Coma Score > 9 within the first 28 days of follow-up • ICU mortality (time frame: 90 days): death before ICU discharge • ICU-free days to day 28 (time frame: 28 days) will be defined as the number of days alive and out of the ICU until follow-up day 28 • ICU length of stay (time frame: 90 days): duration of the need for intensive care after randomization • Hospital length of stay (time frame: 90 days): duration of hospitalisation after randomization
Starting date	September 2018
Contact information	SD Mentzelopoulos; sdmentzelopoulos@yahoo.com
Notes	

AKI: acute kidney injury.
bCAM: brief confusion assessment method.
CAM: confusion assessment method.
CDC: Centers for Diseases Control and Prevention.
CLIF: chronic liver failure consortium.
DCFD: delirium-free and coma-free days.
DIC: disseminated intravenous coagulopathy.
ED: emergency department.
G: gastric.
GI: gastrointestinal.
ICU: intensive care unit.
IL: interleukin.
IV: intravenous.
KDIGO: Kidney Disease: Improving Global Outcomes.
LOS: length of stay.
NaCl: sodium chloride.
PCT: procalcitonin.
RASS: Richmond Agitation-Sedation Scale.
RRT: renal replacement therapy.
SOFA: sequential organ function assessment.
TNF: tumour necrosis factor.

VVFD: vasopressor-ventilator-free days.

DATA AND ANALYSES

Comparison 1. Corticosteroids versus placebo or usual care

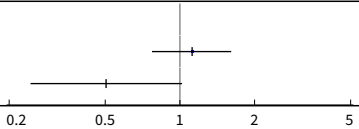
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 28-Day all-cause mortality	50	11233	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.84, 0.99]
1.1 Studies reporting actual 28-day mortality	32	9387	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.87, 1.00]
1.2 Studies reporting short-term mortality at other timing	18	1846	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.95]
2 28-Day all-cause mortality - sensitivity analysis based on methodological quality	38		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Adequate generation of allocation sequence	35	10076	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.87, 0.99]
2.2 Adequate allocation concealment	34	9972	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.87, 0.99]
2.3 Blinded trials	34	9894	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.87, 0.99]
2.4 Studies judged at low risk of bias	17	7896	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.84, 0.98]
3 28-Day all-cause mortality by subgroups based on study drug	47	11017	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.84, 1.00]
3.1 Hydrocortisone	25	6518	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.83, 1.05]
3.2 Hydrocortisone plus fludrocortisone	3	1564	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.98]
3.3 Prednisone/Prednisolone	5	1236	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.71, 1.33]
3.4 Methylprednisolone/Dexamethasone	14	1699	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.61, 1.09]
4 28-Day all-cause mortality by subgroups based on treatment dose/duration	44	10812	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.86, 0.97]
4.1 Long course of low-dose corticosteroids	39	9902	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.97]

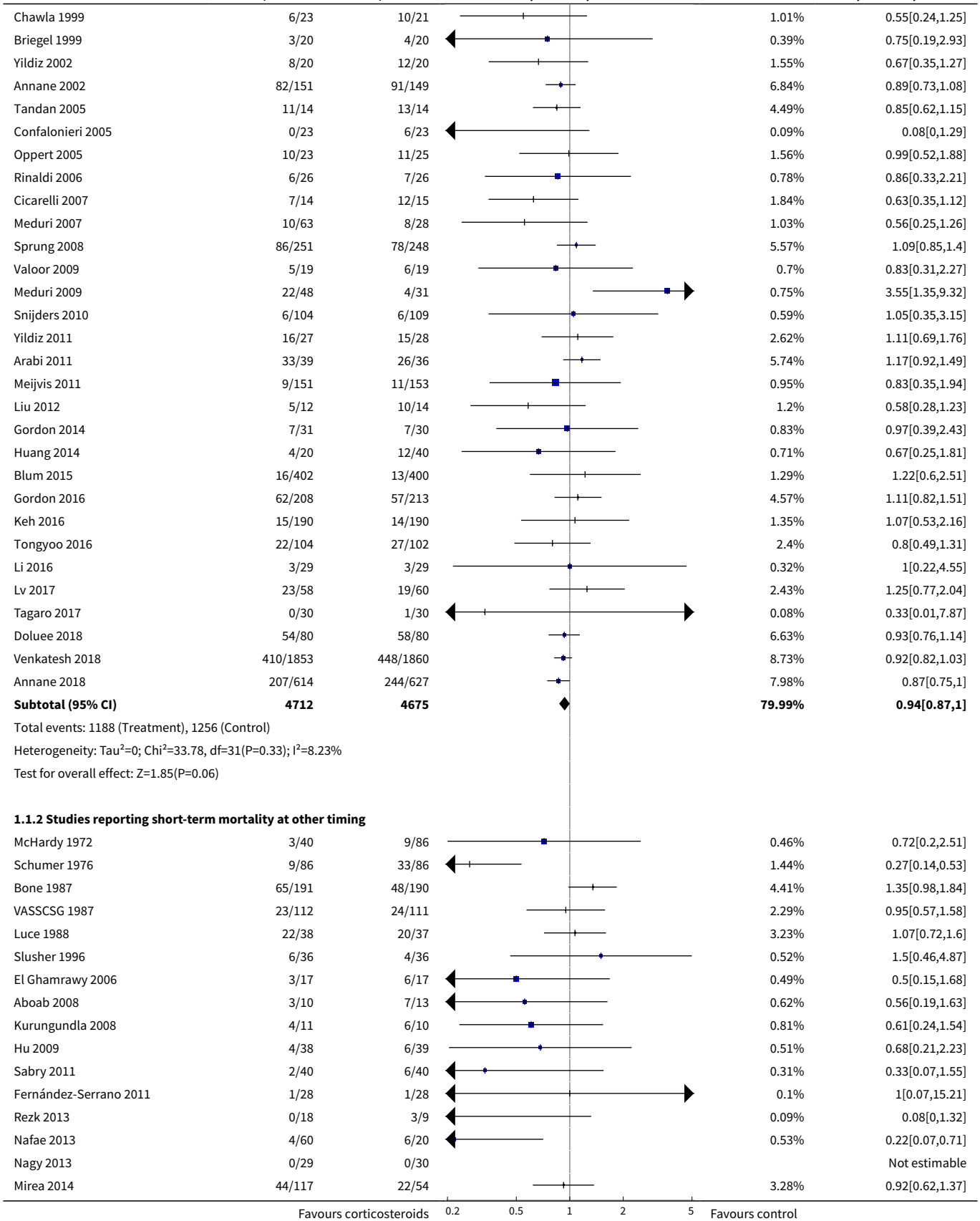
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Short course of high-dose corticosteroids	5	910	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.16]
5 28-Day all-cause mortality based on mode of drug administration	45	9978	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.82, 0.99]
5.1 Intravenous bolus	27	4749	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.02]
5.2 Continuous infusion	18	5229	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.66, 1.07]
6 28-Day all-cause mortality based on mode of drug termination	47	10906	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.83, 1.00]
6.1 Without taper off	30	8770	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.78, 0.98]
6.2 With taper off	17	2136	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.18]
7 28-Day all-cause mortality by subgroups based on age	45		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Adults	40	10169	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.83, 1.00]
7.2 Children	5	278	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.56, 2.09]
8 28-Day all-cause mortality by subgroups based on targeted population	50		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Sepsis	10	1358	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.89, 1.37]
8.2 Septic shock only	23	7428	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.83, 1.00]
8.3 Sepsis and ARDS	4	311	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.45, 0.98]
8.4 Sepsis and community-acquired pneumonia	13	2038	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.50, 1.00]
9 28-Day mortality in participants with critical illness-related corticosteroid insufficiency	12	1079	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.03]
10 90-Day all-cause mortality	7	5934	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.87, 1.00]
11 Long-term mortality	7	6236	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.91, 1.03]
12 Intensive care unit mortality	18	7267	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.83, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Hospital mortality	26	8183	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.82, 0.99]
14 Number of participants with shock reversal at day 7	16	6711	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.13, 1.34]
15 Number of participants with shock reversal at 28 days	13	6779	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [1.03, 1.08]
16 SOFA score at day 7	10	2157	Mean Difference (IV, Random, 95% CI)	-1.37 [-1.84, -0.90]
17 Length of intensive care unit stay for all participants	21	7612	Mean Difference (IV, Random, 95% CI)	-1.07 [-1.95, -0.19]
18 Length of intensive care unit stay for survivors	10	778	Mean Difference (IV, Fixed, 95% CI)	-2.19 [-3.93, -0.46]
19 Length of hospital stay for all participants	22	8795	Mean Difference (IV, Random, 95% CI)	-1.63 [-2.93, -0.33]
20 Length of hospital stay for survivors	9	710	Mean Difference (IV, Random, 95% CI)	-4.11 [-8.50, 0.28]
21 Number of participants with adverse events	31		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Gastroduodenal bleeding	26	5231	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.85, 1.35]
21.2 Superinfection	25	5356	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.19]
21.3 Hyperglycaemia	20	8594	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.13, 1.22]
21.4 Hypernatraemia	6	5069	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.34, 2.06]
21.5 Muscle weakness	6	6145	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.01, 1.44]
21.6 Neuropsychiatric event	8	6941	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.53, 1.39]
21.7 Stroke	4	2842	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.41, 1.68]
21.8 Cardiac event	6	3567	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.66, 1.88]

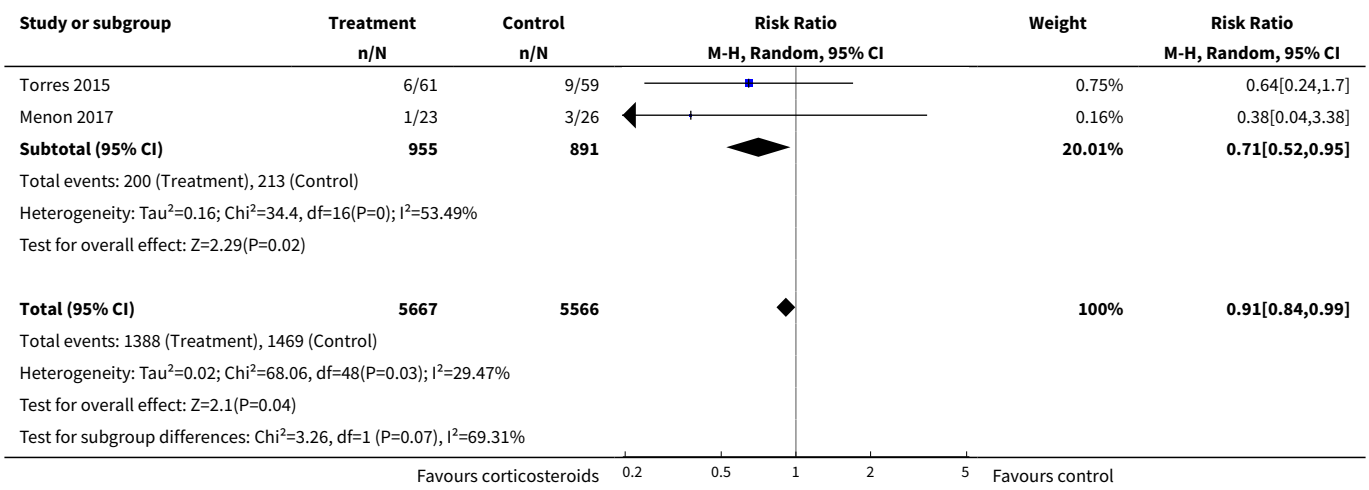
Analysis 1.1. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 1 28-Day all-cause mortality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Studies reporting actual 28-day mortality					
Sprung 1984	33/43	11/16		3.62%	1.12[0.77,1.61]
Bollaert 1998	7/22	12/19		1.34%	0.5[0.25,1.02]

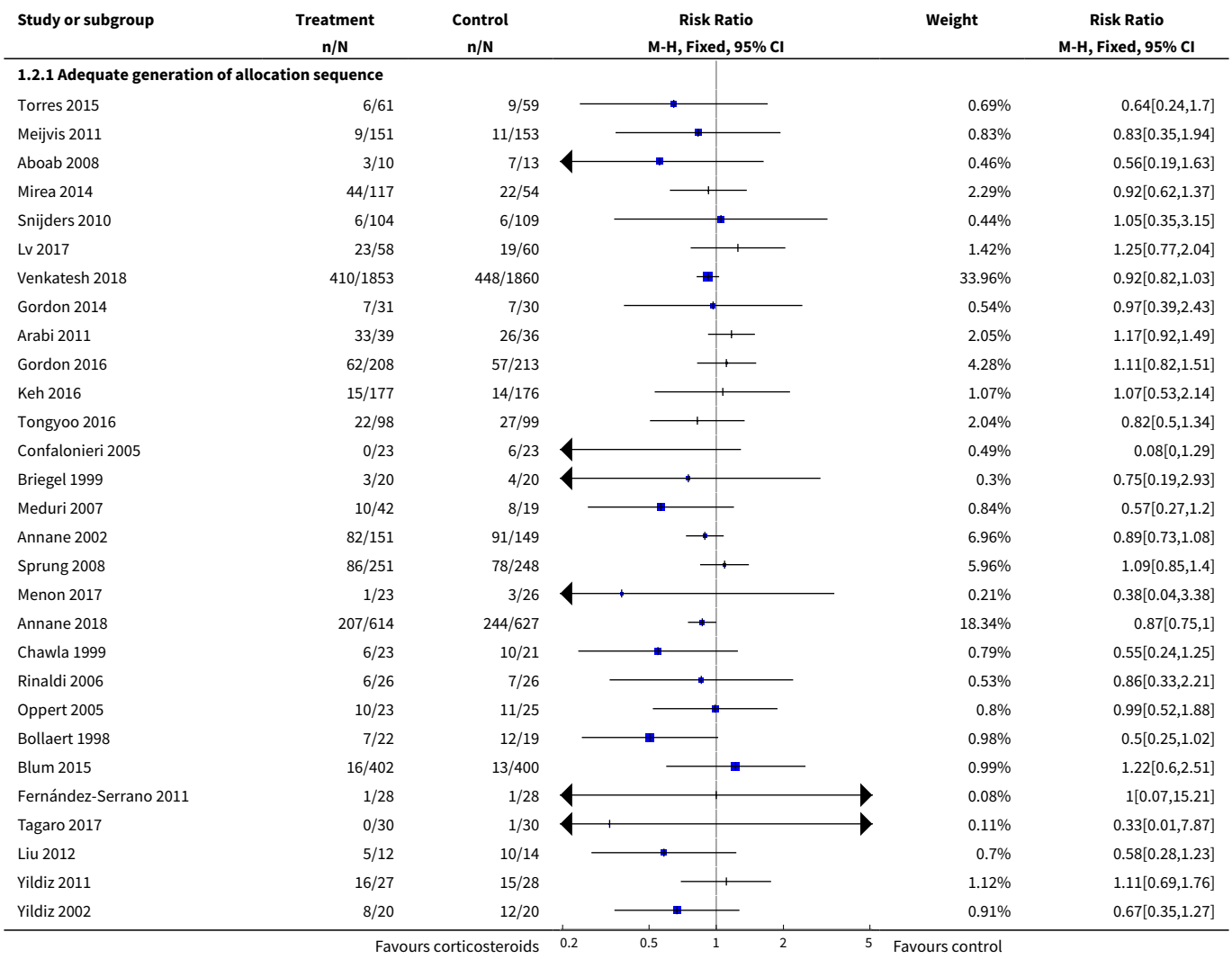


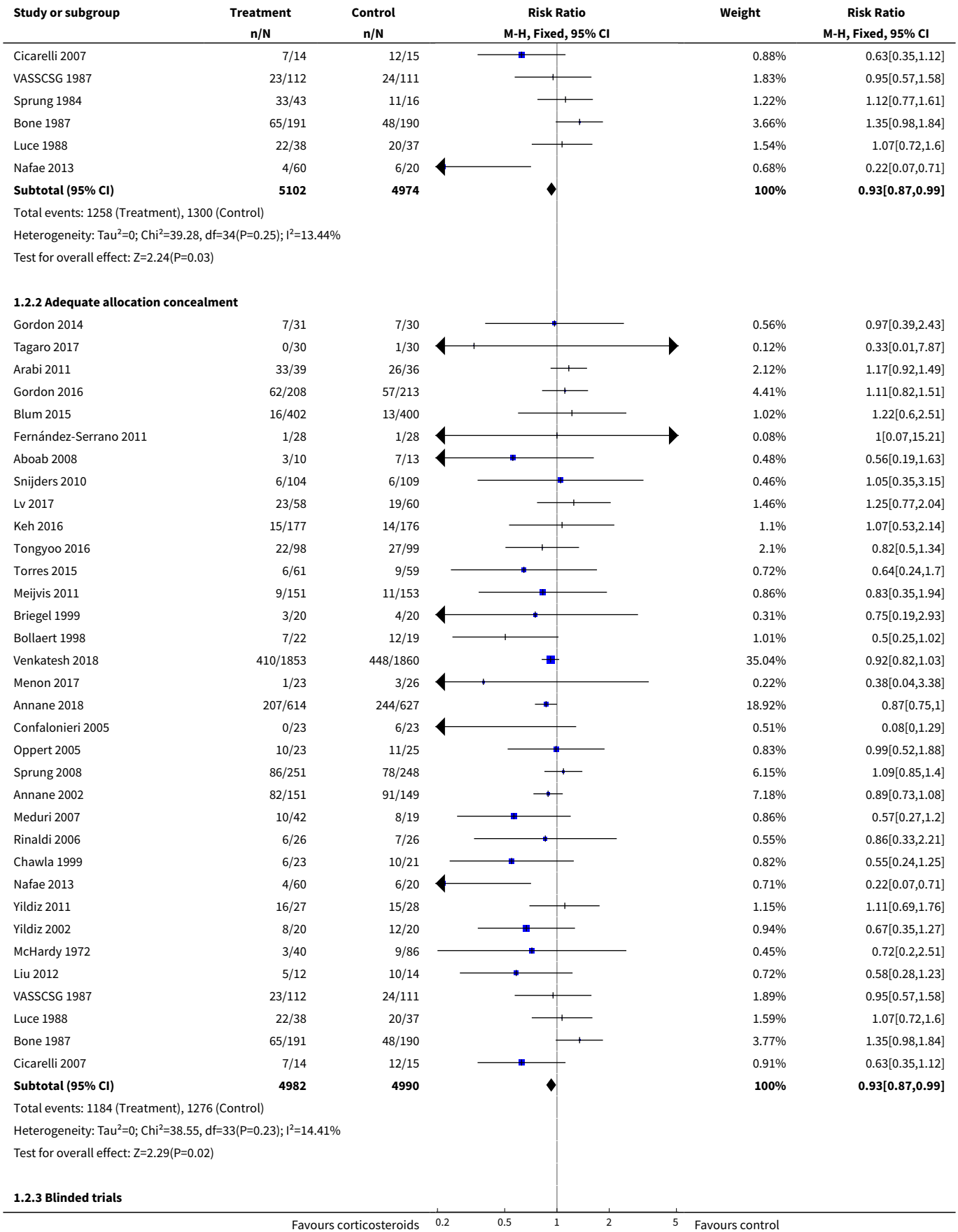


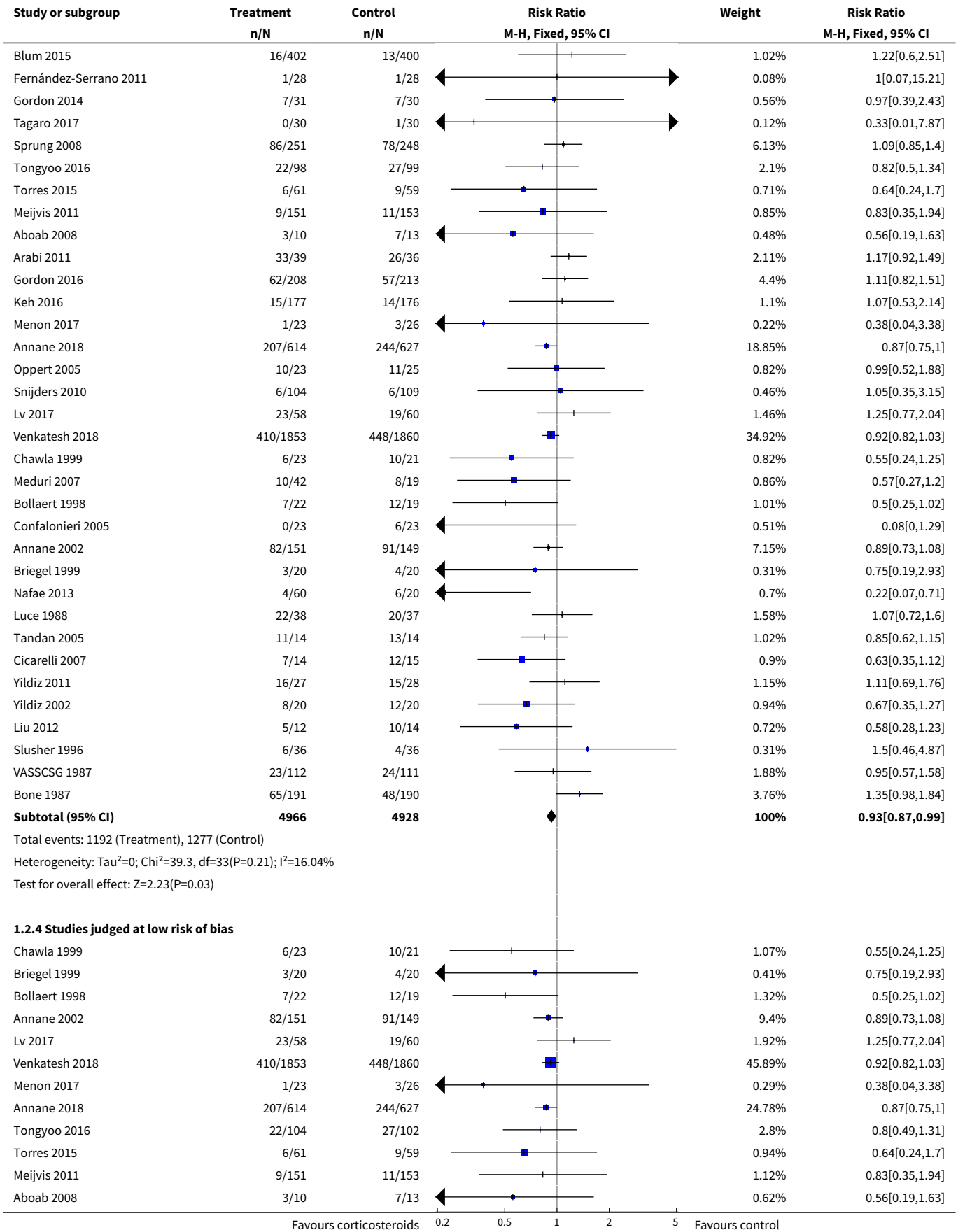
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chawla 1999	6/23	10/21		1.01%	0.55[0.24,1.25]
Briegel 1999	3/20	4/20		0.39%	0.75[0.19,2.93]
Yildiz 2002	8/20	12/20		1.55%	0.67[0.35,1.27]
Annane 2002	82/151	91/149		6.84%	0.89[0.73,1.08]
Tandan 2005	11/14	13/14		4.49%	0.85[0.62,1.15]
Confalonieri 2005	0/23	6/23		0.09%	0.08[0,1.29]
Oppert 2005	10/23	11/25		1.56%	0.99[0.52,1.88]
Rinaldi 2006	6/26	7/26		0.78%	0.86[0.33,2.21]
Cicarelli 2007	7/14	12/15		1.84%	0.63[0.35,1.12]
Meduri 2007	10/63	8/28		1.03%	0.56[0.25,1.26]
Sprung 2008	86/251	78/248		5.57%	1.09[0.85,1.4]
Valoor 2009	5/19	6/19		0.7%	0.83[0.31,2.27]
Meduri 2009	22/48	4/31		0.75%	3.55[1.35,9.32]
Snijders 2010	6/104	6/109		0.59%	1.05[0.35,3.15]
Yildiz 2011	16/27	15/28		2.62%	1.11[0.69,1.76]
Arabi 2011	33/39	26/36		5.74%	1.17[0.92,1.49]
Meijvis 2011	9/151	11/153		0.95%	0.83[0.35,1.94]
Liu 2012	5/12	10/14		1.2%	0.58[0.28,1.23]
Gordon 2014	7/31	7/30		0.83%	0.97[0.39,2.43]
Huang 2014	4/20	12/40		0.71%	0.67[0.25,1.81]
Blum 2015	16/402	13/400		1.29%	1.22[0.6,2.51]
Gordon 2016	62/208	57/213		4.57%	1.11[0.82,1.51]
Keh 2016	15/190	14/190		1.35%	1.07[0.53,2.16]
Tongyoo 2016	22/104	27/102		2.4%	0.8[0.49,1.31]
Li 2016	3/29	3/29		0.32%	1[0.22,4.55]
Lv 2017	23/58	19/60		2.43%	1.25[0.77,2.04]
Tagaro 2017	0/30	1/30		0.08%	0.33[0.01,7.87]
Doluee 2018	54/80	58/80		6.63%	0.93[0.76,1.14]
Venkatesh 2018	410/1853	448/1860		8.73%	0.92[0.82,1.03]
Annane 2018	207/614	244/627		7.98%	0.87[0.75,1]
Subtotal (95% CI)	**4712**	**4675**		**79.99%**	**0.94[0.87,1]**
Total events: 1188 (Treatment), 1256 (Control)					
Heterogeneity: Tau²=0; Chi²=33.78, df=31(P=0.33); I²=8.23%					
Test for overall effect: Z=1.85(P=0.06)					
1.1.2 Studies reporting short-term mortality at other timing					
McHardy 1972	3/40	9/86		0.46%	0.72[0.2,2.51]
Schumer 1976	9/86	33/86		1.44%	0.27[0.14,0.53]
Bone 1987	65/191	48/190		4.41%	1.35[0.98,1.84]
VASSCSG 1987	23/112	24/111		2.29%	0.95[0.57,1.58]
Luce 1988	22/38	20/37		3.23%	1.07[0.72,1.6]
Slusher 1996	6/36	4/36		0.52%	1.5[0.46,4.87]
El Ghamrawy 2006	3/17	6/17		0.49%	0.5[0.15,1.68]
Aboab 2008	3/10	7/13		0.62%	0.56[0.19,1.63]
Kurungundla 2008	4/11	6/10		0.81%	0.61[0.24,1.54]
Hu 2009	4/38	6/39		0.51%	0.68[0.21,2.23]
Sabry 2011	2/40	6/40		0.31%	0.33[0.07,1.55]
Fernández-Serrano 2011	1/28	1/28		0.1%	1[0.07,15.21]
Rezk 2013	0/18	3/9		0.09%	0.08[0,1.32]
Nafae 2013	4/60	6/20		0.53%	0.22[0.07,0.71]
Nagy 2013	0/29	0/30			Not estimable
Mirea 2014	44/117	22/54		3.28%	0.92[0.62,1.37]

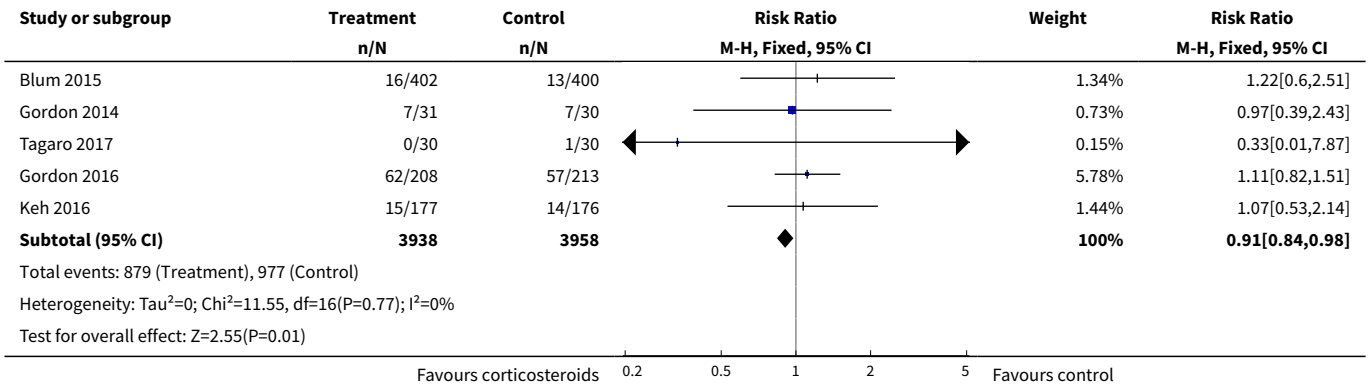


Analysis 1.2. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 2 28-Day all-cause mortality - sensitivity analysis based on methodological quality.

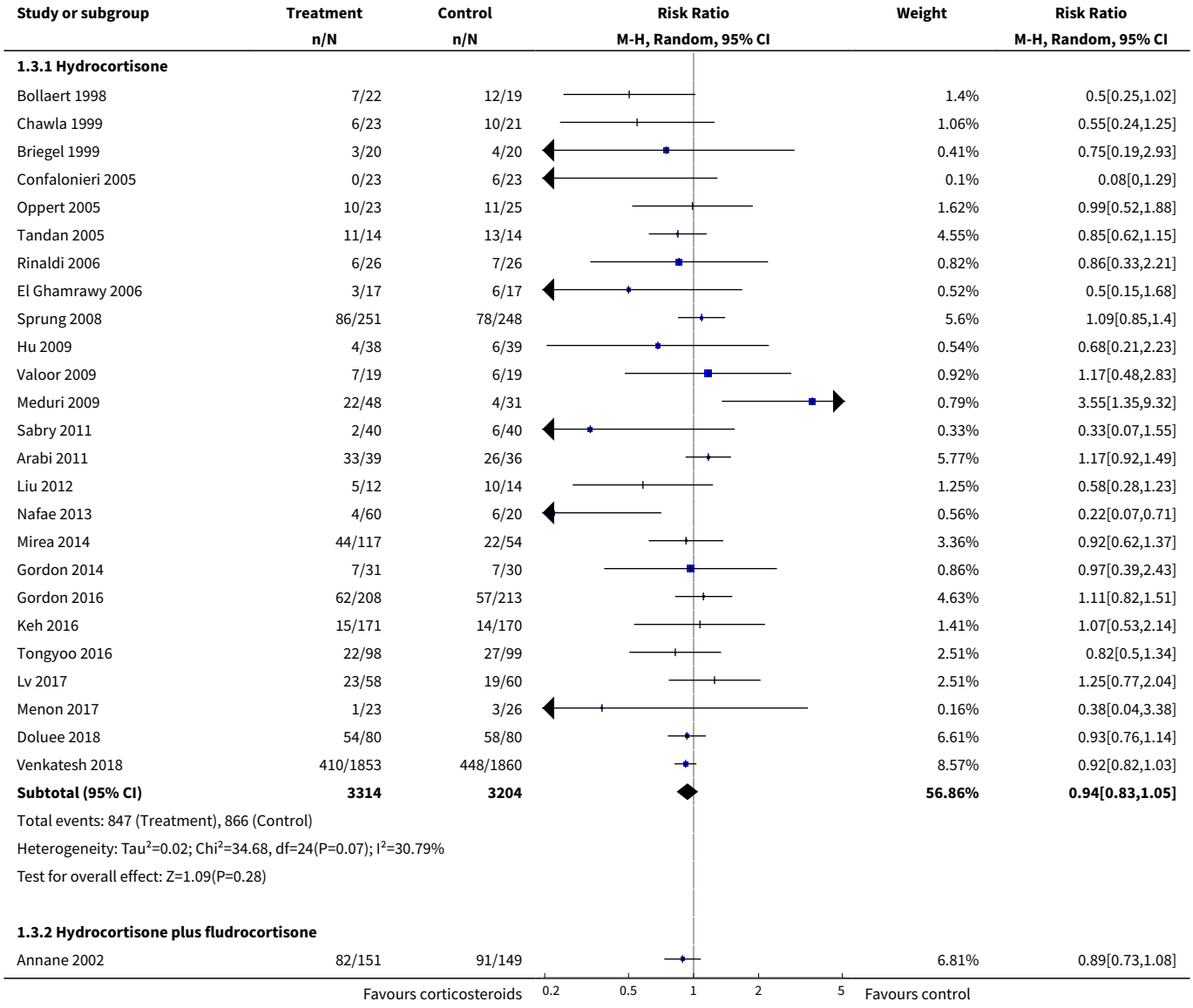


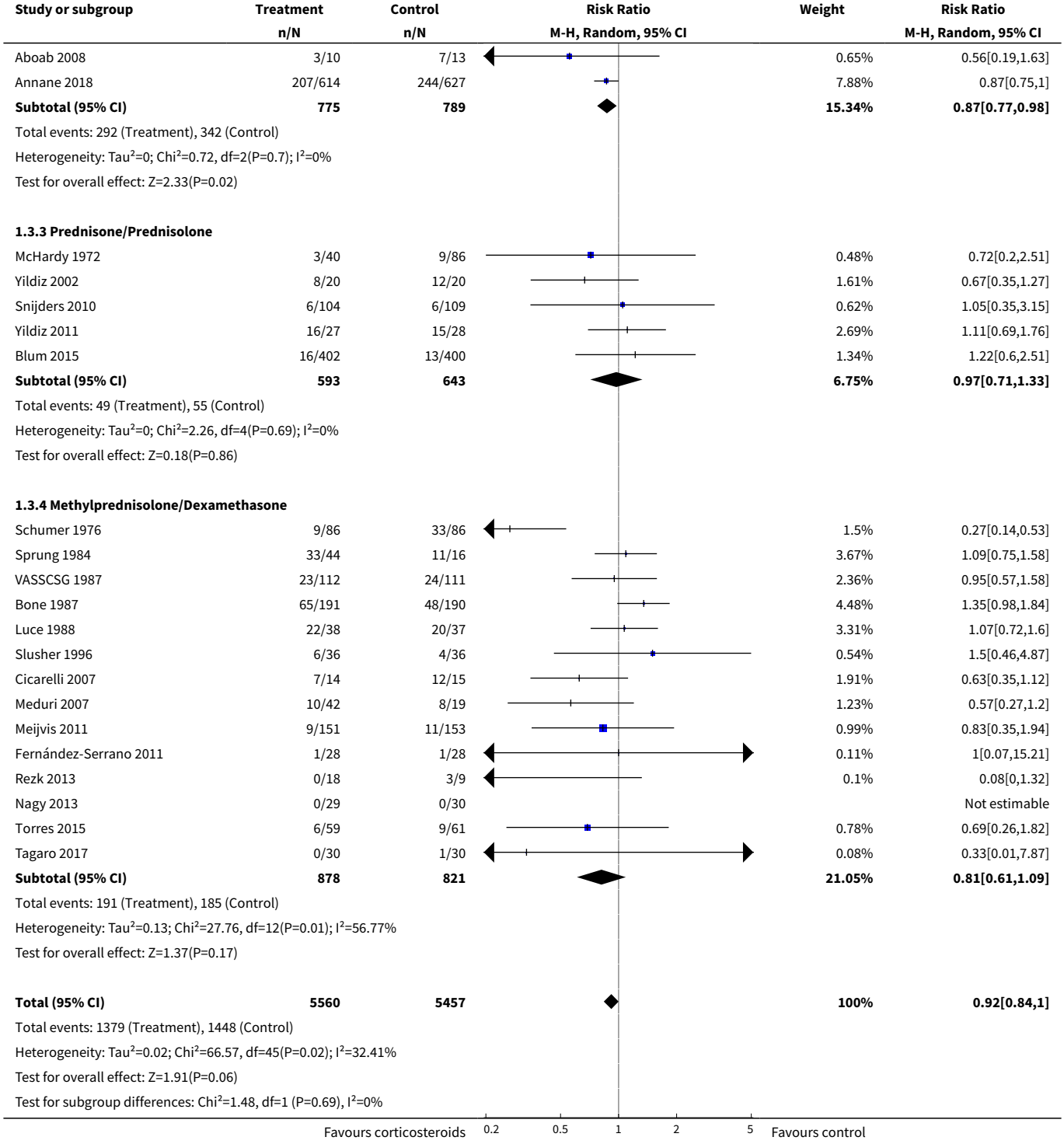






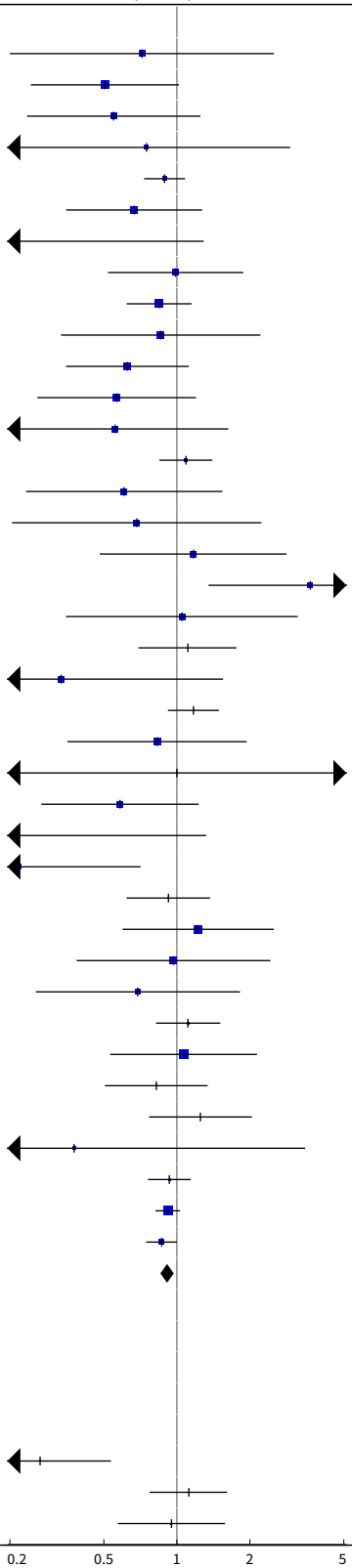
Analysis 1.3. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 3 28-Day all-cause mortality by subgroups based on study drug.

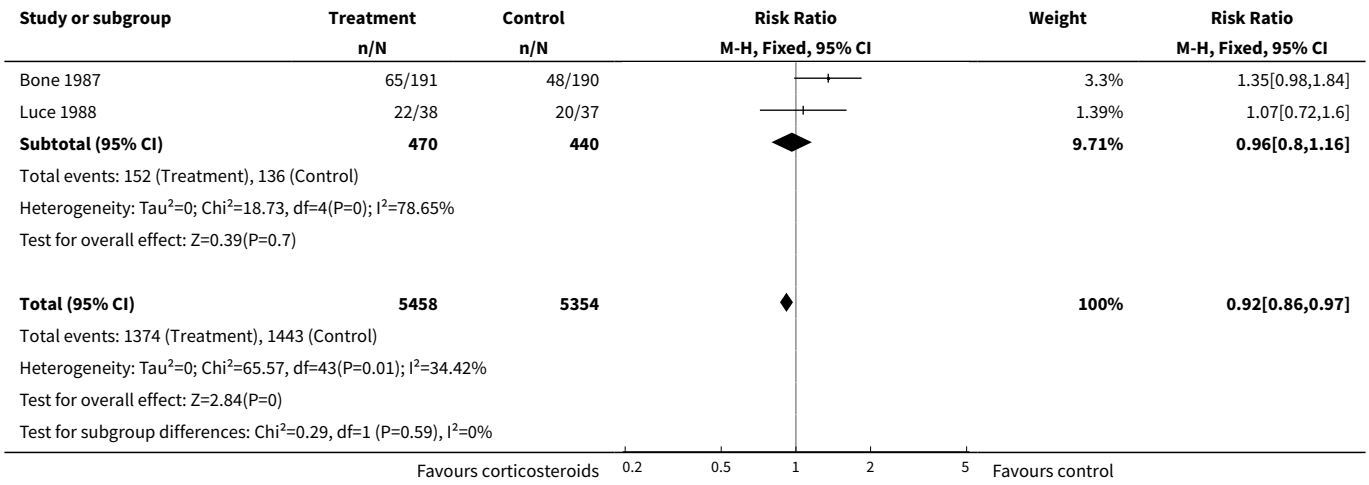




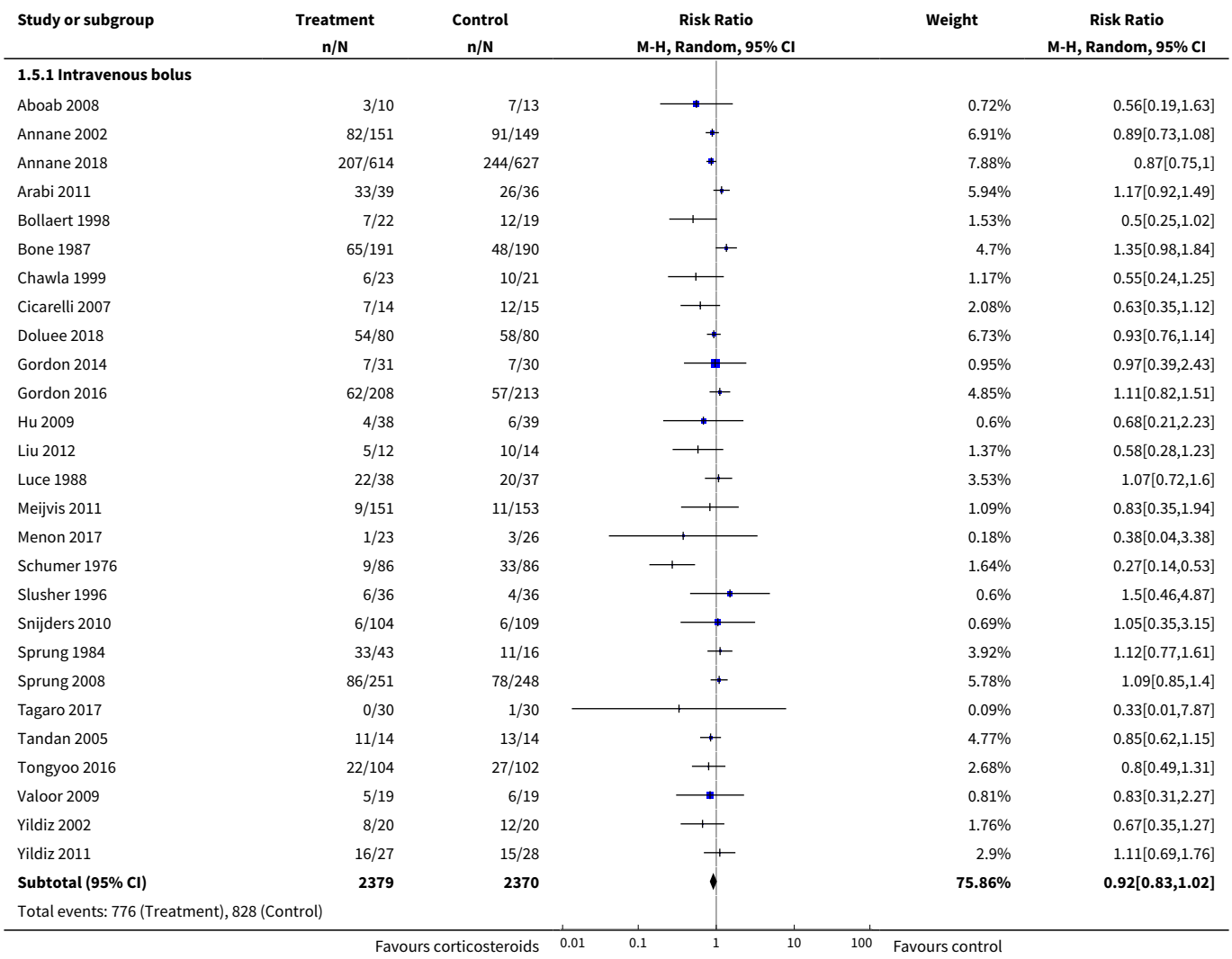
Analysis 1.4. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 4 28-Day all-cause mortality by subgroups based on treatment dose/duration.

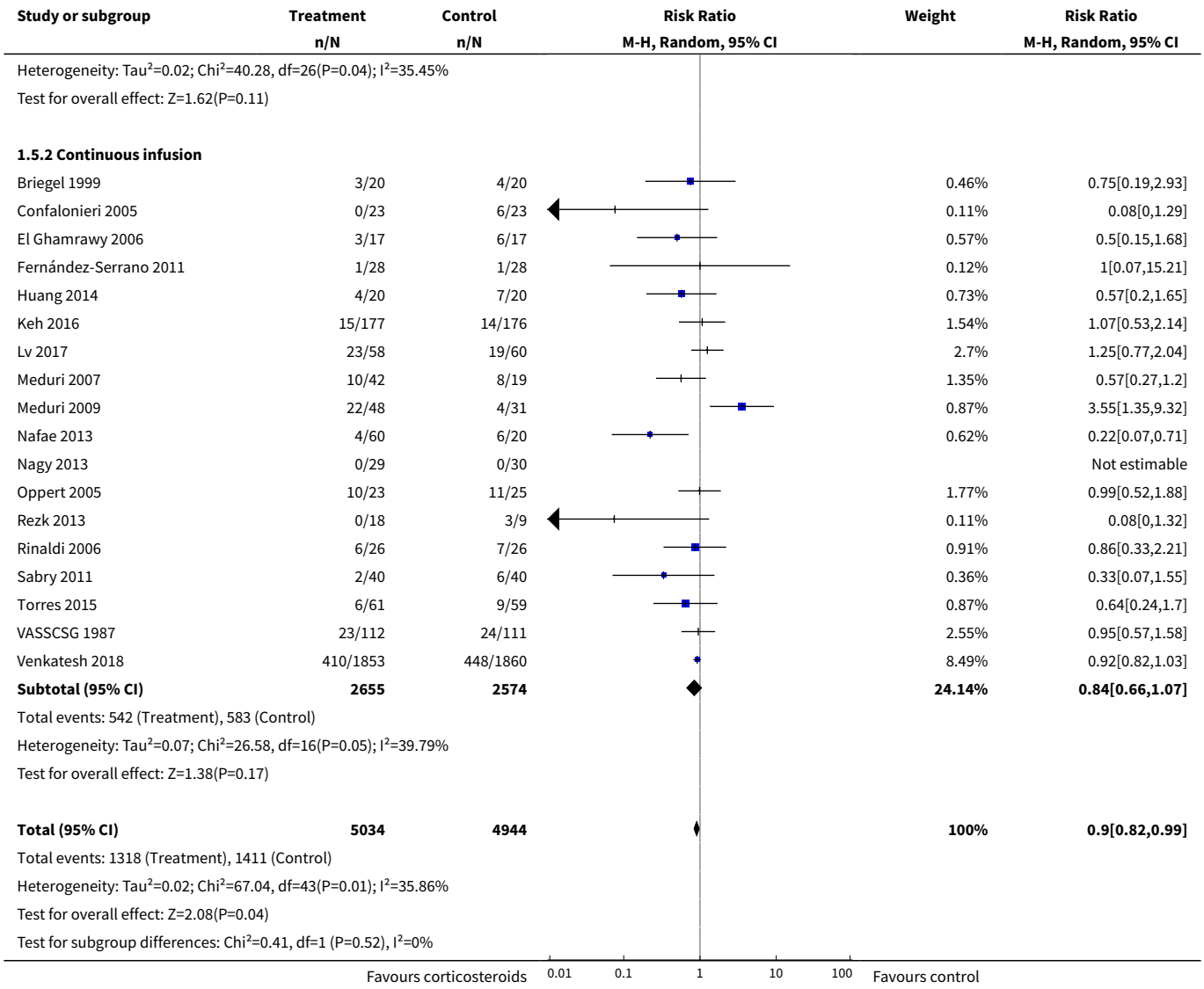
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Long course of low-dose corticosteroids					
McHardy 1972	3/40	9/86		0.39%	0.72[0.2,2.51]
Bollaert 1998	7/22	12/19		0.88%	0.5[0.25,1.02]
Chawla 1999	6/23	10/21		0.72%	0.55[0.24,1.25]
Briegel 1999	3/20	4/20		0.27%	0.75[0.19,2.93]
Annane 2002	82/151	91/149		6.28%	0.89[0.73,1.08]
Yildiz 2002	8/20	12/20		0.82%	0.67[0.35,1.27]
Confalonieri 2005	0/23	6/23		0.45%	0.08[0,1.29]
Oppert 2005	10/23	11/25		0.72%	0.99[0.52,1.88]
Tandan 2005	11/14	13/14		0.89%	0.85[0.62,1.15]
Rinaldi 2006	6/26	7/26		0.48%	0.86[0.33,2.21]
Cicarelli 2007	7/14	12/15		0.79%	0.63[0.35,1.12]
Meduri 2007	10/42	8/19		0.76%	0.57[0.27,1.2]
Aboab 2008	3/10	7/13		0.42%	0.56[0.19,1.63]
Sprung 2008	86/251	78/248		5.38%	1.09[0.85,1.4]
Kurungundla 2008	4/11	6/10		0.43%	0.61[0.24,1.54]
Hu 2009	4/38	6/39		0.41%	0.68[0.21,2.23]
Valoor 2009	7/19	6/19		0.41%	1.17[0.48,2.83]
Meduri 2009	22/48	4/31		0.33%	3.55[1.35,9.32]
Snijders 2010	6/104	6/109		0.4%	1.05[0.35,3.15]
Yildiz 2011	16/27	15/28		1.01%	1.11[0.69,1.76]
Sabry 2011	2/40	6/40		0.41%	0.33[0.07,1.55]
Arabi 2011	33/39	26/36		1.85%	1.17[0.92,1.49]
Meijvis 2011	9/151	11/153		0.75%	0.83[0.35,1.94]
Fernández-Serrano 2011	1/28	1/28		0.07%	1[0.07,15.21]
Liu 2012	5/12	10/14		0.63%	0.58[0.28,1.23]
Rezk 2013	0/18	3/9		0.31%	0.08[0,1.32]
Nafae 2013	4/60	6/20		0.62%	0.22[0.07,0.71]
Mirea 2014	44/117	22/54		2.06%	0.92[0.62,1.37]
Blum 2015	16/402	13/400		0.89%	1.22[0.6,2.51]
Gordon 2014	7/31	7/30		0.49%	0.97[0.39,2.43]
Torres 2015	6/59	9/61		0.61%	0.69[0.26,1.82]
Gordon 2016	62/208	57/213		3.86%	1.11[0.82,1.51]
Keh 2016	15/171	14/170		0.96%	1.07[0.53,2.14]
Tongyoo 2016	22/98	27/99		1.84%	0.82[0.5,1.34]
Lv 2017	23/58	19/60		1.28%	1.25[0.77,2.04]
Menon 2017	1/23	3/26		0.19%	0.38[0.04,3.38]
Doluee 2018	54/80	58/80		3.98%	0.93[0.76,1.14]
Venkatesh 2018	410/1853	448/1860		30.66%	0.92[0.82,1.03]
Annane 2018	207/614	244/627		16.56%	0.87[0.75,1]
Subtotal (95% CI)	**4988**	**4914**		**90.29%**	**0.91[0.86,0.97]**
Total events: 1222 (Treatment), 1307 (Control)					
Heterogeneity: Tau²=0; Chi²=45.73, df=38(P=0.18); I²=16.9%					
Test for overall effect: Z=2.86(P=0)					
1.4.2 Short course of high-dose corticosteroids					
Schumer 1976	9/86	33/86		2.26%	0.27[0.14,0.53]
Sprung 1984	33/43	11/16		1.1%	1.12[0.77,1.61]
VASSCSG 1987	23/112	24/111		1.65%	0.95[0.57,1.58]



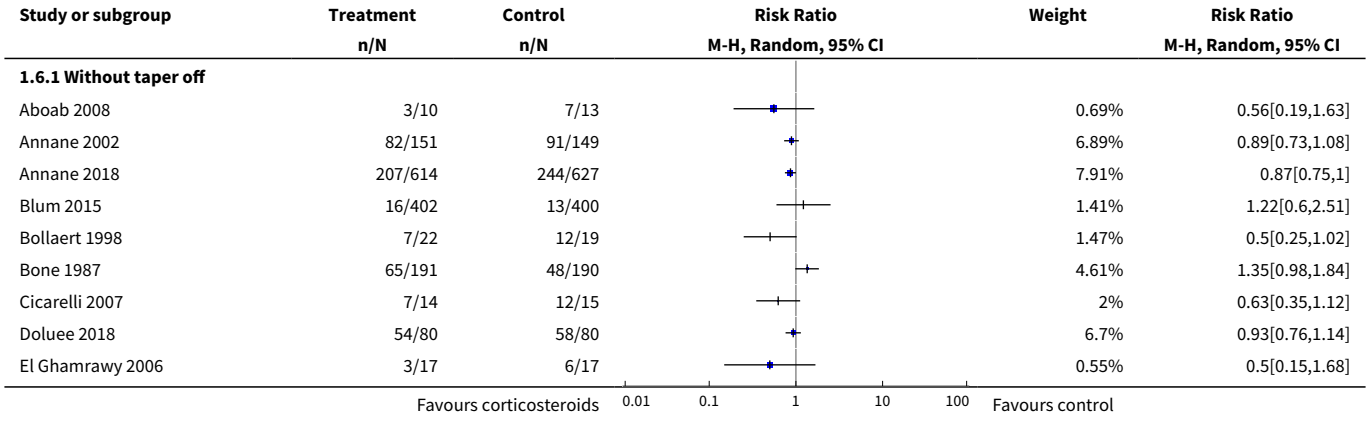


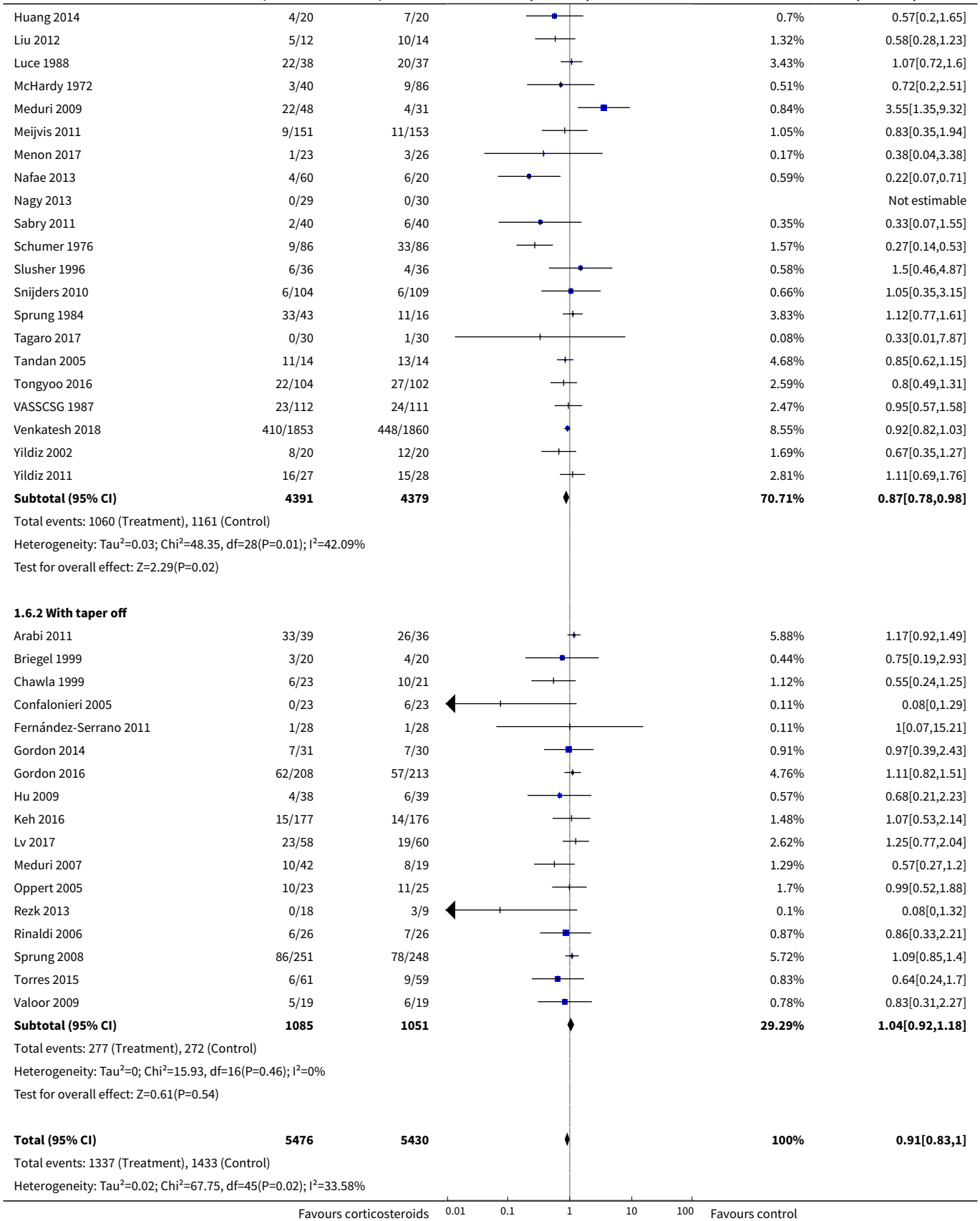
Analysis 1.5. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 5 28-Day all-cause mortality based on mode of drug administration.



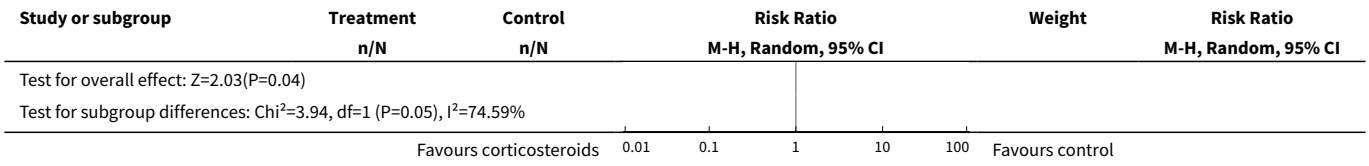


Analysis 1.6. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 6 28-Day all-cause mortality based on mode of drug termination.

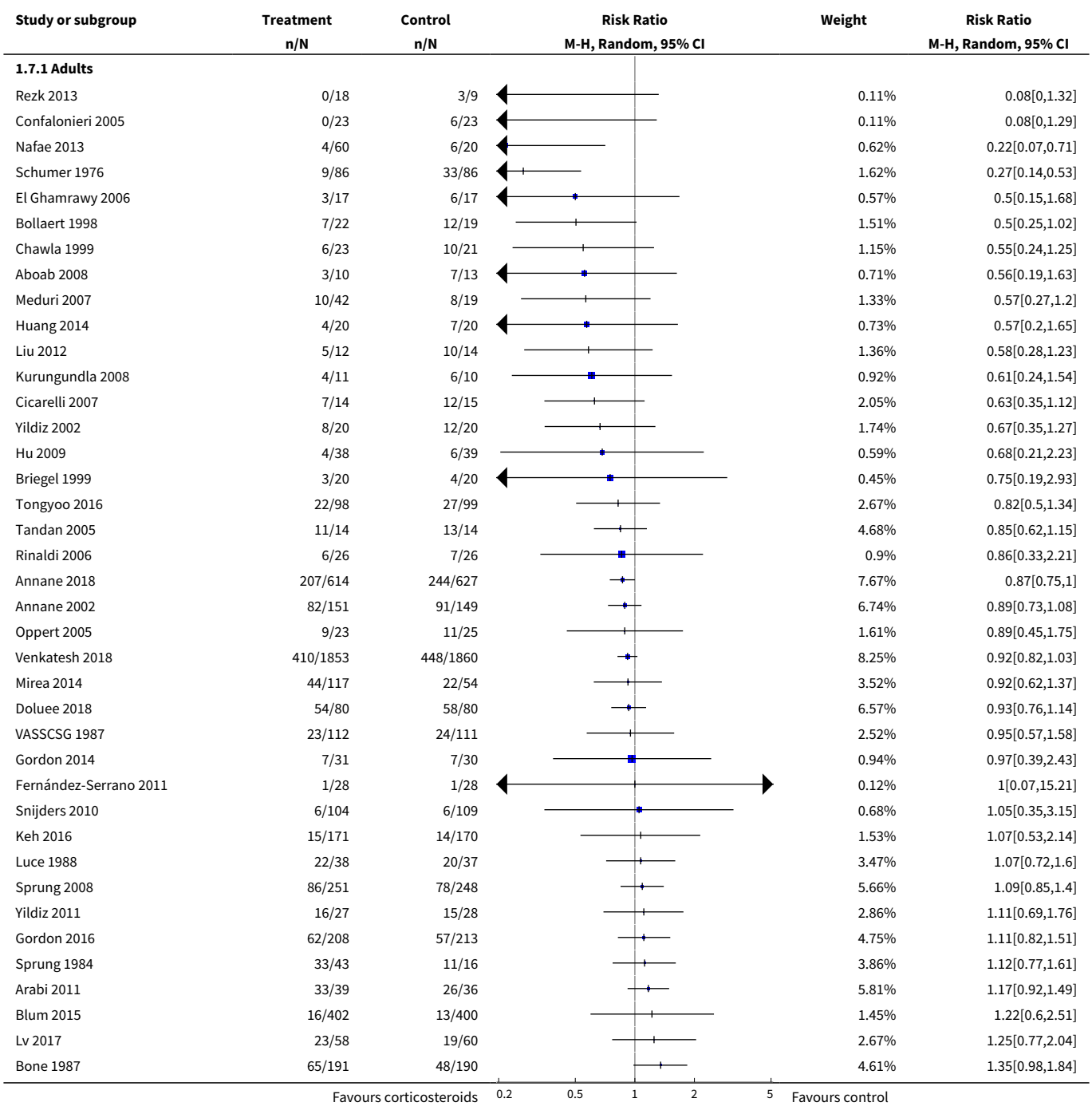


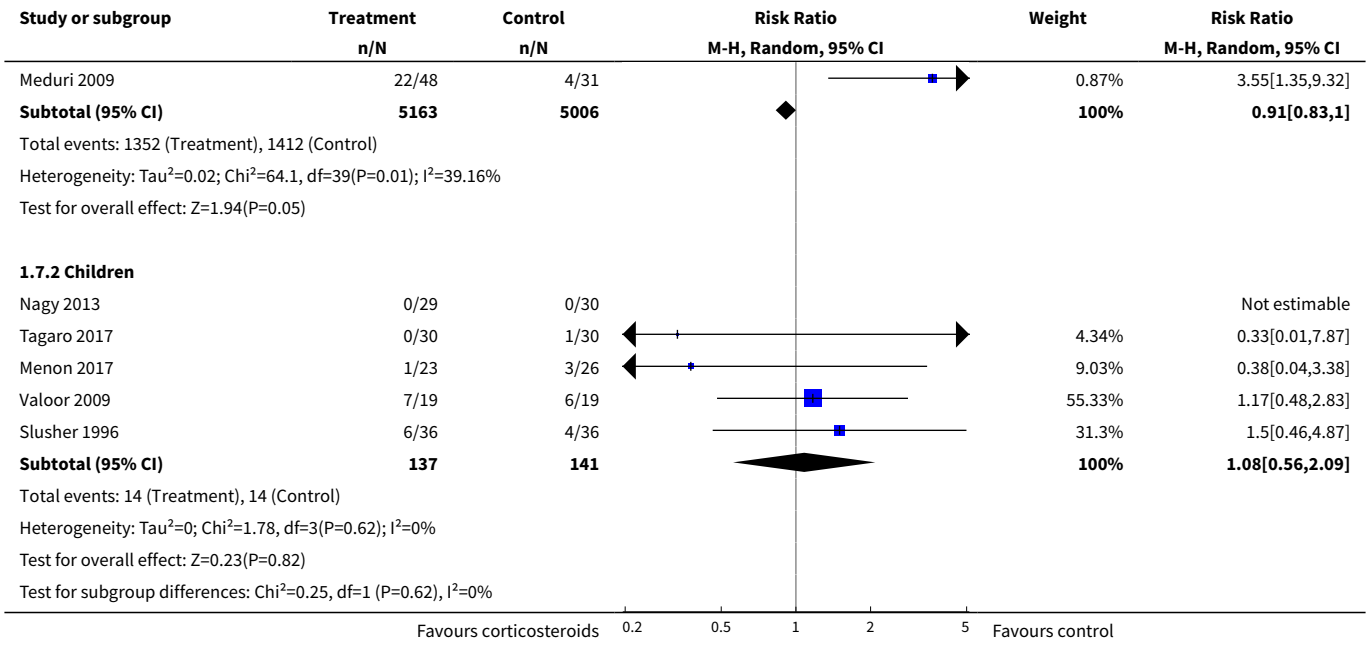


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Huang 2014	4/20	7/20		0.7%	0.57[0.2,1.65]
Liu 2012	5/12	10/14		1.32%	0.58[0.28,1.23]
Luce 1988	22/38	20/37		3.43%	1.07[0.72,1.6]
McHardy 1972	3/40	9/86		0.51%	0.72[0.2,2.51]
Meduri 2009	22/48	4/31		0.84%	3.55[1.35,9.32]
Meijvis 2011	9/151	11/153		1.05%	0.83[0.35,1.94]
Menon 2017	1/23	3/26		0.17%	0.38[0.04,3.38]
Nafae 2013	4/60	6/20		0.59%	0.22[0.07,0.71]
Nagy 2013	0/29	0/30			Not estimable
Sabry 2011	2/40	6/40		0.35%	0.33[0.07,1.55]
Schumer 1976	9/86	33/86		1.57%	0.27[0.14,0.53]
Slusher 1996	6/36	4/36		0.58%	1.5[0.46,4.87]
Snijders 2010	6/104	6/109		0.66%	1.05[0.35,3.15]
Sprung 1984	33/43	11/16		3.83%	1.12[0.77,1.61]
Tagaro 2017	0/30	1/30		0.08%	0.33[0.01,7.87]
Tandan 2005	11/14	13/14		4.68%	0.85[0.62,1.15]
Tongyoo 2016	22/104	27/102		2.59%	0.8[0.49,1.31]
VASSCSG 1987	23/112	24/111		2.47%	0.95[0.57,1.58]
Venkatesh 2018	410/1853	448/1860		8.55%	0.92[0.82,1.03]
Yildiz 2002	8/20	12/20		1.69%	0.67[0.35,1.27]
Yildiz 2011	16/27	15/28		2.81%	1.11[0.69,1.76]
Subtotal (95% CI)	**4391**	**4379**		**70.71%**	**0.87[0.78,0.98]**
Total events: 1060 (Treatment), 1161 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=48.35, df=28(P=0.01); I^2=42.09%					
Test for overall effect: Z=2.29(P=0.02)					
1.6.2 With taper off					
Arabi 2011	33/39	26/36		5.88%	1.17[0.92,1.49]
Briegel 1999	3/20	4/20		0.44%	0.75[0.19,2.93]
Chawla 1999	6/23	10/21		1.12%	0.55[0.24,1.25]
Confalonieri 2005	0/23	6/23		0.11%	0.08[0,1.29]
Fernández-Serrano 2011	1/28	1/28		0.11%	1[0.07,15.21]
Gordon 2014	7/31	7/30		0.91%	0.97[0.39,2.43]
Gordon 2016	62/208	57/213		4.76%	1.11[0.82,1.51]
Hu 2009	4/38	6/39		0.57%	0.68[0.21,2.23]
Keh 2016	15/177	14/176		1.48%	1.07[0.53,2.14]
Lv 2017	23/58	19/60		2.62%	1.25[0.77,2.04]
Meduri 2007	10/42	8/19		1.29%	0.57[0.27,1.2]
Oppert 2005	10/23	11/25		1.7%	0.99[0.52,1.88]
Rezk 2013	0/18	3/9		0.1%	0.08[0,1.32]
Rinaldi 2006	6/26	7/26		0.87%	0.86[0.33,2.21]
Sprung 2008	86/251	78/248		5.72%	1.09[0.85,1.4]
Torres 2015	6/61	9/59		0.83%	0.64[0.24,1.7]
Valoor 2009	5/19	6/19		0.78%	0.83[0.31,2.27]
Subtotal (95% CI)	**1085**	**1051**		**29.29%**	**1.04[0.92,1.18]**
Total events: 277 (Treatment), 272 (Control)					
Heterogeneity: Tau^2=0; Chi^2=15.93, df=16(P=0.46); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					
Total (95% CI)	**5476**	**5430**		**100%**	**0.91[0.83,1]**
Total events: 1337 (Treatment), 1433 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=67.75, df=45(P=0.02); I^2=33.58%					

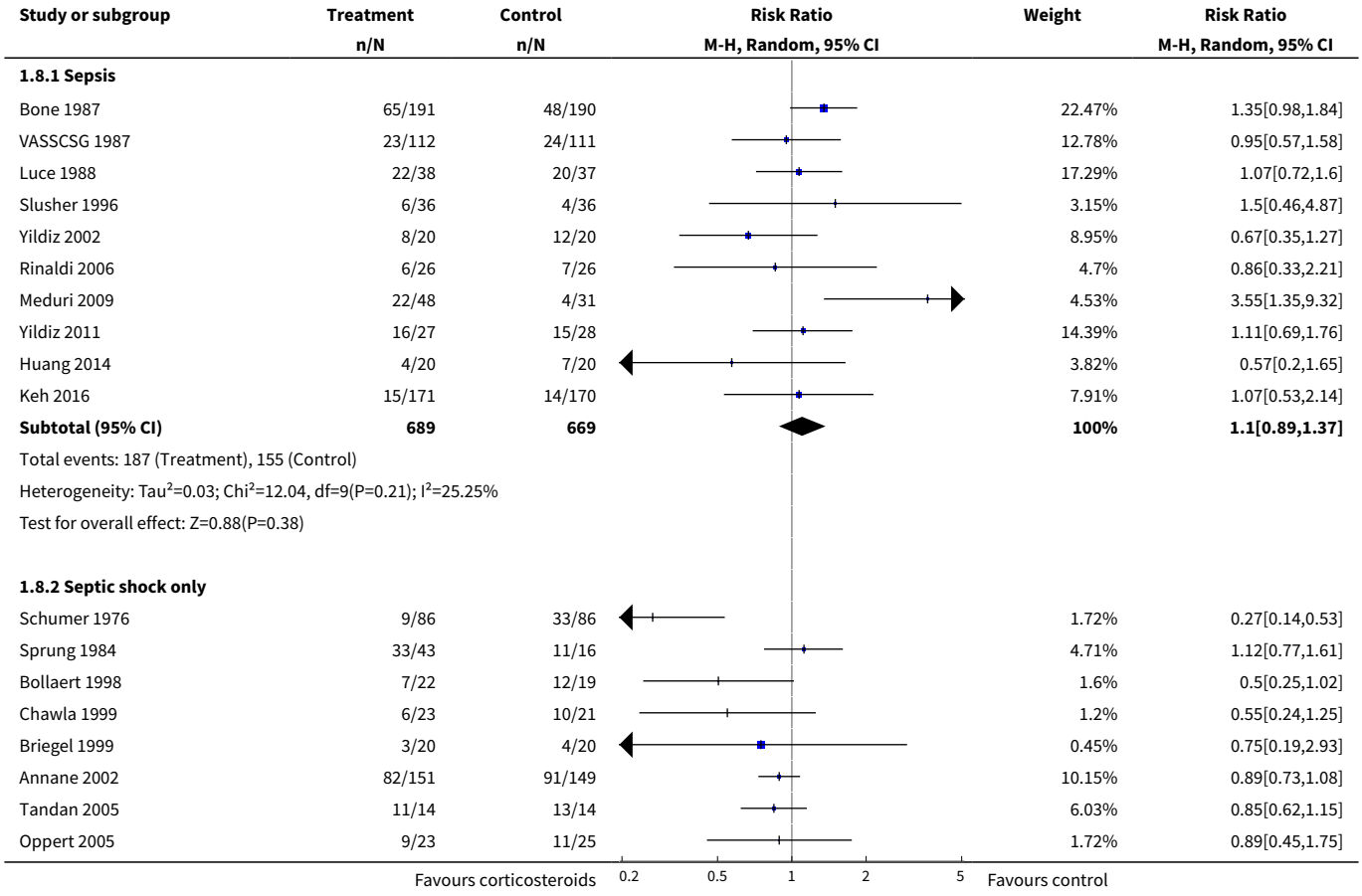


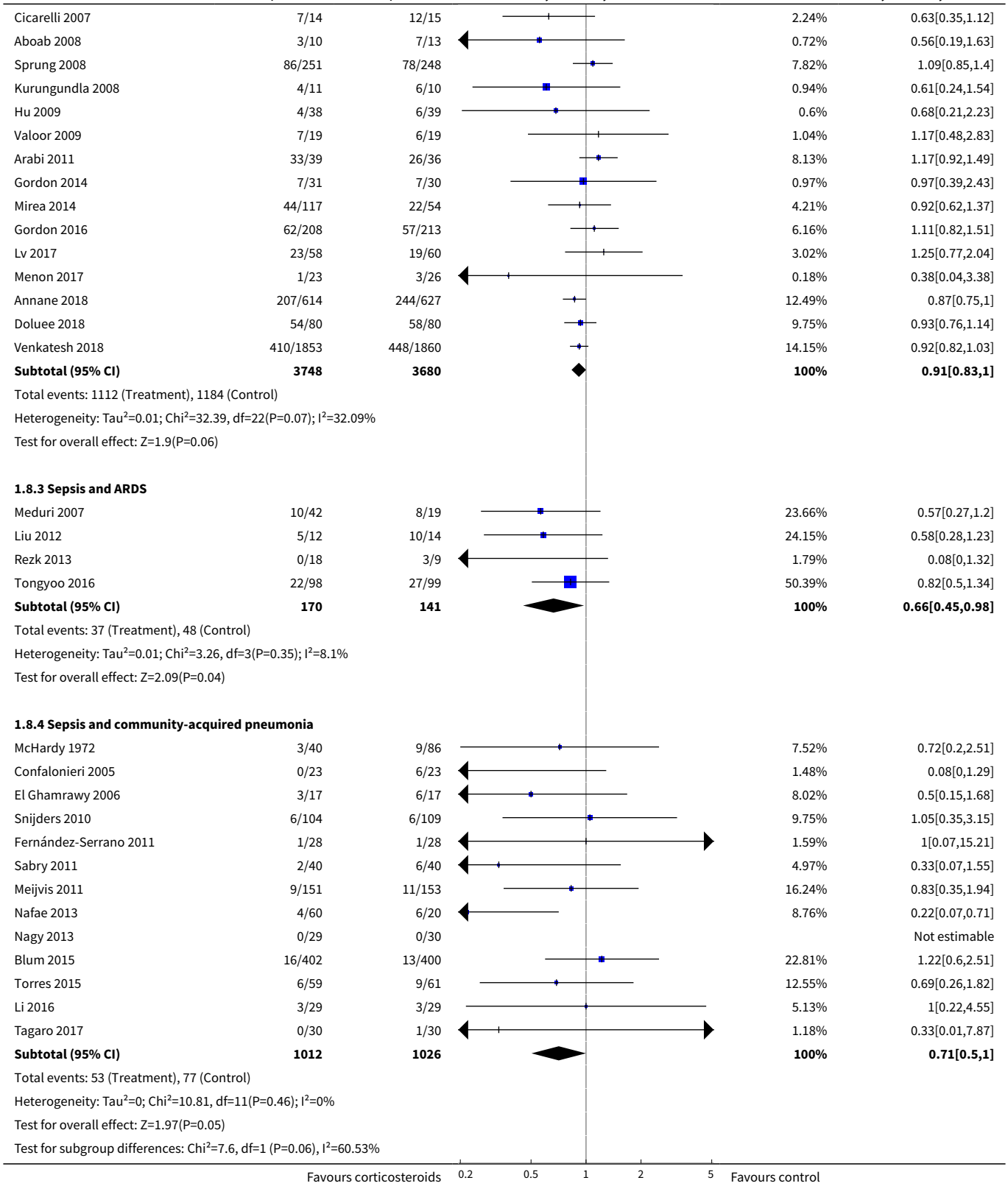
Analysis 1.7. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 7 28-Day all-cause mortality by subgroups based on age.





Analysis 1.8. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 8 28-Day all-cause mortality by subgroups based on targeted population.





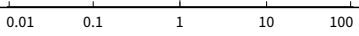
Analysis 1.9. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 9 28-Day mortality in participants with critical illness-related corticosteroid insufficiency.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aboab 2008	3/10	7/13		2.18%	0.56[0.19,1.63]
Annane 2002	60/114	73/115		26.02%	0.83[0.66,1.04]
Annane 2018	101/198	115/228		38.27%	1.01[0.84,1.22]
Bollaert 1998	3/8	6/9		2.02%	0.56[0.21,1.54]
Kurungundla 2008	4/11	6/10		2.25%	0.61[0.24,1.54]
Liu 2012	5/12	10/14		3.3%	0.58[0.28,1.23]
Meduri 2007	5/10	3/6		1.34%	1[0.36,2.75]
Oppert 2005	5/12	6/14		1.98%	0.97[0.39,2.4]
Sprung 2008	49/125	39/108		14.98%	1.09[0.78,1.51]
Tandan 2005	11/14	13/14		4.65%	0.85[0.62,1.15]
Yildiz 2002	2/5	5/9		1.28%	0.72[0.21,2.44]
Yildiz 2011	3/6	8/14		1.72%	0.88[0.35,2.2]
Total (95% CI)	**525**	**554**		**100%**	**0.92[0.82,1.03]**
Total events: 251 (Treatment), 291 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.2, df=11(P=0.78); I^2=0%					
Test for overall effect: Z=1.41(P=0.16)					

Favours corticosteroids — Favours control

Analysis 1.10. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 10 90-Day all-cause mortality.

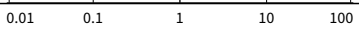
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2002	95/150	106/149		10.36%	0.89[0.76,1.04]
Annane 2018	264/614	308/627		29.69%	0.88[0.78,0.99]
Briegel 1999	5/20	6/20		0.58%	0.83[0.3,2.29]
Keh 2016	34/177	28/176		2.74%	1.21[0.77,1.9]
Meduri 2007	18/63	12/28		1.62%	0.67[0.37,1.19]
Tongyoo 2016	34/98	40/99		3.88%	0.86[0.6,1.23]
Venkatesh 2018	511/1853	526/1860		51.14%	0.98[0.88,1.08]
Total (95% CI)	**2975**	**2959**		**100%**	**0.93[0.87,1]**
Total events: 961 (Treatment), 1026 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.88, df=6(P=0.56); I^2=0%					
Test for overall effect: Z=1.96(P=0.05)					



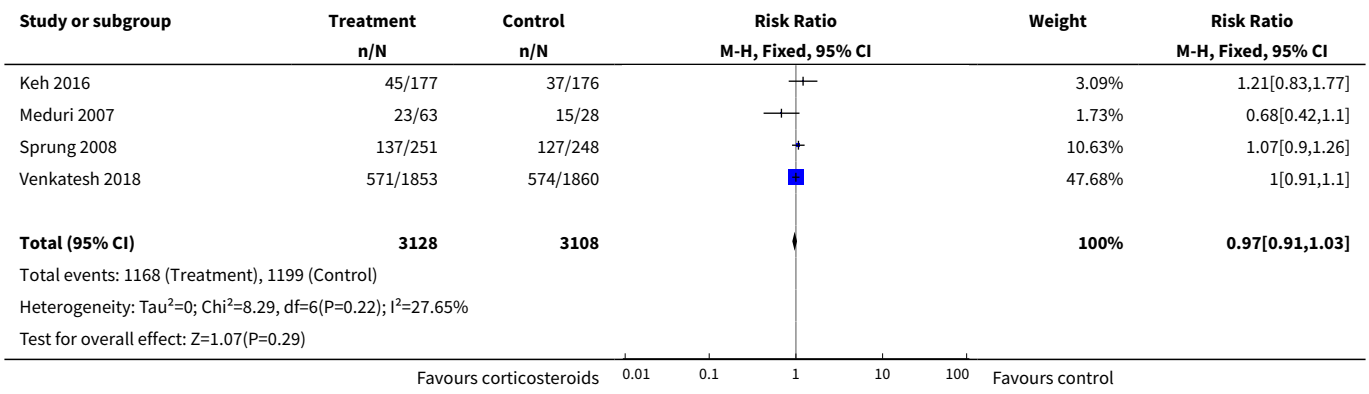
Favours corticosteroids — Favours control

Analysis 1.11. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 11 Long-term mortality.

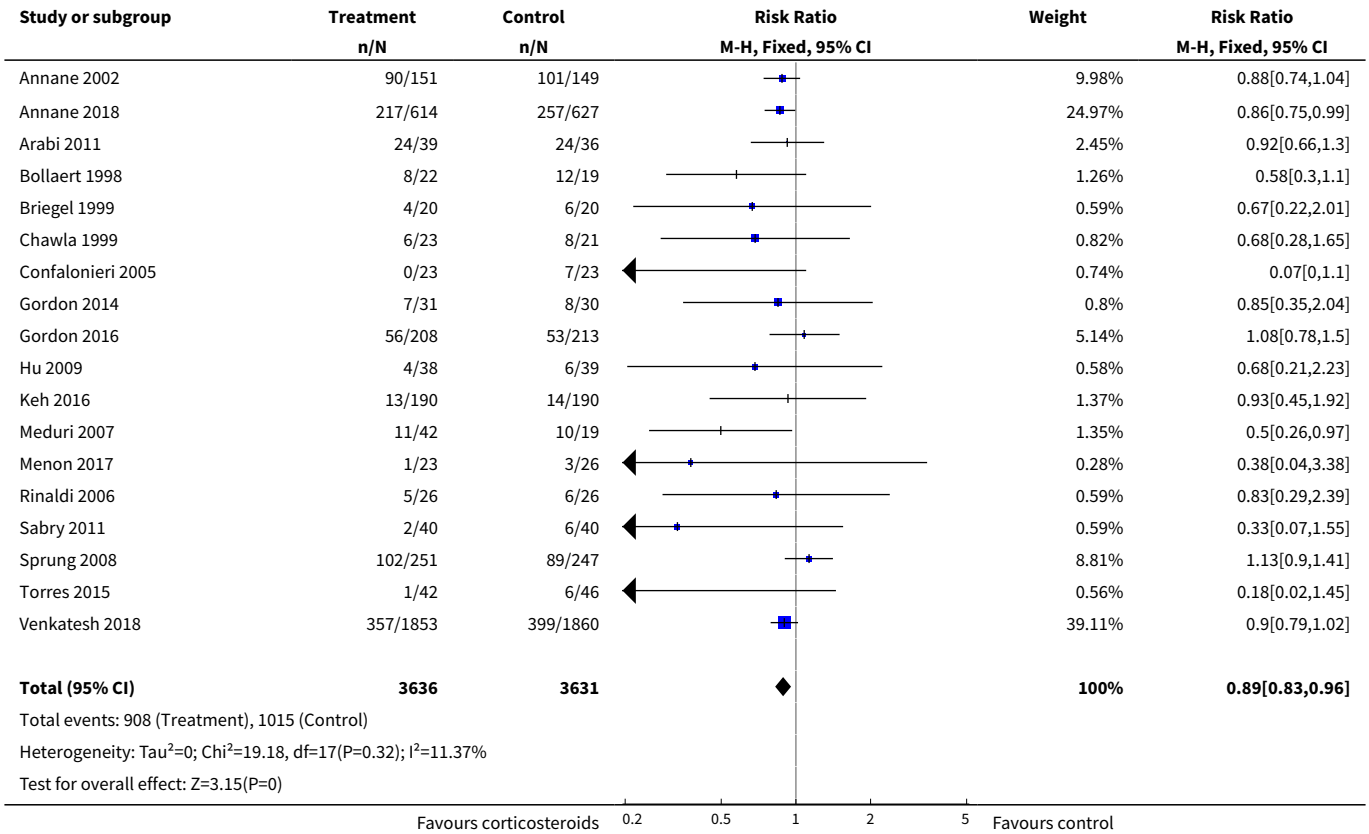
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2002	102/150	112/149		9.35%	0.9[0.78,1.04]
Annane 2018	285/614	328/627		27.01%	0.89[0.79,0.99]
Briegel 1999	5/20	6/20		0.5%	0.83[0.3,2.29]



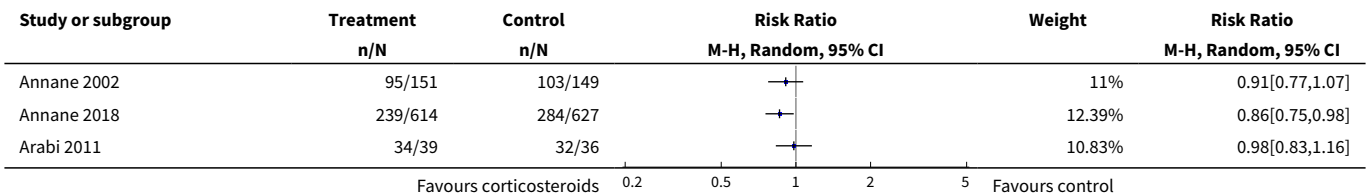
Favours corticosteroids — Favours control

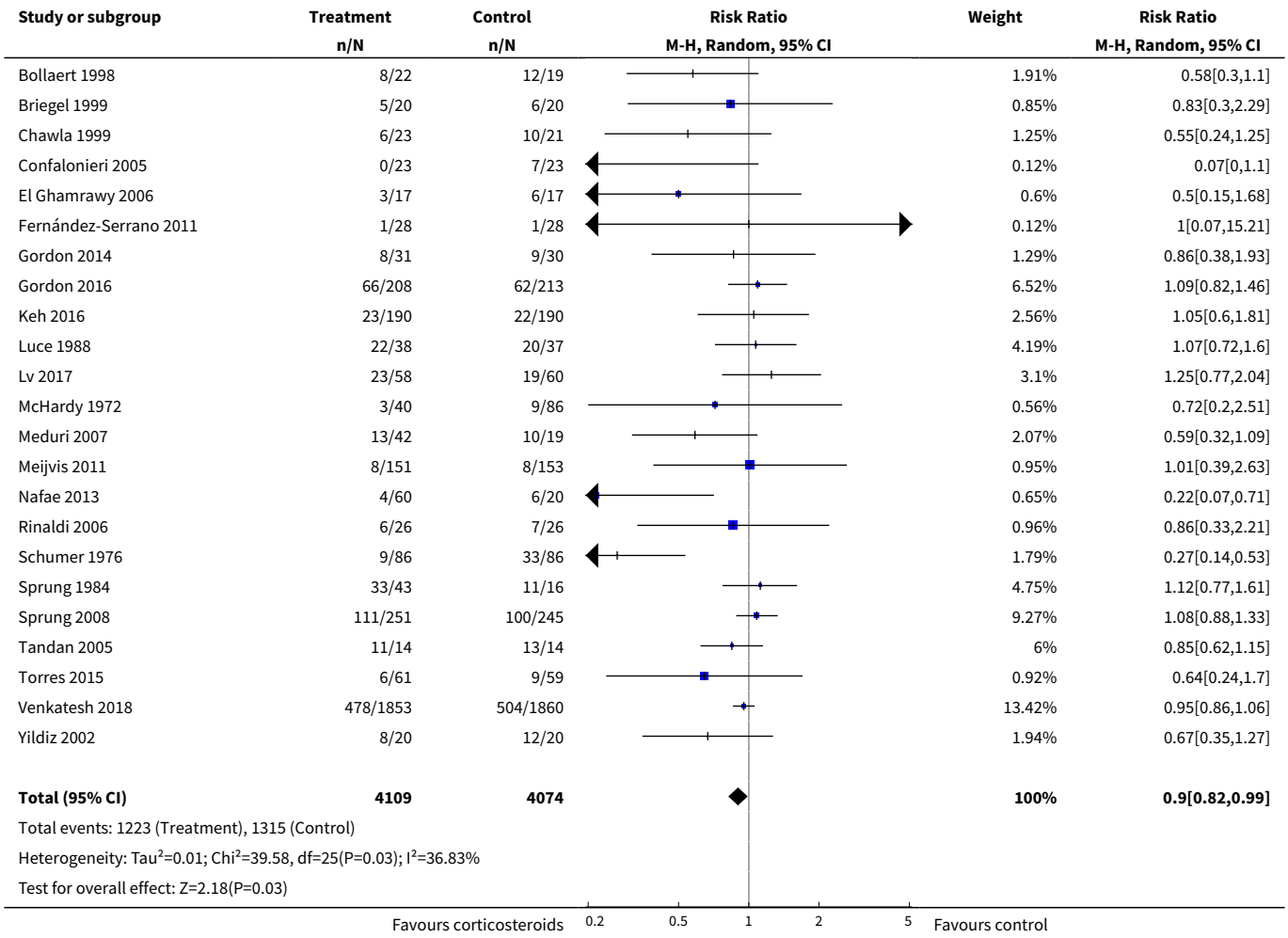


Analysis 1.12. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 12 Intensive care unit mortality.

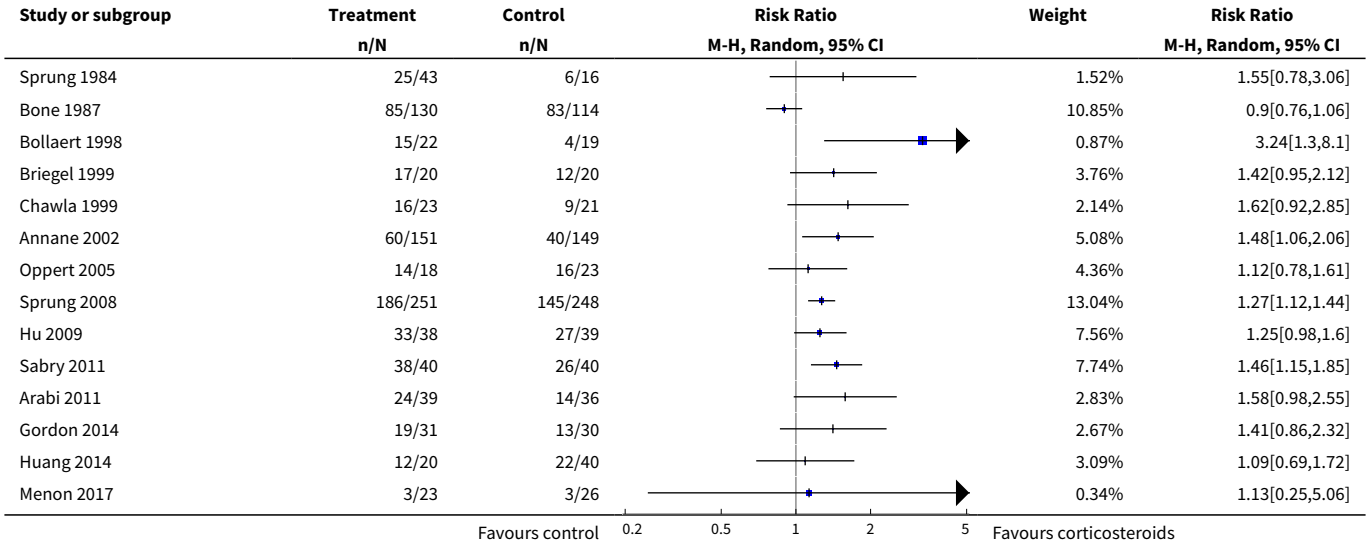


Analysis 1.13. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 13 Hospital mortality.





Analysis 1.14. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 14 Number of participants with shock reversal at day 7.

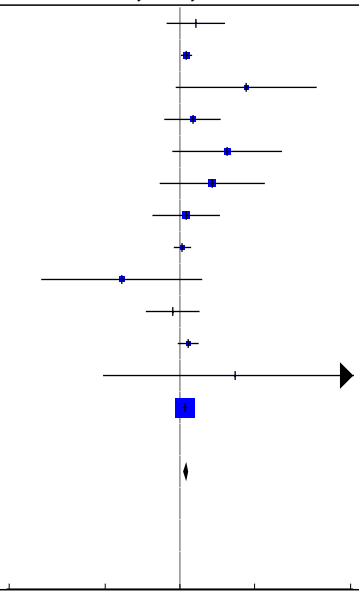


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2018	501/614	474/627		16.7%	1.08[1.02,1.14]
Venkatesh 2018	1594/1898	1274/1902		17.46%	1.25[1.21,1.3]
Total (95% CI)	**3361**	**3350**		**100%**	**1.23[1.13,1.34]**
Total events: 2642 (Treatment), 2168 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=43.87, df=15(P=0); I^2=65.81%					
Test for overall effect: Z=4.66(P<0.0001)					

Favours control — Favours corticosteroids

Analysis 1.15. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 15 Number of participants with shock reversal at 28 days.

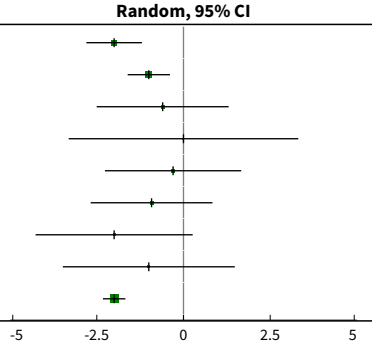
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2002	67/151	57/149		2.19%	1.16[0.88,1.52]
Annane 2018	522/614	502/627		18.95%	1.06[1.01,1.12]
Bollaert 1998	15/22	7/19		0.29%	1.85[0.96,3.56]
Briegel 1999	18/20	16/20		0.61%	1.13[0.86,1.46]
Chawla 1999	17/23	10/21		0.4%	1.55[0.93,2.58]
Doluee 2018	27/80	20/80		0.76%	1.35[0.83,2.2]
Gordon 2014	23/31	21/30		0.81%	1.06[0.78,1.45]
Gordon 2016	179/208	179/213		6.75%	1.02[0.95,1.11]
Liu 2012	5/12	10/14		0.35%	0.58[0.28,1.23]
Lv 2017	38/58	42/60		1.58%	0.94[0.73,1.2]
Sprung 2008	200/251	183/248		7.02%	1.08[0.98,1.19]
Tandan 2005	5/14	3/14		0.11%	1.67[0.49,5.67]
Venkatesh 2018	1651/1898	1579/1902		60.17%	1.05[1.02,1.08]
Total (95% CI)	**3382**	**3397**		**100%**	**1.06[1.03,1.08]**
Total events: 2767 (Treatment), 2629 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.81, df=12(P=0.46); I^2=0%					
Test for overall effect: Z=4.83(P<0.0001)					



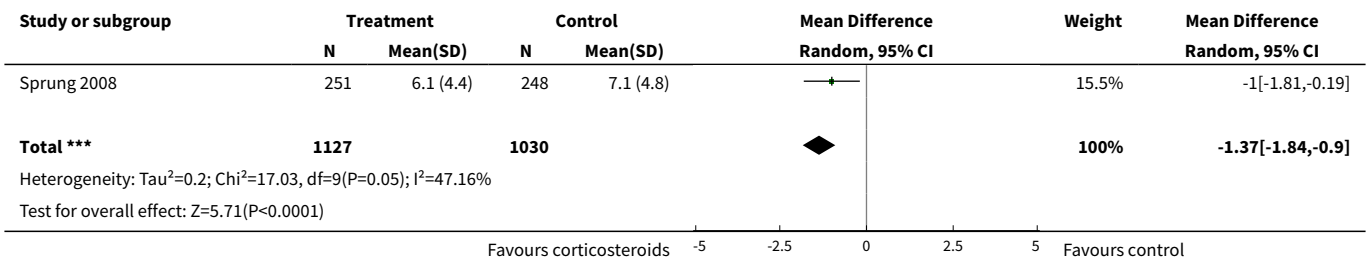
Favours control — Favours corticosteroids

Analysis 1.16. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 16 SOFA score at day 7.

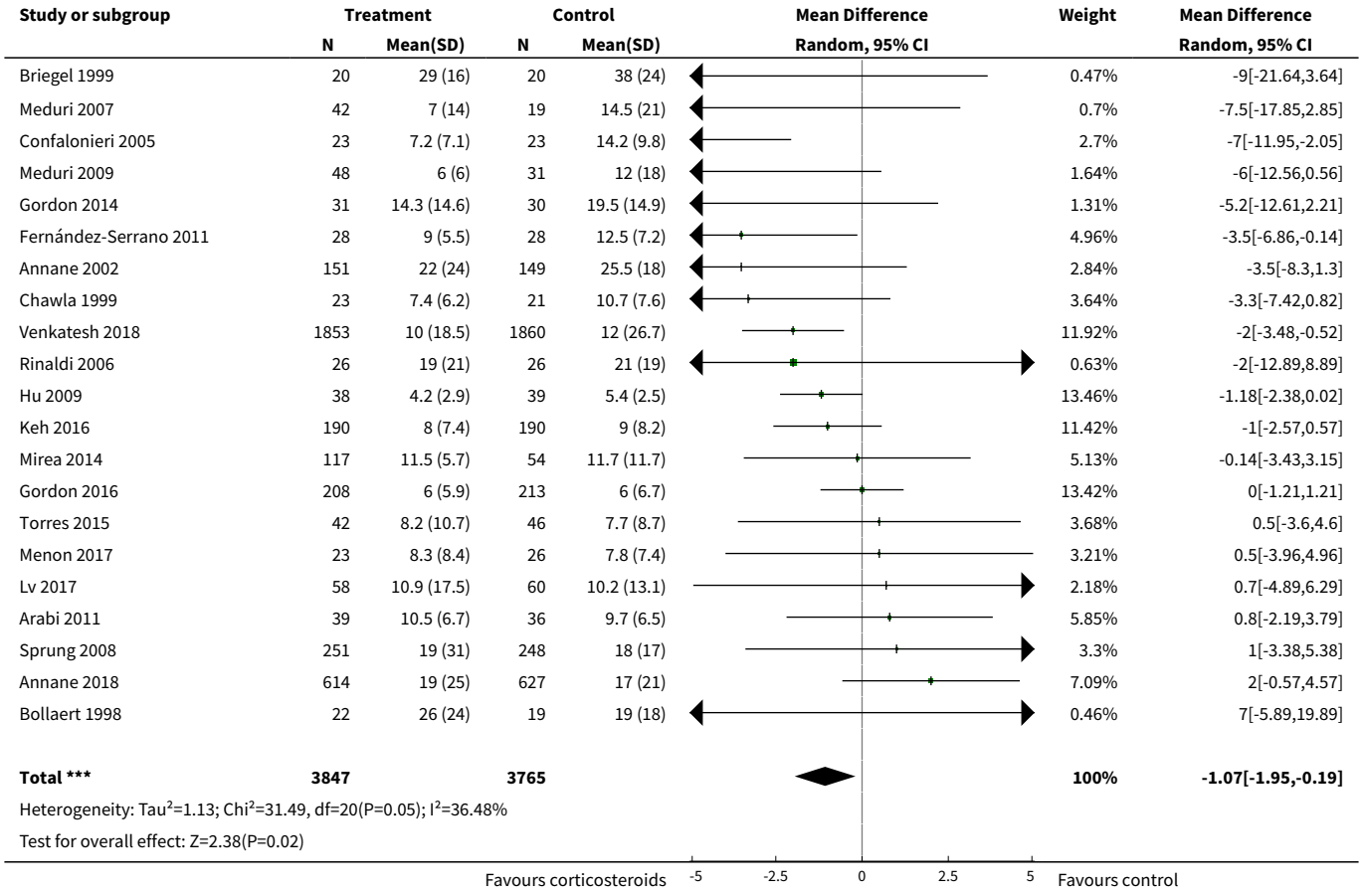
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Annane 2002	151	7.5 (3)	149	9.5 (4)		15.63%	-2[-2.8,-1.2]
Annane 2018	440	6 (4)	414	7 (5)		19.32%	-1[-1.61,-0.39]
Arabi 2011	39	11.7 (4.2)	36	12.3 (4.2)		5.03%	-0.6[-2.5,1.3]
Cicarelli 2007	15	9 (4)	14	9 (5)		1.88%	0[-3.31,3.31]
Gordon 2014	31	6.2 (4.3)	30	6.5 (3.5)		4.77%	-0.3[-2.26,1.66]
Mirea 2014	117	7.7 (6)	54	8.6 (5.2)		5.73%	-0.92[-2.68,0.84]
Oppert 2005	23	6 (4)	25	8 (4)		3.74%	-2[-4.27,0.27]
Rinaldi 2006	20	1 (4)	20	2 (4)		3.19%	-1[-3.48,1.48]
Sabry 2011	40	1 (0.5)	40	3 (0.9)		25.21%	-2[-2.32,-1.68]



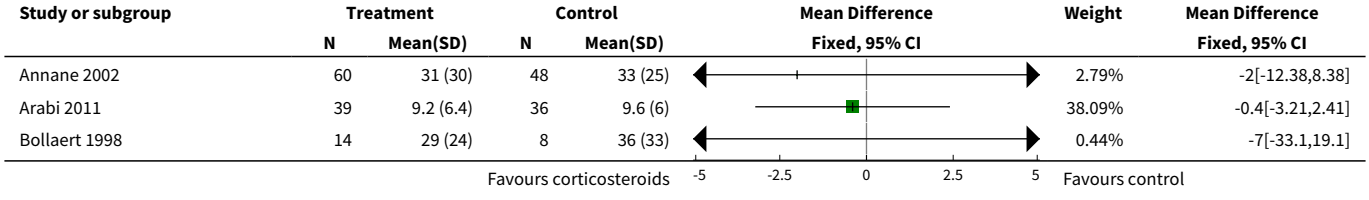
Favours corticosteroids — Favours control

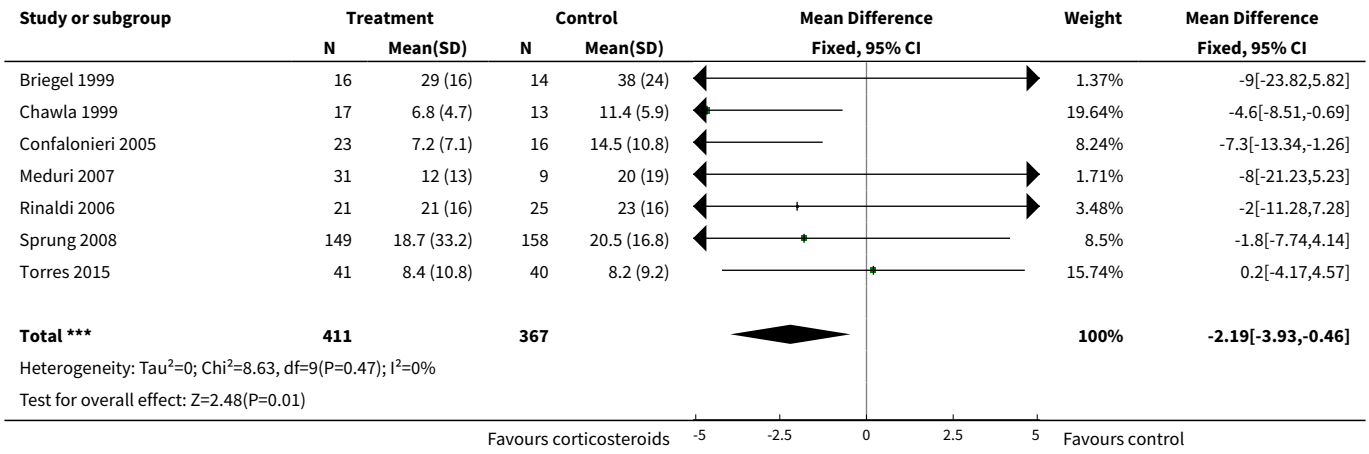


Analysis 1.17. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 17 Length of intensive care unit stay for all participants.

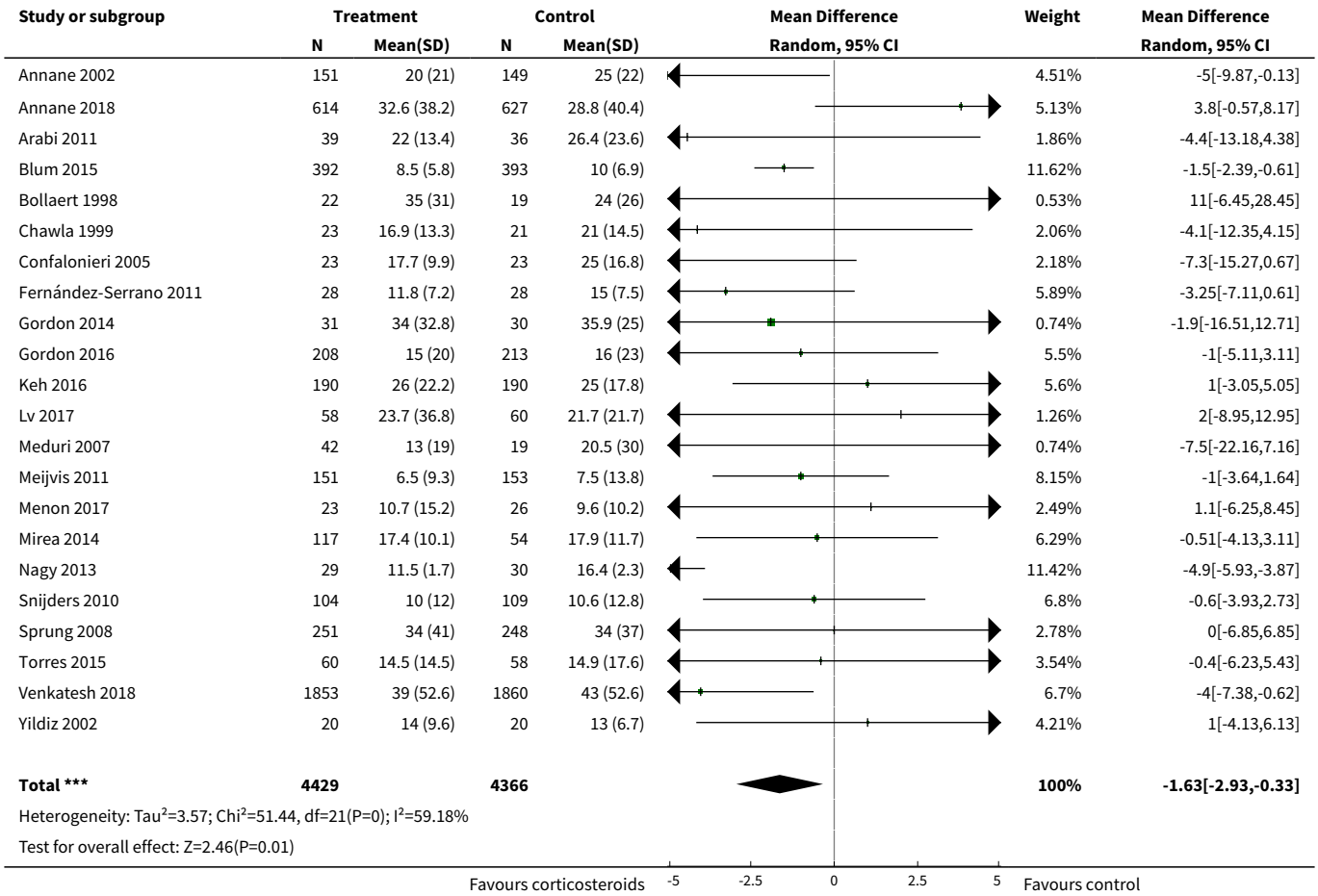


Analysis 1.18. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 18 Length of intensive care unit stay for survivors.





Analysis 1.19. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 19 Length of hospital stay for all participants.

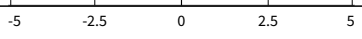


Analysis 1.20. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 20 Length of hospital stay for survivors.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Annane 2002	55	60 (60)	46	48 (28)		5.06%	12[-5.8,29.8]
Arabi 2011	39	27.2 (12.8)	36	43.3 (34)		9.47%	-16.1[-27.91,-4.29]
Bollaert 1998	14	42.7 (24.2)	7	44 (36.7)		2%	-1.3[-31.3,28.7]
Chawla 1999	17	11.9 (8.2)	11	18.3 (10.4)		16.47%	-6.4[-13.68,0.88]
Confalonieri 2005	23	17.7 (9.9)	16	29.4 (17.9)		12.25%	-11.7[-21.36,-2.04]
Meduri 2007	29	22 (31)	9	41 (43)		1.97%	-19[-49.27,11.27]
Sprung 2008	140	42.8 (45.2)	145	42.1 (39.2)		11.98%	0.7[-9.14,10.54]
Torres 2015	54	15.4 (15)	49	16.3 (18.8)		17.88%	-0.9[-7.51,5.71]
Yildiz 2002	12	7 (5)	8	8 (5)		22.92%	-1[-5.47,3.47]
Total * **	**383**		**327**			**100%**	**-4.11[-8.5,0.28]**

Heterogeneity: Tau²=16.69; Chi²=14.16, df=8(P=0.08); I²=43.5%

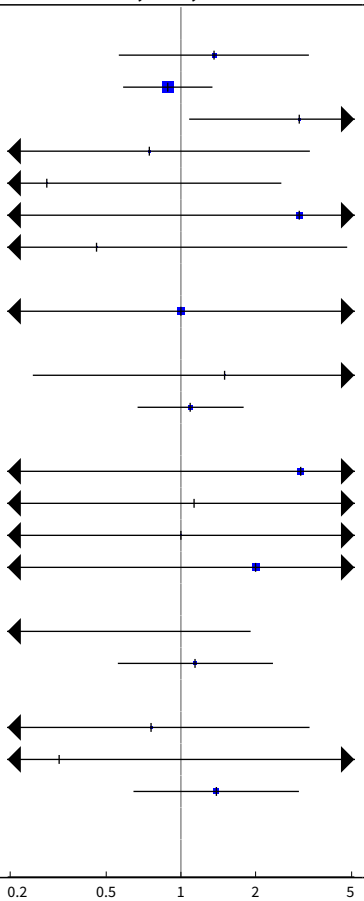
Test for overall effect: Z=1.83(P=0.07)



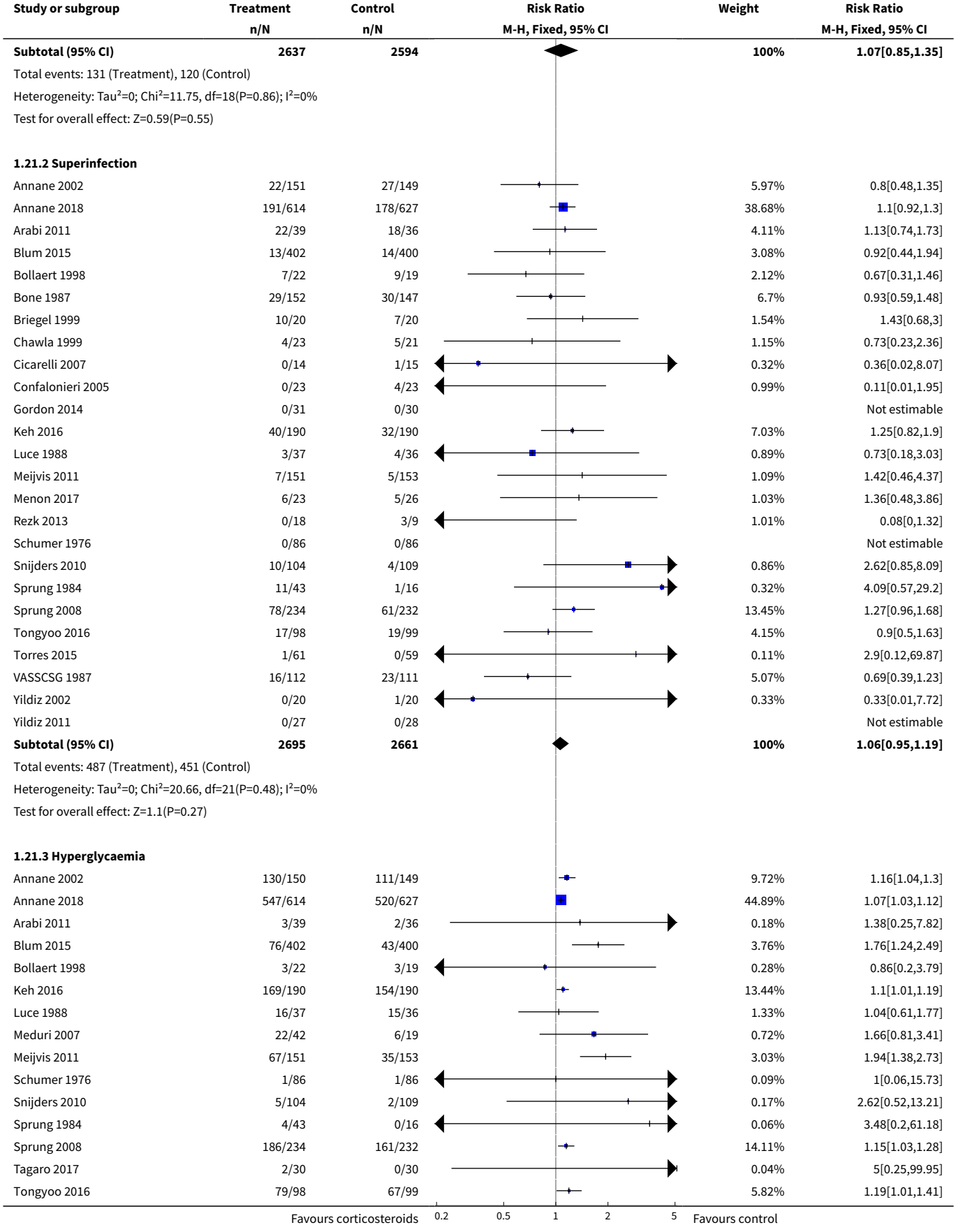
Favours corticosteroids — Favours control

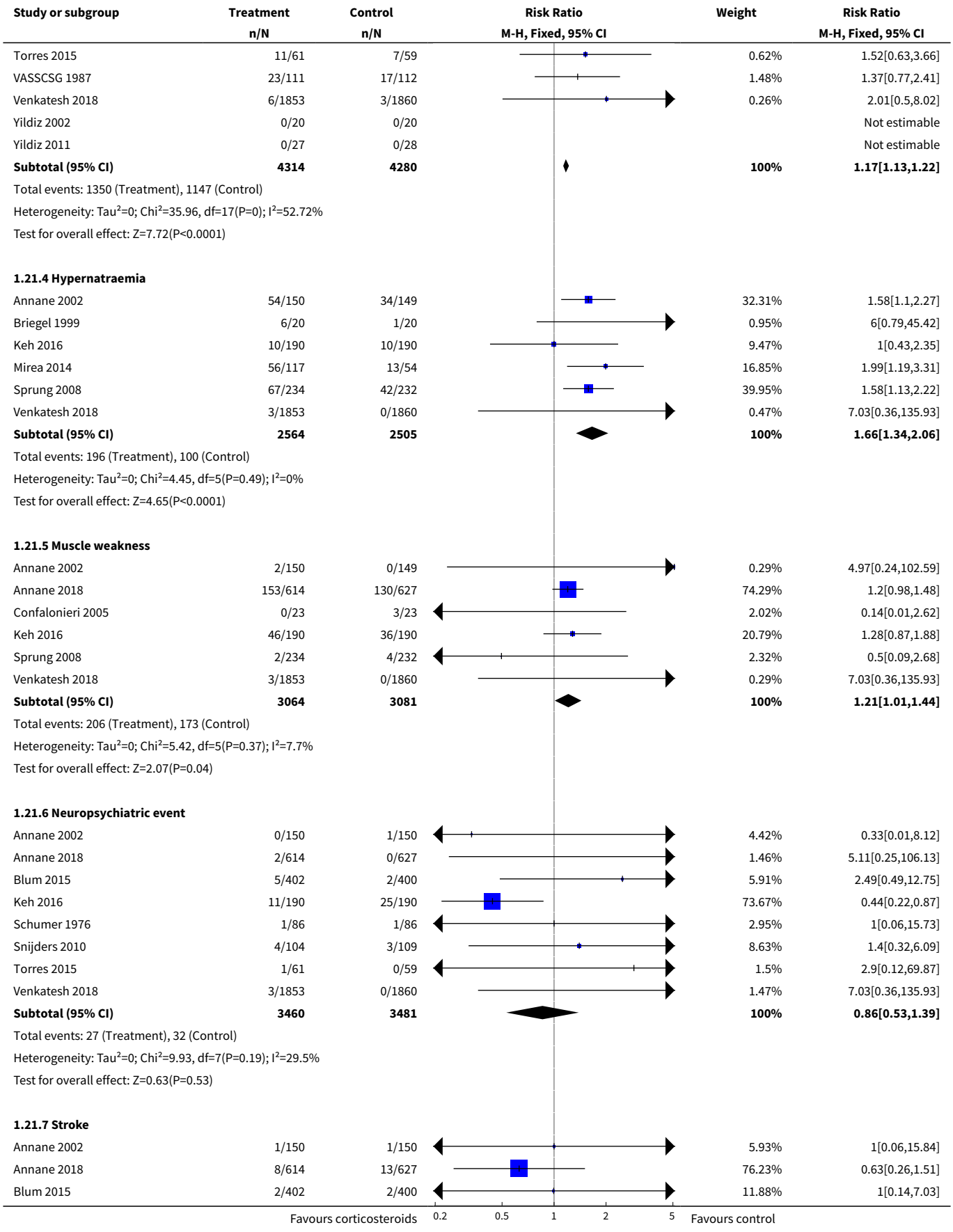
Analysis 1.21. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 21 Number of participants with adverse events.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.21.1 Gastroduodenal bleeding					
Annane 2002	11/151	8/149		6.56%	1.36[0.56,3.28]
Annane 2018	39/614	45/627		36.3%	0.89[0.58,1.34]
Arabi 2011	13/39	4/36		3.39%	3[1.08,8.36]
Blum 2015	3/402	4/400		3.27%	0.75[0.17,3.31]
Bollaert 1998	1/22	3/19		2.62%	0.29[0.03,2.54]
Briegel 1999	1/20	0/20		0.41%	3[0.13,69.52]
Chawla 1999	1/23	2/21		1.7%	0.46[0.04,4.68]
Cicarelli 2007	0/14	0/15			Not estimable
Confalonieri 2005	1/23	1/23		0.82%	1[0.07,15.04]
Gordon 2014	0/31	0/30			Not estimable
Keh 2016	3/190	2/190		1.63%	1.5[0.25,8.88]
Luce 1988	18/37	16/36		13.22%	1.09[0.67,1.79]
Meduri 2007	0/42	0/19			Not estimable
Meijvis 2011	1/151	0/153		0.4%	3.04[0.12,74.03]
Menon 2017	2/23	2/26		1.53%	1.13[0.17,7.39]
Sabry 2011	2/40	2/40		1.63%	1[0.15,6.76]
Schumer 1976	2/86	1/86		0.82%	2[0.18,21.65]
Snijders 2010	0/104	0/109			Not estimable
Sprung 1984	1/43	2/16		2.38%	0.19[0.02,1.91]
Sprung 2008	15/234	13/232		10.64%	1.14[0.56,2.35]
Tagaro 2017	0/30	0/30			Not estimable
Tongyoo 2016	3/98	4/99		3.24%	0.76[0.17,3.3]
Torres 2015	0/61	1/59		1.24%	0.32[0.01,7.76]
VASSCSG 1987	14/112	10/111		8.19%	1.39[0.64,2.99]
Yildiz 2002	0/20	0/20			Not estimable
Yildiz 2011	0/27	0/28			Not estimable

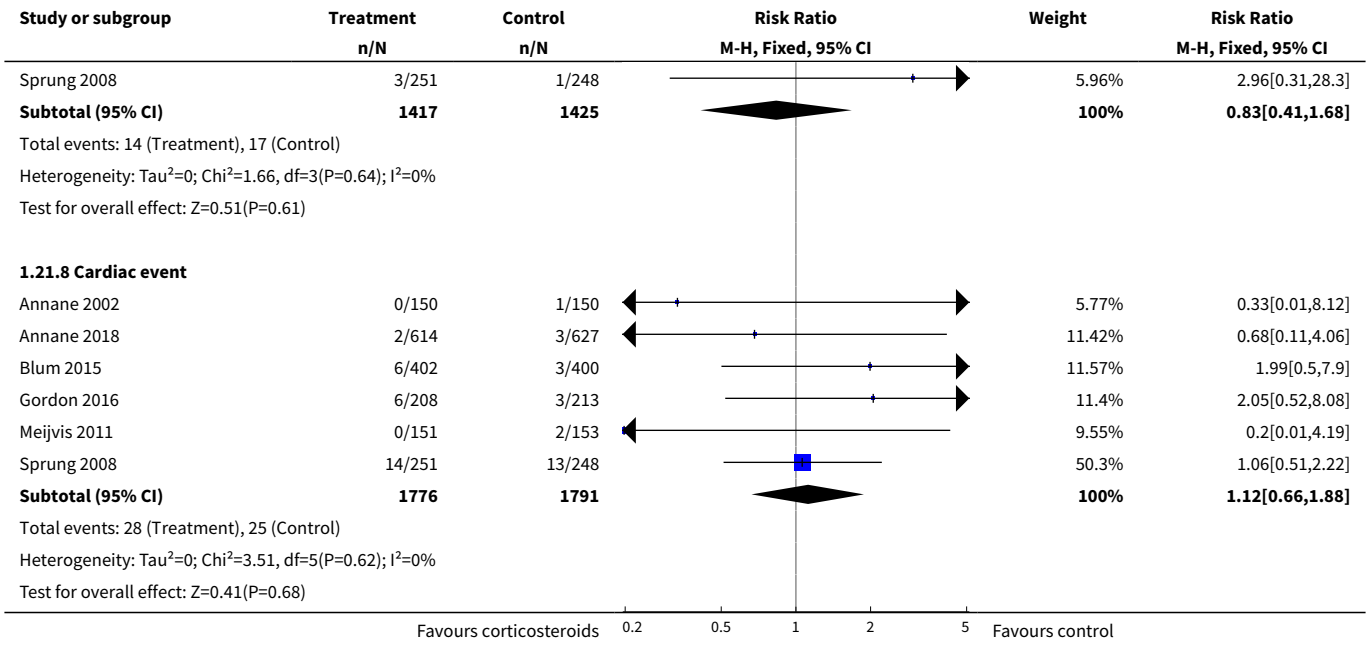


Favours corticosteroids — Favours control





Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Torres 2015	11/61	7/59		0.62%	1.52[0.63,3.66]
VASSCSG 1987	23/111	17/112		1.48%	1.37[0.77,2.41]
Venkatesh 2018	6/1853	3/1860		0.26%	2.01[0.5,8.02]
Yildiz 2002	0/20	0/20			Not estimable
Yildiz 2011	0/27	0/28			Not estimable
Subtotal (95% CI)	**4314**	**4280**		**100%**	**1.17[1.13,1.22]**
Total events: 1350 (Treatment), 1147 (Control)					
Heterogeneity: Tau²=0; Chi²=35.96, df=17(P=0); I²=52.72%					
Test for overall effect: Z=7.72(P<0.0001)					
1.21.4 Hypernatraemia					
Annane 2002	54/150	34/149		32.31%	1.58[1.1,2.27]
Briegel 1999	6/20	1/20		0.95%	6[0.79,45.42]
Keh 2016	10/190	10/190		9.47%	1[0.43,2.35]
Mirea 2014	56/117	13/54		16.85%	1.99[1.19,3.31]
Sprung 2008	67/234	42/232		39.95%	1.58[1.13,2.22]
Venkatesh 2018	3/1853	0/1860		0.47%	7.03[0.36,135.93]
Subtotal (95% CI)	**2564**	**2505**		**100%**	**1.66[1.34,2.06]**
Total events: 196 (Treatment), 100 (Control)					
Heterogeneity: Tau²=0; Chi²=4.45, df=5(P=0.49); I²=0%					
Test for overall effect: Z=4.65(P<0.0001)					
1.21.5 Muscle weakness					
Annane 2002	2/150	0/149		0.29%	4.97[0.24,102.59]
Annane 2018	153/614	130/627		74.29%	1.2[0.98,1.48]
Confalonieri 2005	0/23	3/23		2.02%	0.14[0.01,2.62]
Keh 2016	46/190	36/190		20.79%	1.28[0.87,1.88]
Sprung 2008	2/234	4/232		2.32%	0.5[0.09,2.68]
Venkatesh 2018	3/1853	0/1860		0.29%	7.03[0.36,135.93]
Subtotal (95% CI)	**3064**	**3081**		**100%**	**1.21[1.01,1.44]**
Total events: 206 (Treatment), 173 (Control)					
Heterogeneity: Tau²=0; Chi²=5.42, df=5(P=0.37); I²=7.7%					
Test for overall effect: Z=2.07(P=0.04)					
1.21.6 Neuropsychiatric event					
Annane 2002	0/150	1/150		4.42%	0.33[0.01,8.12]
Annane 2018	2/614	0/627		1.46%	5.11[0.25,106.13]
Blum 2015	5/402	2/400		5.91%	2.49[0.49,12.75]
Keh 2016	11/190	25/190		73.67%	0.44[0.22,0.87]
Schumer 1976	1/86	1/86		2.95%	1[0.06,15.73]
Snijders 2010	4/104	3/109		8.63%	1.4[0.32,6.09]
Torres 2015	1/61	0/59		1.5%	2.9[0.12,69.87]
Venkatesh 2018	3/1853	0/1860		1.47%	7.03[0.36,135.93]
Subtotal (95% CI)	**3460**	**3481**		**100%**	**0.86[0.53,1.39]**
Total events: 27 (Treatment), 32 (Control)					
Heterogeneity: Tau²=0; Chi²=9.93, df=7(P=0.19); I²=29.5%					
Test for overall effect: Z=0.63(P=0.53)					
1.21.7 Stroke					
Annane 2002	1/150	1/150		5.93%	1[0.06,15.84]
Annane 2018	8/614	13/627		76.23%	0.63[0.26,1.51]
Blum 2015	2/402	2/400		11.88%	1[0.14,7.03]



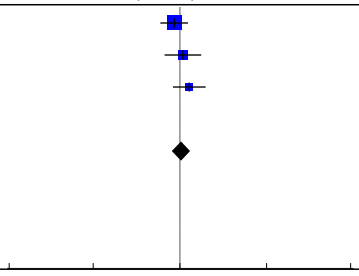
Comparison 2. Continuous infusion versus bolus administration of corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 28-Day all-cause mortality	3	310	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.81, 1.31]
2 90-Day all-cause mortality	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.61, 1.22]
3 Long-term mortality	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.02, 1.81]
4 Intensive care unit mortality	4	358	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.80, 1.29]
5 Hospital mortality	2	240	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.25]
6 Number of participants with shock reversal at day 7	4	358	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.59, 1.10]
7 Number of participants with shock reversal at day 28	1	70	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.45, 1.34]
8 SOFA score at day 7	3	260	Mean Difference (IV, Fixed, 95% CI)	1.00 [-0.25, 2.26]
9 Length of intensive care unit stay for all participants	3	310	Mean Difference (IV, Random, 95% CI)	-1.05 [-4.54, 2.45]
10 Length of hospital stay for all participants	3	310	Mean Difference (IV, Random, 95% CI)	0.01 [-5.05, 5.07]
11 Number of participants with adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Gastrointestinal bleeding	2	193	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.10, 6.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 Superinfection	2	193	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.37, 3.33]
11.3 Hyperglycaemia	3	310	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.47, 1.71]
11.4 Hypernatraemia	2	187	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.34, 1.61]
11.5 Muscle weakness	1	70	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.13, 5.98]
11.6 Neuropsychiatric event	1	70	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.50, 4.86]
11.7 Stroke	1	70	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.8 Cardiac event	1	70	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

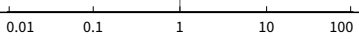
Analysis 2.1. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 1 28-Day all-cause mortality.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hyvernat 2016	28/63	31/60		46.13%	0.86[0.59,1.24]
Mirea 2014	22/59	20/58		29.3%	1.08[0.67,1.76]
Tilouche 2019	23/37	16/33		24.57%	1.28[0.83,1.98]
Total (95% CI)	**159**	**151**		**100%**	**1.03[0.81,1.31]**
Total events: 73 (Experimental), 67 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.94, df=2(P=0.38); I^2=0%					
Test for overall effect: Z=0.23(P=0.82)					

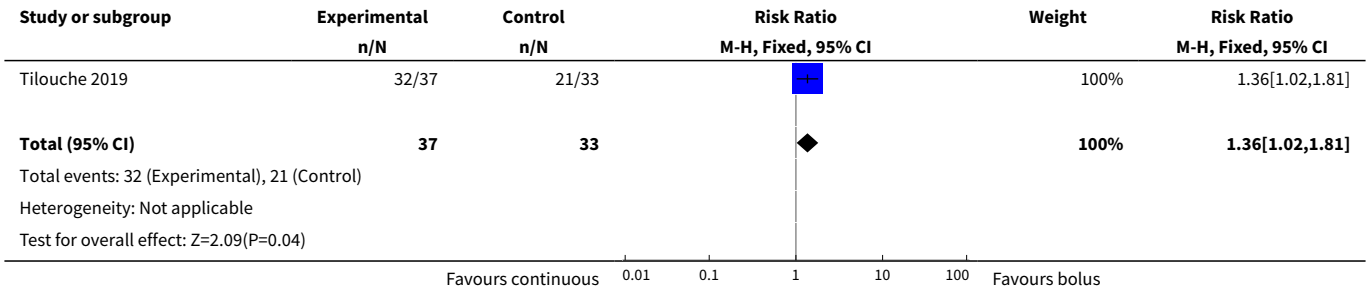


Analysis 2.2. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 2 90-Day all-cause mortality.

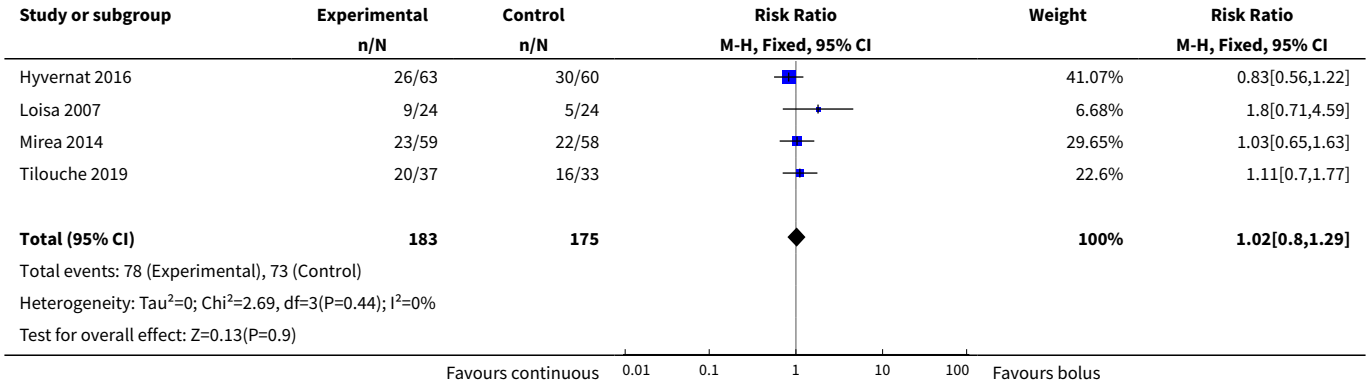
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hyvernat 2016	30/63	33/60		100%	0.87[0.61,1.22]
Total (95% CI)	**63**	**60**		**100%**	**0.87[0.61,1.22]**
Total events: 30 (Experimental), 33 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					



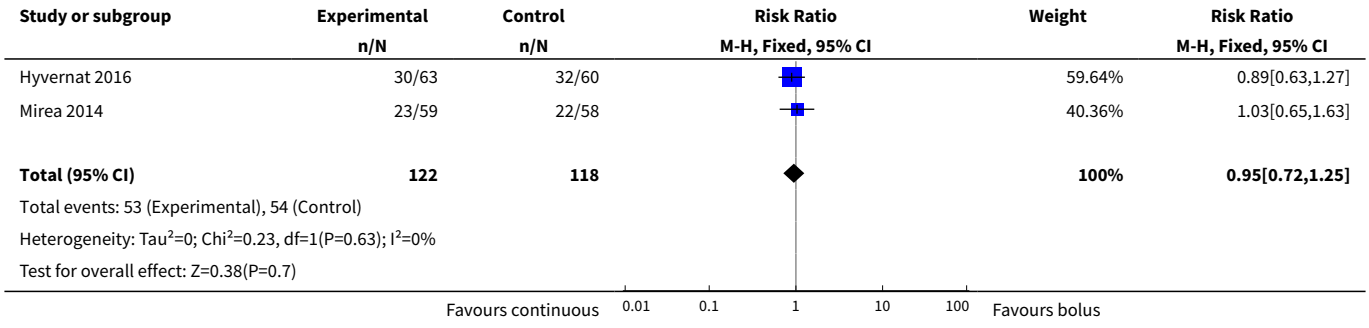
Analysis 2.3. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 3 Long-term mortality.



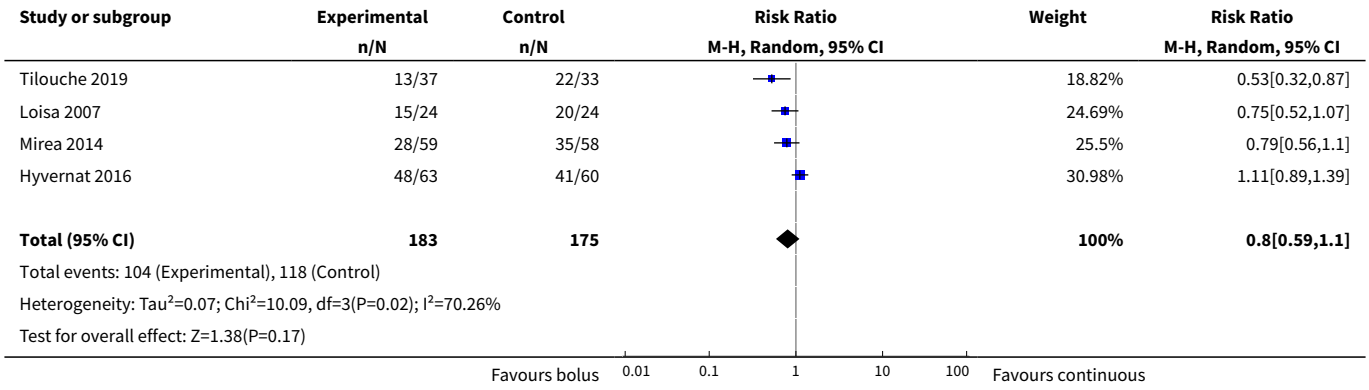
Analysis 2.4. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 4 Intensive care unit mortality.



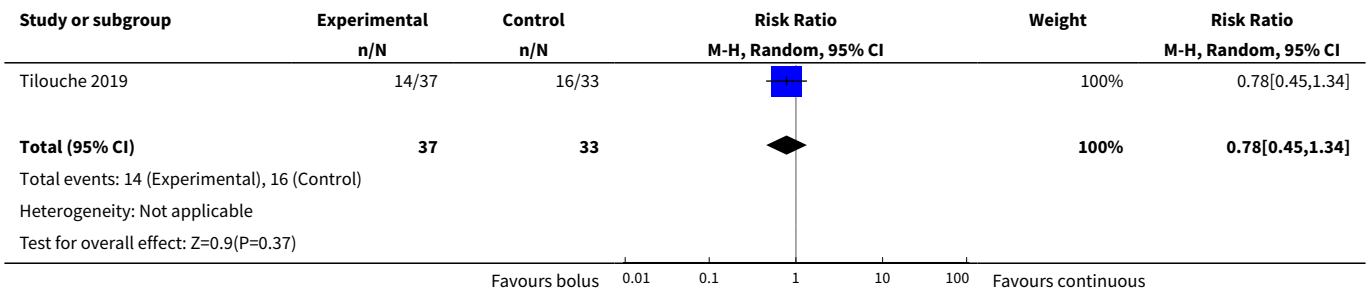
Analysis 2.5. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 5 Hospital mortality.



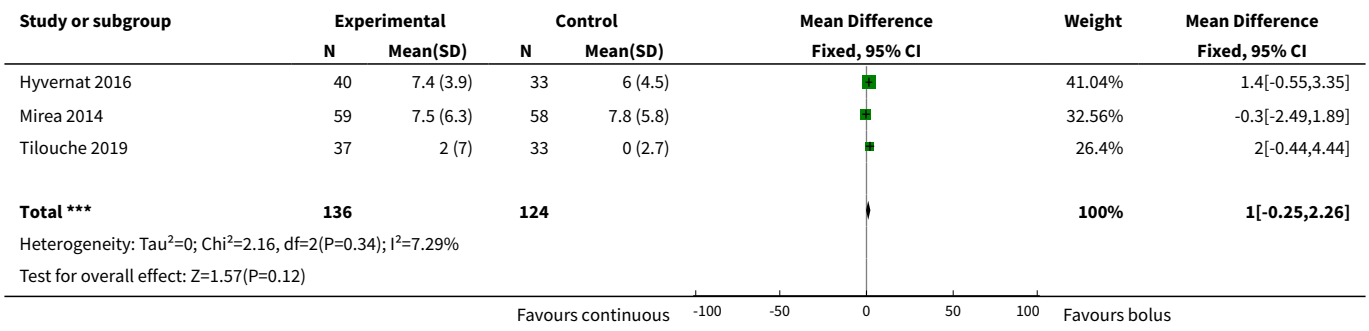
Analysis 2.6. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 6 Number of participants with shock reversal at day 7.



Analysis 2.7. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 7 Number of participants with shock reversal at day 28.

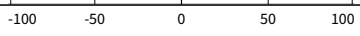


Analysis 2.8. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 8 SOFA score at day 7.



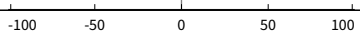
Analysis 2.9. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 9 Length of intensive care unit stay for all participants.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hyvernat 2016	63	13.3 (13.9)	60	10.8 (10.4)		28.31%	2.5[-1.83,6.83]
Mirea 2014	59	11.2 (5.7)	58	11.9 (5.7)		42.56%	-0.7[-2.77,1.37]
Tilouche 2019	37	11 (7.5)	33	16 (10)		29.14%	-5[-9.18,-0.82]
Total ***	**159**		**151**			**100%**	**-1.05[-4.54,2.45]**
Heterogeneity: Tau^2=6.36; Chi^2=6.1, df=2(P=0.05); I^2=67.23%							
Test for overall effect: Z=0.59(P=0.56)							



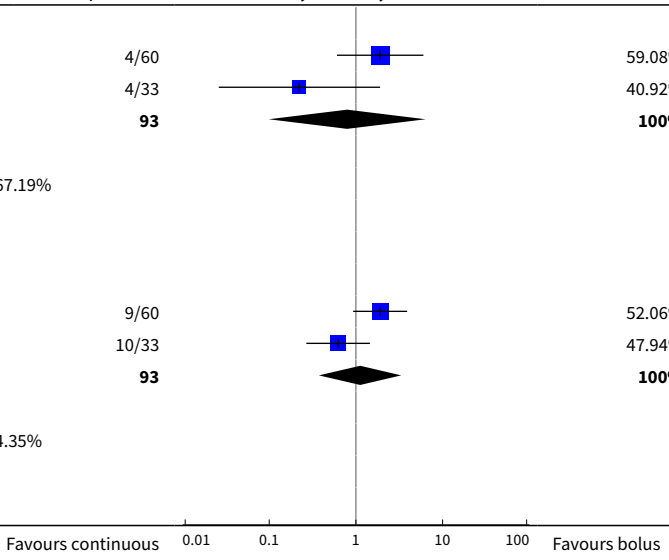
Analysis 2.10. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 10 Length of hospital stay for all participants.

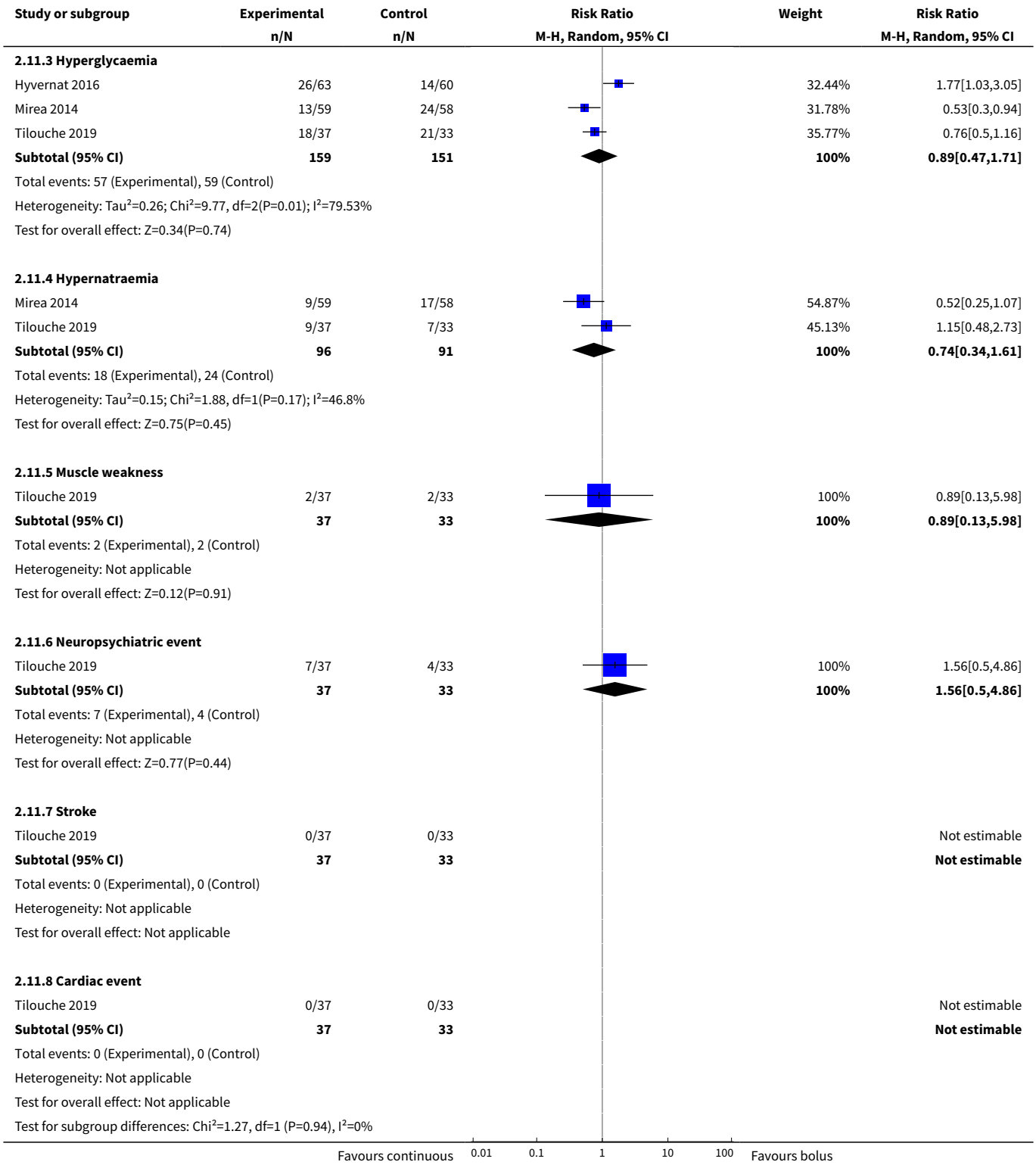
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hyvernat 2016	63	24.3 (22.8)	60	17.5 (16.2)		25.29%	6.8[-0.16,13.76]
Mirea 2014	59	17 (10.4)	58	17.7 (9.9)		38.65%	-0.7[-4.38,2.98]
Tilouche 2019	37	13 (8)	33	17 (10)		36.06%	-4[-8.28,0.28]
Total ***	**159**		**151**			**100%**	**0.01[-5.05,5.07]**
Heterogeneity: Tau^2=13.71; Chi^2=6.73, df=2(P=0.03); I^2=70.26%							
Test for overall effect: Z=0(P=1)							



Analysis 2.11. Comparison 2 Continuous infusion versus bolus administration of corticosteroids, Outcome 11 Number of participants with adverse events.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 Gastrointestinal bleeding					
Hyvernat 2016	8/63	4/60		59.08%	1.9[0.6,6]
Tilouche 2019	1/37	4/33		40.92%	0.22[0.03,1.9]
Subtotal (95% CI)	**100**	**93**		**100%**	**0.79[0.1,6.37]**
Total events: 9 (Experimental), 8 (Control)					
Heterogeneity: Tau^2=1.57; Chi^2=3.05, df=1(P=0.08); I^2=67.19%					
Test for overall effect: Z=0.22(P=0.83)					
2.11.2 Superinfection					
Hyvernat 2016	18/63	9/60		52.06%	1.9[0.93,3.9]
Tilouche 2019	7/37	10/33		47.94%	0.62[0.27,1.45]
Subtotal (95% CI)	**100**	**93**		**100%**	**1.12[0.37,3.33]**
Total events: 25 (Experimental), 19 (Control)					
Heterogeneity: Tau^2=0.46; Chi^2=3.9, df=1(P=0.05); I^2=74.35%					
Test for overall effect: Z=0.2(P=0.84)					





ADDITIONAL TABLES

Table 1. Continuous infusion compared to bolus administration of corticosteroids for children and adults with sepsis

Continuous infusion compared to bolus administration of corticosteroids for children and adults with sepsis

Patient or population: children and adults with sepsis
Setting: hospitalized patients; trials were performed in France, Tunisia, Romania, and Finland
Intervention: continuous infusion
Comparison: bolus administration of corticosteroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with bolus administration of corticosteroids	Risk with continuous infusion				
28-Day all-cause mortality	Study population		RR 1.03 (0.81 to 1.31)	310 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b]	Evidence is very uncertain about the effect of continuous infusion on 28-day all-cause mortality
	444 per 1000	457 per 1000 (359 to 581)				
Long-term mortality[c]	Study population		RR 1.36 (1.02 to 1.81)	70 (1 RCT)	⊕⊖⊖⊖ Very low[d,e,f]	Evidence is very uncertain about the effect of continuous infusion on long-term mortality
	636 per 1000	865 per 1000 (649 to 1000)				
Hospital mortality	Study population		RR 0.95 (0.72 to 1.25)	240 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,g]	Evidence is very uncertain about the effect of continuous infusion on hospital mortality
	458 per 1000	435 per 1000 (329 to 572)				
Length of intensive care unit stay for all participants in days	Mean length of intensive care unit stay for all participants was 13 days	MD 1.05 lower (4.54 lower to 2.45 higher)	-	310 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b,h]	Evidence is very uncertain about the effect of continuous infusion on length of intensive care unit stay for all participants
Length of hospital stay for all participants in days	Mean length of hospital stay for all participants was 17 days	MD 0.01 higher (5.05 lower to 5.07 higher)	-	310 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b,h]	Evidence is very uncertain about the effect of continuous infusion on length of hospital stay for all participants
Number of participants with adverse events - superinfection (up to longest follow-up)	Study population		RR 1.12 (0.37 to 3.33)	193 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,h]	Evidence is very uncertain about the effect of continuous infusion on number of participants with adverse events - superinfection
	204 per 1000	229 per 1000 (76 to 680)				
Number of participants with adverse events - muscle weakness (up	Study population		RR 0.89 (0.13 to 5.98)	70 (1 RCT)	⊕⊕⊖⊖ Low[d,e]	Evidence suggests that continuous infusion may result in little to no difference in the number of participants with adverse events - muscle weakness
	61 per 1000	54 per 1000 (8 to 362)				

Table 1. Continuous infusion compared to bolus administration of corticosteroids for children and adults with sepsis *(Continued)*

to longest follow-up)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

The unit of measure for length of stay is days.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level as only one of the four trials was judged as having low risk of bias.
[b]Downgraded one level as trials were small and the 95% confidence interval was large.
[d]Downgraded one level as the only trial reporting this outcome was open-labelled and at high risk of performance bias.
[e]Downgraded one level as only one trial reported this outcome.
[f]Downgraded one level as the observed increase in risk of dying in the long term is not consistent with treatment effects on 28-day mortality.
[g]Downgraded one level as results show some heterogeneity.
[h]Downgraded two levels as heterogeneity in the results is strong.
[c]Long-term mortality was assessed up to six months.

Table 2. Recent systematic reviews about the use of corticosteroids in sepsis

Author	Number of trials	Primary outcome	No of patients	Estimate	95% CI
Ni 2018	19	28-Day mortality	7035	Sepsis: RR = 0.91	0.85 to 0.98
				Septic shock: RR = 0.92	0.85 to 0.99
Allen 2018	6	Not stated	5689	Only qualitative assessment	Only qualitative assessment
Rochwerg 2018	42	28- to 31-day mortality	10,194	RR = 0.93	0.84 to 1.03
Rygard 2018	22	Short-term mortality	7297	RR = 0.96	0.91 to 1.02
Fang 2018	37	28-Day mortality	9564	RR = 0.90	0.82 to 0.98

APPENDICES

Appendix 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

Appendix 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

Appendix 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

Appendix 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*)

Appendix 5. Unpublished data obtained from trial authors

Studies	Type of unpublished data provided by primary authors
Annane 2002	Full access to individual data, details for randomization, and blinding procedures
Annane 2010	Full access to individual data, details for randomization, and blinding procedures
Annane 2018	Full access to individual data, details for randomization, and blinding procedures
Arabi 2011	Full access to individual data
Bollaert 1998	Full access to individual data, details for randomization, and blinding procedures. Additional information on adrenal function (data according to the review definition: delta cortisol ≤ 9 µg/dL). Additional information for ICU length of stay and adverse events
Briegel 1999	Full access to individual data, details for randomization, and blinding procedures. Additional information for ICU length of stay and adverse events
Chawla 1999	Details for randomization and blinding procedures. Additional information for mortality, shock reversal, and ICU length of stay and adverse events
Cicarelli 2007	Details for randomization and blinding procedures
Confalonieri 2005	Full access to individual data, details for randomization, and blinding procedures
Gordon 2014	Full access to individual data, details for randomization, and blinding procedures
Gordon 2016	Full access to individual data, details for randomization, and blinding procedures
Hyvernat 2016	Full access to individual data, details for randomization, and blinding procedures
Keh 2003	Details for randomization and blinding procedures. Additional information for adverse events
Keh 2016	Full access to individual data, details for randomization, and blinding procedures
Liu 2012	Full access to individual data, details for randomization, and blinding procedures

(Continued)

Meduri 2007	Details for randomization and blinding procedures. Additional information for subgroups of patients with sepsis or septic shock on mortality, ICU and hospital length of stay, and adverse events
Meduri 2009	Full access to individual data, details for randomization, and blinding procedures
Meijvis 2011	Separate information for patients with sepsis
Mirea 2014	Full access to individual data, details for randomization, and blinding procedures
Oppert 2005	Details for randomization and blinding procedures. Additional information for mortality, for outcomes of patients randomized and not analysed, shock reversal, and adverse events
Rinaldi 2006	Details for randomization and blinding procedures. Additional information for mortality, for outcomes of patients randomized and not analysed, and adverse events
Sprung 1984	Additional information for 28-day all-cause mortality
Sprung 2008	Full access to individual data, details for randomization, and blinding procedures
Tandan 2005	Details for randomization and blinding procedures
Tilouche 2019	Additional information for mortality data at 6 months and 1 year, number of patients with shock reversal at day 28, mean and SD value for SOFA score at day 7, number of patients with at least 1 episode of severe glycaemia > 180 mg/dL
Tongyoo 2016	Full access to individual data, details for randomization, and blinding procedures
Torres 2015	Details for randomization and blinding procedures. Additional information for mortality, shock reversal, SOFA, length of stay, and adverse events
Yildiz 2002	Details for randomization and blinding procedures. Additional information for mortality, hospital length of stay, and adverse events

Appendix 6. Methodological quality of studies

	Adequate	Inadequate	Unclear
Generation of allocation sequence	Aboab 2008; Annane 2002; Annane 2010; Annane 2018; Arabi 2011; Blum 2015; Bollaert 1998; Bone 1987; Briegel 1999; Chawla 1999; Cicarelli 2007; Confalonieri 2005; Fernández-Serrano 2011; Gordon 2014; Gordon 2016; Huang 2014; Hyvernat 2016; Keh 2003; Keh 2016; Klastersky 1971; Liu 2012; Luce 1988; Lv 2017; Meduri 2007; Meduri 2009; Meijvis 2011; Menon 2017; Mirea 2014; Nagy 2013; Ngaosuwan 2018; Oppert 2005; Rinaldi 2006; Slusher 1996; Snijders 2010; Sprung 1984; Sprung 2008; Tagaro 2017; Tilouche 2019; Tongyoo 2016; Torres 2015; VASSCSG 1987; Venkatesh 2018; Yildiz 2002; Yildiz 2011	Lucas 1984; Schumer 1976; Wagner 1955	CSG 1963; Doluee 2018; El Ghamrawy 2006; El-Nawawy 2017; Hu 2009; Huh 2007; Kurungundla 2008; Li 2016; Loisa 2007; McHardy 1972; Mikami 2007; Nafae 2013; Rezk 2013; Sabry 2011; Sui 2013; Tandan 2005; Valoor 2009
Allocation concealment	Aboab 2008; Annane 2002; Annane 2010; Annane 2018; Arabi 2011; Blum 2015; Bollaert 1998; Bone 1987; Briegel 1999; Chawla 1999; Cicarelli 2007; Confalonieri 2005; CSG 1963; Doluee 2018; Fernández-Serrano 2011; Gordon 2014; Gordon 2016; Hyvernat 2016; Keh 2003; Keh	Lucas 1984; Nagy 2013; Schumer 1976; Sprung 1984; Wagner 1955	El Ghamrawy 2006; El-Nawawy 2017; Hu 2009; Huang 2014; Huh 2007; Kurungundla 2008; Li 2016; Liu 2012; Loisa 2007; Mika-

(Continued)

	2016; Klastersky 1971; Luce 1988; Lv 2017; McHardy 1972; Meduri 2007; Meduri 2009; Meijvis 2011; Menon 2017; Oppert 2005; Rinaldi 2006; Slusher 1996; Snijders 2010; Sprung 2008; Tagaro 2017; Tilouche 2019; Tongyoo 2016; Torres 2015; VASSCSG 1987; Venkatesh 2018; Yildiz 2002; Yildiz 2011		mi 2007; Mirea 2014; Nafae 2013; Ngaosuwan 2018; Rezk 2013; Sabry 2011; Sui 2013; Tandan 2005; Valoor 2009; Zhou 2015
Blinding	Aboab 2008; Annane 2002; Annane 2018; Arabi 2011; Blum 2015; Bollaert 1998; Bone 1987; Briegel 1999; Chawla 1999; Cicarelli 2007; Confalonieri 2005; El-Nawawy 2017; Fernández-Serrano 2011; Huh 2007; Hyvernat 2016; Keh 2003; Klastersky 1971; Luce 1988; Lv 2017; Meduri 2007; Meduri 2009; Meijvis 2011; Menon 2017; Mikami 2007; Ngaosuwan 2018; Oppert 2005; Rinaldi 2006; Slusher 1996; Snijders 2010; Sprung 2008; Tagaro 2017; Tandan 2005; Tongyoo 2016; Torres 2015; VASSCSG 1987; Venkatesh 2018; Yildiz 2002; Yildiz 2011	Annane 2010; Huang 2014; Li 2016; Lucas 1984; McHardy 1972; Mikami 2007; Mirea 2014; Nagy 2013; Sprung 1984; Sui 2013; Tilouche 2019; Valoor 2009; Wagner 1955; Zhou 2015	CSG 1963; El Ghamrawy 2006; Doluee 2018; Hu 2009; Kurungundla 2008; Liu 2012; Loisa 2007; Nafae 2013; Rezk 2013; Sabry 2011; Schumer 1976
Loss to follow-up	Aboab 2008; Annane 2002; Annane 2010; Annane 2018; Arabi 2011; Blum 2015; Bollaert 1998; Briegel 1999; Doluee 2018; El Ghamrawy 2006; El-Nawawy 2017; Hu 2009; Huang 2014; Hyvernat 2016; Keh 2003; Lucas 1984; Lv 2017; McHardy 1972; Meduri 2007; Meduri 2009; Meijvis 2011; Menon 2017; Mirea 2014; Nagy 2013; Ngaosuwan 2018; Rezk 2013; Sabry 2011; Snijders 2010; Sprung 2008; Tagaro 2017; Tilouche 2019; Tongyoo 2016; Torres 2015; Valoor 2009; VASSCSG 1987; Venkatesh 2018; Yildiz 2011	Fernández-Serrano 2011	Bone 1987; Chawla 1999; Cicarelli 2007; Confalonieri 2005; CSG 1963; Huh 2007; Klastersky 1971; Kurungundla 2008; Li 2016; Liu 2012; Loisa 2007; Luce 1988; Mikami 2007; Nafae 2013; Oppert 2005; Rinaldi 2006; Schumer 1976; Slusher 1996; Sprung 1984; Sui 2013; Tandan 2005; Zhou 2015

FEEDBACK

Feedback, 9 May 2013

Summary

Annane et al in their systematic review of corticosteroids for treating severe sepsis and septic shock concluded “a long course of low dose corticosteroids reduced mortality without inducing major complications” (Annane 2004; updated 2010). This was based on a subgroup analysis, as all doses/durations of corticosteroids for septic shock did not show a benefit in reduction of mortality.

Given that the two largest trials have contradicting results (Annane 2002; Sprung 2008), we were interested in looking into these trials. Upon our review, we feel that the risk of bias assessment for these trials has not adequately addressed the issue of incomplete data. In one trial (Sprung 2008), authors used a per-protocol analysis for their adverse event data; this was subsequently used in this review. Neither the trial nor the review addresses the reasons for this approach. Using per-protocol data is not the preferred method of outcome reporting, as it does not allow for preservation of randomization. Section 14.6.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* specifically asks whether any patients were excluded in reporting of adverse events. Participants who experience unfavourable adverse events may drop out of the trial. When the per-protocol analysis is used, adverse effect results may therefore be biased in favour of steroids. The same scenario can be applied for the placebo group.

In another trial (Annane 2002), we are concerned with the way data were collected and reported for adverse events. Events are reported as being “possibly related to steroids” and “possibly related to vasopressors”. We are unsure as to how one would know whether or not an adverse event was related to the intervention. Neither the review nor the trial specifically outlines the adjusting procedure for determining whether or not adverse events were due to steroids. Patients in the intensive care unit have many risk factors for infection - GI bleeding, psychiatric disorders (e.g. delirium) - therefore it seems inappropriate to try to ascertain whether or not the event was secondary to steroids. Section 14.6.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* explains how clinical trials may have a well-designed method for collecting data for the primary outcome, but in fact may take a retrospective, unblinded approach to collecting adverse event data. An extension of the CONSORT statement for harm also echoes this, recommending that clinical trials should explicitly define how data for adverse events were defined, collected, and analysed (Ioannidis 2004).

As Annane 2002 was a randomized controlled trial, adverse events would not require assessment of whether or not they were thought to be due to treatment. Randomization should take care of confounding factors and thus should be able to show differences (if they truly exist) in adverse events. In our opinion, preference should be given to all-cause adverse events for this reason.

Last, we note that in Analysis 1.12 for "superinfection", the percentage of participants with an event was used instead of the actual number of events in Annane 2002. For example, the number of events for the treatment arm should have been "22", but "15" was used instead.

Given that these issues on selective reporting - Annane 2002 - and incomplete data surrounding the two largest trials of this review have not been adequately addressed in the risk of bias assessments, we find it difficult to conclude at this time on the safety profile of corticosteroid use in treating severe sepsis and septic shock. We look forward to hearing your response to our concerns.

Reply

We are grateful to Dr. Harbin and colleagues for their comments on the Cochrane review on corticosteroids for severe sepsis and septic shock.

Dr. Harbin and colleagues questioned the validity of the concluding statement of this review that corticotherapy was overall well tolerated apart from inducing hyperglycaemia and hypernatraemia. Indeed, they pointed out that Sprung and colleagues reported serious adverse events as per-protocol (Sprung 2008). In fact, in this trial, data for adverse events were reported only for 466 of 499 patients. We have now reported this information in the risk of bias table in a revised version of the review.

Annane and colleagues reported in their main paper the number of participants with any serious adverse events in each treatment arm as per intent-to-treat analysis (Annane 2002). All serious adverse events that were observed were reported in each treatment group. Serious adverse events were further classified according to what was known about complications of corticosteroids or catecholamines. For example, all superinfections, gastroduodenal bleeding, metabolic disorders, and psychiatric disorders that occurred at any time from randomization were reported and further classified in a blinded manner as possibly related to corticosteroids. Thus, no manipulation of data occurred. All serious adverse events were carefully scrutinized and reported in the manuscript, and additional unpublished information (i.e. raw data) was available during preparation of the Cochrane review.

Finally, Dr. Harbin and colleagues highlighted an error in numbers used for Analysis 1.12 (number of participants with superinfection) that is now corrected in the revised version of the review. This modification did not significantly alter the direction and the magnitude of the pooled estimate for evaluation of serious adverse events. Thus, we believe that the conclusion statement - that treatment with corticosteroids in patients with sepsis or septic shock is well tolerated apart from metabolic disorders - is still valid.

Contributors

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Reply:

Djillali Annane

Feedback, 9 November 2017

Summary

1. Annane and colleagues, in their systematic review (Annane 2015), concluded that “a long course of low dose corticosteroids reduced mortality without inducing major complications”. This was based on a subgroup analysis, analysis of outcome 1.4, so we pursued it in greater detail. Upon our review, we found that the forest plot was created using a fixed-effect model. However, the largest trial - Sprung 2008 - carried only 21.5% weight, and the second largest trial - Annane 2002 - was allotted a larger weight of 25.1%. Although we acknowledge that given that I^2 was 16%, a fixed-effect model was chosen, we felt that because these two trials had conflicting results, suggesting clinical heterogeneity, a random-effects model would have been a more conservative and more appropriate approach in this scenario. We took the initiative to re-create the forest plot using a random-effects model, and we found that the treatment effect became not statistically significant. This suggests that perhaps the conclusion is not as simple as “a long course of low dose corticosteroids reduced mortality” in severe sepsis and septic shock.
2. Furthermore, when we reviewed Summary of findings for the main comparison, we noticed that footnote “a” states that the certainty of evidence for the primary outcome was downgraded due to “1 of the 2 largest trials [showing] no survival benefit”. We feel that this sentence implies that the other largest trial did show a survival benefit, and may mislead the readers to believe so. However, both of the largest trials did not show a statistical benefit for corticosteroids compared to placebo for mortality benefits in sepsis and septic shock (Annane 2002; Sprung 2008). One trial simply showed that there was no increase in mortality, but did not show a reduction in mortality.

3. Based on our findings, we feel that there could be an alternative interpretation of the results of these trials. This review includes studies from 1976 to 2015, and when we look at studies published before 2002, the studies as a group show a more convincing trend toward mortality benefit with corticosteroids. In contrast, studies published after 2002 show more conflicting results. This may suggest that medical therapy today is better for treating sepsis and hence the benefits from corticosteroids are not as apparent as was previously thought. In contrast to the conclusion stated by the review authors, we feel that this review presents inconclusive evidence for mortality benefit with corticosteroid use in septic patients. We look forward to your response.

Reply

1. The planned analysis was to use a fixed-effect model unless heterogeneity across trials could be suspected (i.e. squared I statistic > 30%). We weighted studies by the amount of information they contribute (more specifically, by the inverse variances of their effect estimates). It is also important to highlight that CORTICUS - Sprung 2008 - was terminated prematurely (after 500 participants were recruited out of 800 expected) owing to low recruitment rate and loss of equipoise among investigators. Changing from fixed- to random-effects models did not change the magnitude nor the direction of the point estimate (RR 0.87 vs 0.88) and slightly enlarged the 95% CI 0.78 to 0.97 versus 0.77 to 1.00. Thus, we do not believe that the conclusion from our systematic review was not supported by data analysis, and we disagree about over-interpreting the data.
2. In the trial Annane 2002, the primary outcome was time to death in non-responders to ACTH testing (modified intent-to-treat analysis). The primary analysis for the primary outcome in this trial showed a statistically significant increase in survival time (P = 0.02). The CORTICUS trial - Sprung 2008 - found no significant effect of treatment on mortality. Thus, we do not believe that we have misinterpreted (misreported) findings from the Annane 2002 or Sprung 2008 trial.
3. The pooled RR of dying from trials published before 2002 was 0.90 (95% CI 0.75 to 1.07). The pooled RR of dying from trials published from 2002 was 0.89 (95% CI 0.80 to 1.00). Thus, no evidence suggests that the effect of corticosteroids on mortality differed between trials published before 2002 versus those published since 2002. Finally, new trials have been published since the last update of this review, including Keh et al JAMA 2016; Bi et al PLoSOne 2016; Menon et al Ped CCM 2017; El Nawawy The Pediatric Infectious Disease Journal 2016; Qing-quan Lv et al Am J Emerg Med 2017; and Tongyoo et al. Critical Care 2016; and two large trials are about to be published in the very next future (ADRENAl, n = 3800 and APROCCHSS, n = 1241). Thus, we believe that there is a need to update the review in light of these newly published studies.

Contributors

Summary

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We do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment.

Reply

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WHAT'S NEW

Date	Event	Description
25 July 2019	New search has been performed	We reran the search from October 2014 to 31 March 2019. The search was updated again 25 July 2019.
25 July 2019	New citation required but conclusions have not changed	A new search of the literature revealed 25 additional trials. Cumulative evidence from 48 trials including 11,114 patients confirmed the direction and magnitude of the point estimate for 28-day mortality with narrow confidence interval limits. The review found evidence for a significant reduction in ICU and hospital

Date	Event	Description
		mortality, and in ICU and hospital length of stay. The review now includes evidence for a reduction in mid-term (90-day) to long-term (up to 1 year) mortality by corticosteroids. We made several changes to the Methods section. • We now include treatment effects on mortality at 90 days, and at longest follow-up beyond 3 months and up to 1 year • We have included the new Sepsis 3 definition for the selection of type of participants • We have added new adverse events (i.e. neuropsychiatric events, stroke, and cardiac events) • We have added subgroup analyses based on modes of administration of corticosteroids (e.g. continuous vs bolus administration, mode of drug termination, i.e. stopping with or without taper-off) • We have conducted sensitivity analysis for trials judged at low risk of bias • We introduced a new comparison that is a direct comparison of continuous infusion vs intermittent bolus of corticosteroids

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 1, 2004

Date	Event	Description
14 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care
4 May 2018	Feedback has been incorporated	New Feedback and reply posted in review
18 January 2016	Amended	Typo corrected in plain language summary (it was made clear that corticosteroids decreased the number of organs that were not functioning properly (organ failure))
30 November 2015	New citation required and conclusions have changed	A new search of the literature revealed 9 additional trials. Cumulated evidence from 33 trials confirmed the direction and the magnitude of the point estimate for 28-day mortality with narrow confidence interval limits. Thus, this update suggests moderate evidence for reduced 28-day mortality with corticosteroids in the primary analysis. Evidence also confirms significant interactions between the relative risk of dying at 28 days and treatment modalities (lower doses and longer durations yielded better chance of survival) and patient case mix (patients with septic shock, sepsis-related acute respiratory distress syndrome (ARDS) or community-acquired pneumonia may be more likely to benefit from corticosteroids). We decided to change the title to "Corticosteroids for treating sepsis" owing to recent changes in the definition of sepsis, suggesting that the term "severe sepsis" should be avoided. We made several changes to the Methods section. • We now exclude quasi-randomized trials (3 trials)

Date	Event	Description
		• We changed the definition of "long course" from at least 5 days to at least 3 days. Indeed, and in keeping with the Surviving Sepsis Campaign recommendation, corticosteroids are often given at full dose until cessation of vasopressor therapy, which may occur faster than 5 days • We changed the definition of "low dose" from 300 mg or less per day to 400 mg or less per day. Indeed, no consensus has been reached on the optimal dose, and several randomized controlled trials testing so-called "low-dose" corticosteroids used variable doses up to 400 mg • According to findings from meta-regression analysis, changes in the definitions of "low dose" and "long course" might have had a negative impact on the observed survival benefit of corticosteroids. Indeed, we found that both longer duration and lower dose were associated with better survival rates Sensitivity analyses based on methodological quality are now restricted to the primary outcome. We used random-effects models only in cases of heterogeneity with an I^2 statistic > 30%. Otherwise, we used fixed-effect models.
30 November 2015	New search has been performed	We reran the search from October 2009 to October 2014
14 August 2013	Feedback has been incorporated	Feedback was submitted and was responded to. An error in numbers used for Analysis 1.12 (number of participants with superinfection) has been corrected in the amended version of this review. 'Risk of bias' tables and 'Summary of findings' tables have also been amended.
1 November 2010	New search has been performed	• We reran the searches from August 2003 to October 2009 • We found 21 new trials. Of those 21 trials, we included 9 randomized controlled trials in this update (Annane 2010; Cicarelli 2007; Confalonieri 2005; Huh 2007; Meduri 2007; Oppert 2005; Rinaldi 2006; Sprung 2008; Tandan 2005); we excluded 3 (Cicarelli 2006; Kaufman 2008; Mikami 2007), and 9 are ongoing (IRSCTN99675218 2006; NCT00127985 2005; NCT00149123 2005; NCT00368381 2008; NCT00471640 2008; NCT00562835 2008; NCT00625209 2008; NCT00670254 2008; NCT00732277 2008) • Two (Oppert 2002; Sprung 2002) of the 3 previous ongoing studies (Oppert 2002; Sprung 2002; Tayer 2002) have now been published and are included in this update as Oppert 2005 and Sprung 2008. The third trial has never been completed, and no data are available • In total, this updated review now describes 25 included studies, 10 excluded studies, and 9 ongoing studies • The additional included studies did not change the conclusions of this review • We included 'Risk of bias' and 'Summary of findings' tables in this updated version • Search strategies changed from Silver Platter to Ovid • We changed the statistical analysis by using the random-effects model rather than the fixed-effect model, and we included meta-regression analysis to explore the influence of dose and duration of corticosteroids on risk of death

Date	Event	Description
25 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: Djillali Annane (DA), Eric Bellissant (EB), Pierre Edouard Bollaert (PEB), Josef Briegel (JB), Didier Keh (DK), Yizhak Kupfer (YK), Romain Piracchio (RP), Bram Rochwerg (BR).

Co-ordinating the review: DA.

Undertaking manual searches: DA, PEB, JB, DK, RP, BR.

Screening search results: DA, PEB, JB, DK, YK, RP, BR.

Organizing retrieval of papers: DA, PEB, JB, DK, YK, RP, BR.

Screening retrieved papers against inclusion criteria: DA, PEB, JB, DK, YK, RP, BR.

Appraising the quality of papers: DA, PEB, JB, DK, RP, BR, YK.

Abstracting data from papers: DA, RP, BR.

Writing to authors of papers to ask for additional information: DA.

Providing additional data about papers: DA, PEB, JB, DK, YK.

Obtaining and screening data on unpublished studies: DA, PEB, JB, DK, RP, BR, YK.

Managing data for the review: DA, EB, RP, BR.

Entering data into Review Manager (Review Manager 2014): DA.

Analysing RevMan statistical data: DA, EB, RP, BR.

Performing other statistical analyses not using RevMan: DA .

Performing double entry of data (data entered by person one: DA; data entered by person two: Laurenne Authelet).

Interpreting data: DA, EB, PEB, JB, DK, YK, RP, BR.

Making statistical inferences: EB.

Writing the review: DA, EB, PEB, JB, DK, YK, RP, BR.

Securing funding for the review: DA.

Performing previous work that served as the foundation of the present study: DA, EB, PEB, JB, DK, YK.

Serving as guarantor for the review (one review author): DA.

Taking responsibility for reading and checking the review before submission: DA.

DECLARATIONS OF INTEREST

Djillali Annane is an author of the following studies included in this review: Aboab 2008; Annane 2002; Annane 2010; Annane 2018; Sprung 2008. He obtained funds from the French Minisitry of Health to conduct the following trials: Annane 2002; Annane 2010; and Annane 2018. He has been the chair of the international task force for elaborating 2017 guidelines for the diagnosis and treatment of critical illness-related corticosteroid insufficiency.

Eric Bellissant is an author of the following studies included in this review: Annane 2002; Annane 2018.

Pierre Edouard Bollaert is an author of the following studies included in this review: Annane 2002; Bollaert 1998. He obtained public funds from the University of Nancy to conduct the trial (Bollaert 1998).

Josef Briegel is an author of the following studies included in this review: Briegel 1999; Keh 2016; Sprung 2008. He obtained public funds to conduct the trial (Briegel 1999). He contributed to the international task force for elaborating 2017 guidelines for the diagnosis and treatment of critical illness-related corticosteroid insufficiency. He participated in the European Society of Intensive Care Medicine, the Deutsche interdisziplinäre Vereinigung Intensivmedizin, and the Deutsche Gesellschaft für Anästhesie und Intensivmedizin, and he has given lectures and talks on hydrocortisone treatment for septic shock.

Didier Keh is an author of the following studies included in this review: Keh 2003; Keh 2016; Sprung 2008. He obtained public funds from Charité–Universitätsmedizin Berlin and from the German Federal Ministry of Education and Research to conduct the following trials: Keh 2003; Keh 2016.

Yizhak Kupfer is an author of the following studies included in this review: Chawla 1999. He is a member of the Pfizer/BMS speakers' bureau for epixaban. This product has no relationship to steroids in sepsis. He obtained funds from his institution to conduct the trial (Chawla 1999).

Romain Pirracchio received funding for International Mobility from the Fulbright Foundation and from the Assistance Publique – Hôpitaux de Paris (APHP).

Bram Rochwerg is supported by McMaster University Department of Medicine early career research awards. He has contributed to the international task force for elaborating 2017 guidelines for the diagnosis and treatment of critical illness-related corticosteroid insufficiency. He is a methodologist for American Thoracic Society, European Society of Intensive Care Medicine, and American Society of Haematology.

SOURCES OF SUPPORT

Internal sources

- Hopital Raymond Poincaré, Garches, France.
- University of Versailles Saint Quentin en Yvelines, France.

  Logistical support for literature search

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Update 2019

We have made the following changes from the protocol.

- We now include treatment effects on mortality at 90 days and in the long term (i.e. at longest follow-up available beyond three months). Indeed, with the decline in sepsis-related short-term mortality observed in the past decade, more attention is given to mortality at longer term. The two most recent and largest trials of corticosteroids for septic shock had all-cause mortality at 90 days as the primary outcome and followed up patients to six months.
- We included the new Sepsis 3 definition in the selection of types of participants. For this update, we found no trial that used the Sepsis 3 definition, as all studies were designed before the new definition was available.
- We added new adverse events (i.e. neuropsychiatric events, stroke, and cardiac events). Indeed, with more patients surviving in the short term, adverse events from treatment that may impact patients' long-term outcomes have been given greater attention in sepsis trials. Such adverse events may include muscle weakness, neuropsychiatric events, stroke, and cardiac events, and we have added them to this review.
- We added a subgroup analysis based on modes of administration of corticosteroids (i.e. continuous vs bolus administration, stopping with or without taper off). Indeed, over past decades, increasing use of corticosteroids for sepsis has raised new issues of controversy based on how corticosteroids are administered.
- We conducted sensitivity analysis based on methodological quality by conducting an analysis of all studies judged to be at low risk of bias.
- We introduced a new comparison that is a direct comparison of continuous infusion versus intermittent bolus of corticosteroids.
- We modified the search strategy to increase its sensitivity by adding the search terms "pneumonia", "acute respiratory distress syndrome", and "acute lung injury".

NOTES

This review was initially developed within the Infectious Diseases Group and was transferred to the Anaesthesia Group in May 2005.

Update 2010

The review was updated in 2010 (Annane 2004). At that time, Cochrane updates did not earn a new citation unless they had new review authors or included a change to the conclusions. Review authors found 21 new trials in 2010. Of those 21 trials, they included nine randomized controlled trials in the 2010 update. Additional included studies did not change the conclusions of this review. Therefore the 2010 update did not earn a new citation.

Update 2015

The new search of the literature identified nine additional trials. Accumulated evidence from 33 trials confirmed the direction and magnitude of the point estimate for 28-day mortality with narrow confidence interval limits. Thus, this update suggested moderate evidence for reduced 28-day mortality with corticosteroids in the primary analysis and confirmed significant interactions between the relative risk of dying at 28 days and treatment modalities used (lower doses and longer duration yielded better chance of survival) and the patient case mix included (patients with septic shock, sepsis-related ARDS, or community-acquired pneumonia may be more likely to benefit from corticosteroids).

We decided to change the title to "Corticosteroids for treating sepsis" owing to recent changes in the definition of sepsis, suggesting that the term "severe sepsis" should be avoided.

We made several changes to the Methods section.

- We excluded quasi-randomized trials (three trials).
- We changed the definition of "long course" from at least five days to at least three days. Indeed, and in keeping with the Surviving Sepsis Campaign recommendation, corticosteroids are often given at full dose until cessation of vasopressor therapy, which may occur sooner than five days. We changed the definition of "low dose" from 300 mg or less per day to 400 mg or less per day. Indeed, no consensus has been reached about what should be the optimal dose, and several RCTs testing so called "low-dose" corticosteroids used variable doses up to 400 mg. According to findings from the meta-regression analysis, changes in the definitions of "low dose" and "long course" might have had a negative impact on observed survival benefits of corticosteroids. Indeed, we found that both longer duration and lower dose were associated with better survival rates.
- We incorporated information on how we used the GRADE system and how we selected outcomes for the 'Summary of findings' table.

Sensitivity analyses based on methodological quality are now restricted to the primary outcome.

Random-effects models are used only in cases of heterogeneity, with I^2 statistic > 30%. Otherwise, fixed-effect models are used.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects] [*therapeutic use]; Hospital Mortality; Length of Stay; Randomized Controlled Trials as Topic; Risk Factors; Sepsis [*drug therapy] [*mortality]; Time Factors

MeSH check words

Adult; Child; Humans