

Corticosteroid therapy for sepsis: a clinical practice guideline

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This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (<http://magicproject.org/>) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (<https://app.magicapp.org/>), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

Do corticosteroids reduce death or improve recovery in people with sepsis or septic shock? Our panel make a weak recommendation to give corticosteroids to people with all types and severity of sepsis, based on new evidence. Because we are not certain that they are beneficial, it is also reasonable not to prescribe them. Patients' values and preferences may guide this decision-making process.

This rapid recommendation was triggered by two trials, with differing conclusions whose results might change practice:

- **ADRENAL (3658 patients who had septic shock) found no statistically significant difference in 90 day mortality between the hydrocortisone and placebo groups.¹**
- **APROCCHSS (1241 patients who had septic shock) found that hydrocortisone plus fludrocortisone reduced 90 day mortality.²**

The trials are incorporated into a linked systematic review comparing corticosteroids with placebo.³ This *BMJ* Rapid Recommendation promptly and transparently translates this evidence using GRADE methodology for trustworthy guidelines. Sepsis is a life threatening organ dysfunction from infection. Currently most guidelines advise against

giving corticosteroids in sepsis in the absence of refractory shock, but these guidelines have not taken into account the new evidence. We do not anticipate that new clinical trials will substantively alter the evidence suggesting a small but uncertain mortality reduction. The box below shows publications linked in this Rapid Recommendation package. The main infographic provides an overview of the absolute benefits and harms. The table at the end of the article shows any evidence that has emerged since the publication of this guideline.

Current understanding

Sepsis is life threatening organ dysfunction caused by a dysregulated host response to infection.⁴ In practice, a sepsis-related organ failure assessment (SOFA) score of ≥ 2 in patients with infections is sepsis (table 1).^{4 5} Worldwide, about 30 million people are hospitalised with sepsis every year and up to six million of them die.⁶

Clinicians typically manage sepsis with early, broad spectrum antibiotics. They may provide supportive treatment such as vasoactive drugs and mechanical ventilation. They track and adjust treatment based on clinical signs and laboratory data.⁷ Septic shock is the most severe form of sepsis. These patients experience profound circulatory, metabolic, and cellular abnormalities.^{4 8} They require vasopressors to maintain perfusion pressure and have elevated serum lactate concentrations despite adequate fluid repletion.

Linked articles in the *BMJ* Rapid Recommendation cluster

- Lamontagne F, Rochweg B, Lytvyn L, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. *BMJ* 2018;362:k3284
 - Summary of the results from the Rapid Recommendation process
- Rochweg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. *Crit Care Med* 2018. doi:10.1097/CCM.0000000000003262³
 - Review and meta-analysis of all available randomised trials that assessed corticosteroid therapy for sepsis
- MAGICapp (<https://app.magicapp.org/public/guideline/EZ1w8n>)
 - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

WHAT YOU NEED TO KNOW

- Sepsis is a syndrome of life threatening infection with organ dysfunction, and most guidelines do not advise use of corticosteroids to treat it in the absence of refractory shock
- Two new trials of corticosteroid treatment for sepsis came to differing conclusions
- Corticosteroids may reduce the risk of death by a small amount and increase neuromuscular weakness by a small amount, but the evidence is not definitive
- This guideline makes a weak recommendation for corticosteroids in patients with sepsis; both steroids and no steroids are reasonable management options
- Fully informed patients who value avoiding death over quality of life and function would likely choose corticosteroids

Population



- ✓ Recommendation applies to:
- Adults and children
 - Any infectious source
 - Intra abdominal infections
 - Pneumonia
 - Patients with and without shock

- ✗ Recommendation does **not** apply to:
- Patients with pre-existing adrenal insufficiency
 - Non-infectious causes of shock
 - Anaphylactic
 - Cardiogenic
 - Hypovolaemic
 - Neonates
 - Pregnant women

Comparison

Corticosteroid therapy

Intravenous corticosteroids plus usual care



or

No corticosteroid therapy

Usual care only



Corticosteroids

No corticosteroids

Strong

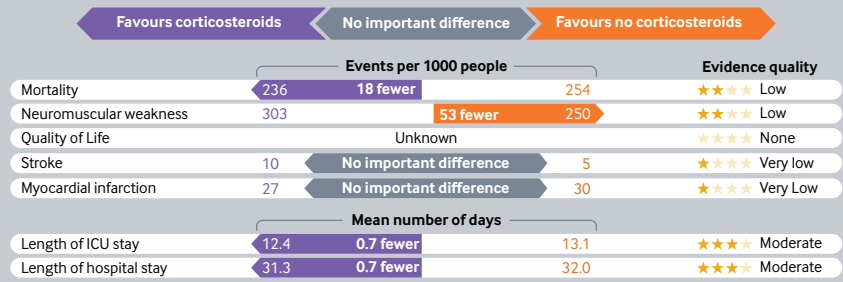
Weak

Weak

Strong

We suggest corticosteroid therapy rather than no corticosteroid therapy. Either option is reasonable.

Comparison of benefits and harms



Key practical issues

Corticosteroids

- Infusion or intermittent bolus dosing
- Monitoring for serum sodium, potassium, and glucose

No corticosteroids

No key practical issues

Preferences and values

Those who place more value on avoiding functional deterioration and maximising quality of life than on avoiding death may be more likely to choose not to use corticosteroids

Risk of death

Patients at greatest risk of death (e.g. those with shock, high qSOFA/SOFA scores) will probably have the greatest reduction in risk of death with corticosteroids

Choice of corticosteroid

There are no clear differences in efficacy or adverse effects between different corticosteroids or corticosteroid combinations. Most studies used hydrocortisone

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Table 1 | Sepsis-related organ failure assessment (SOFA) score to help diagnose sepsis (adapted from Vincent et al⁵)*

System or organ and measure	SOFA score				
	0	1	2	3	4
Respiratory:					
P _a O ₂ /FIO ₂ , mm Hg	≥400	300-399	200-299	100-199 with respiratory support	<100 with respiratory support
Coagulation:					
Platelets, × 10 ³ /μL	≥150	100-149	50-99	20-49	<20
Liver:					
Bilirubin, μmol/L (mg/dL)	<20 (1.2)	20-32 (1.2-1.9)	33-101 (2.0-5.9)	102-204 (6.0-11.9)	>204 (12.0)
Circulatory:					
Mean arterial pressure, mm Hg	≥70	<70	Low dose dopamine or any dose dobutamine	Low-medium dose noradrenalin or adrenalin; medium dose dopamine	High dose noradrenalin, adrenalin, or dopamine
Central nervous system:					
Glasgow Coma Scale score	15	13-14	10-12	6-9	<6
Renal:					
Creatinine, μmol/L (mg/dL)	<110 (1.2)	110-170 (1.2-1.9)	171-299 (2.0-3.4)	300-440 (3.5-4.9)	>440 (5.0)
Urine output, mL/day	–	–	–	<500	<200

*Our recommendation applies to patients with an infection and a SOFA score of ≥2. P_aO₂ = partial pressure of oxygen (arterial). FIO₂ = fraction of inspired oxygen.

Table 2 | Current recommendations for corticosteroid therapy in patients with sepsis

Society	Recommendation regarding corticosteroid use		
	In sepsis	In septic shock	Other situations
"Surviving Sepsis" for SCCM and ESICM, 2016 ⁷	Against	In favour for hypotension refractory to fluid resuscitation and vasopressor	History of adrenal insufficiency or corticosteroid use
CIRCI guidelines for SCCM and ESICM, 2018 ^{12,13}	Against	In favour for shock not responsive to fluid and at least moderate dose vasopressor	Acute respiratory distress syndrome Community acquired pneumonia Bacterial meningitis History of adrenal insufficiency or corticosteroid use
CAEP, 2008 ¹⁴	Against	In favour for haemodynamically unstable patients not responsive to fluid resuscitation and vasopressor	
NICE, 2017 ¹⁵	Not mentioned	Not mentioned	Not mentioned
JSICM, 2018 ¹⁶	Against	In favour for shock not responsive to initial fluid resuscitation and vasoactive drugs	

SCCM = Society of Critical Care Medicine. ESICM = European Society for Intensive Care Medicine. CIRCI = critical illness-related corticosteroid insufficiency. CAEP = Canadian Association of Emergency Physicians. NICE = National Institute for Health and Care Excellence (UK). JSICM = Japanese Society for Intensive Care Medicine.

It is possible that corticosteroids help improve the dys-regulated immune response caused by sepsis⁹ and increase blood pressure if it is low.¹⁰ Some clinicians have found this biological rationale, and results of early studies, compelling. Others disagree and do not use corticosteroids.¹¹

Most professional organisations recommend against corticosteroid use in the absence of refractory shock.¹² Table 2 summarises current professional society guidelines.

The evidence

The linked systematic review identified 42 randomised controlled trials (RCTs) comparing corticosteroids with no corticosteroids (typically placebo).³ Figure 2 provides an overview of the trials and participants.

The systematic review includes total of 10 194 patients who had sepsis. Of the 42 trials included, 24 restricted

enrolment to patients who had septic shock. The typical patient was critically ill—a median of 32% of participants died within the first month. The most common sources of sepsis were pulmonary infections (median 44%) and abdominal infections (median 17%). Most of the RCTs used hydrocortisone alone (n=26), others used hydrocortisone plus fludrocortisone (n=2), methylprednisolone (n=6), prednisolone (n=3), or dexamethasone (n=3) (see fig 2). Although most of the clinical trials included patients who had septic shock, many included patients who did not (16 trials, 2241 patients). The linked systematic review provides detailed trial descriptions, including risk of bias assessments and patient characteristics.³

Subgroups of patients

Corticosteroids did not seem to be more or less effective in particular clinical subgroups, for example:

- Septic shock
- Pneumonia
- Acute respiratory distress syndrome (ARDS)
- Higher baseline risk of death
- Different corticosteroid drugs (such as hydrocortisone, methylprednisolone)
- Different corticosteroid doses
- Different corticosteroid regimens (such as single agents or corticosteroid combinations such as hydrocortisone plus fludrocortisone)
- More recent v older trials
- Trials with higher v lower risk of bias.

Older studies tended to use much higher doses of corticosteroids for a shorter time than are typically used now; the pooled evidence from these older studies is imprecise (few events), and the linked meta-analysis was underpowered to detect important subgroup differences such as by dose. All tests for relative subgroup effects may be underpowered to detect true differences because the effect sizes are small, especially for mortality. Therefore, we cannot be certain that a true subgroup effect does not exist. Future meta-analyses of individual patient data may help to identify populations that benefit more or less from corticosteroids. Until such time, we can only conclude that the evidence applies to all subgroups.

Understanding the recommendation

The main infographic provides an overview including the benefits and harms, and our certainty in the evidence for each outcome.

Absolute benefits and harms

There was better survival in the group taking corticosteroids, but this was not certain. This drives the weak rather than strong recommendation.

Mortality

Corticosteroids may reduce mortality in the first month after admission to an intensive care unit (ICU) by approximately 2%. However, the panel had low certainty that this is true. The confidence interval crosses the line of no difference, and the results were inconsistent, with some RCTs showing a mortality reduction and others showing none.

DATA SOURCES

Use this information to gauge how similar your patients' conditions are to those of people studied in the trials

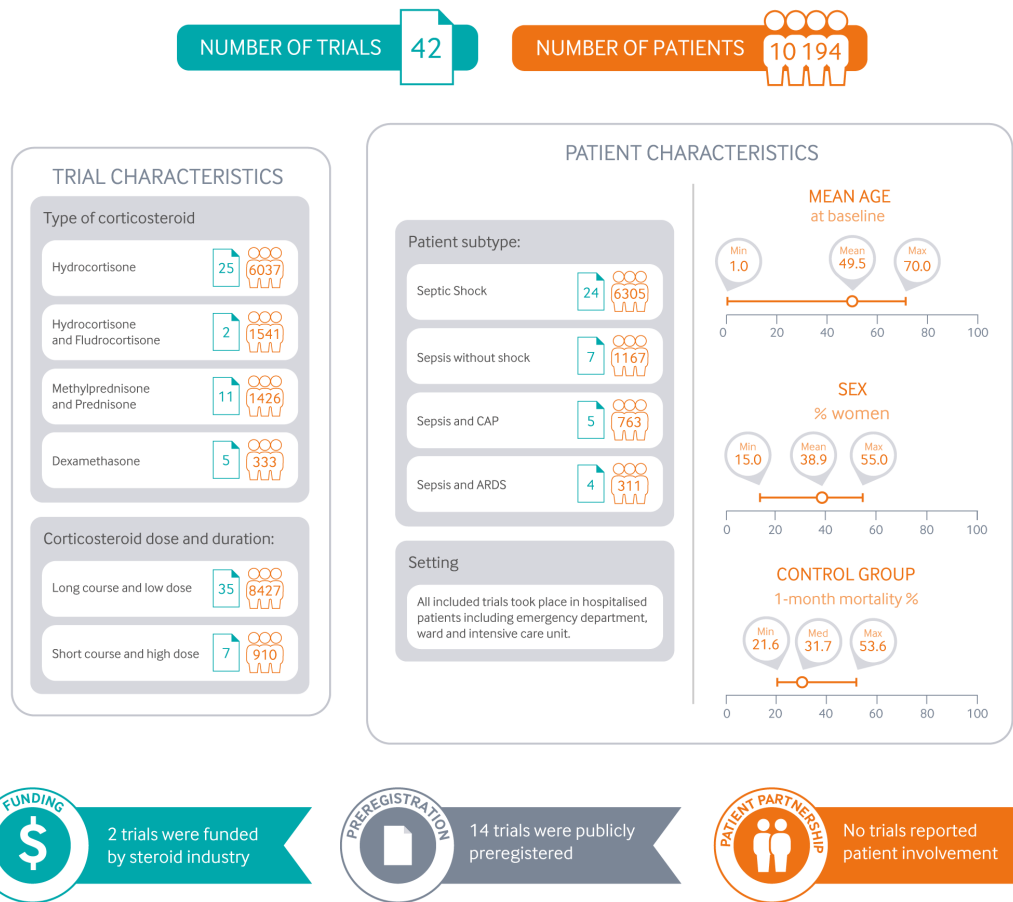


Fig 2 | Characteristics of patients and trials included in systematic review of the use of corticosteroids for treating sepsis³ CAP=community acquired pneumonia. ARDS=acute respiratory distress syndrome.

The effect on longer term mortality (from 60 days to 1 year) was similar. Fewer studies reported this outcome, so, although the results were consistent in the RCTs that did report this outcome, the panel also had low certainty that corticosteroids reduce longer term mortality.

Quality of life

No RCT reported quality of life outcomes at any time point. The ADRENAL study investigators are collecting quality of life data at six months, but these data have not been published.¹⁷

Outcomes of some interest

Corticosteroids may reduce the length of ICU and hospital stay by less than a day each (moderate quality evidence). The impact of corticosteroids on other patient-important outcomes such as stroke and myocardial infarction was extremely uncertain. They may increase the risk of neuromuscular weakness by a small amount (low quality evidence from seven RCTs). Possible explanations include the toxic effects on nerve and muscle cells, and hyperglycaemia from corticosteroid use.¹⁸ Weakness may compromise patients' ability to function independently¹⁹ and delay recovery.²⁰

In two of the seven RCTs evaluating weakness, it was prospectively evaluated one month after enrolment.^{2,21}

Evaluations of neuromuscular weakness, especially in RCTs that relied on investigator identification, were unreliable. The panel therefore believed that the RCTs probably underestimated the risk of neuromuscular weakness.

Outcomes of less importance

Corticosteroids probably increase the risk of hyperglycaemia and hypernatraemia. Corticosteroids probably improve organ function at day 7 and the chance of shock reversal at day 7.

Patient subgroups

Our recommendation applies to all patients with sepsis. There was no meaningful difference in the efficacy of corticosteroids in different groups of patients including those with septic shock, pneumonia, acute respiratory distress syndrome, or other sources of sepsis, or those who were sicker. However, the absolute reduction in mortality from corticosteroids will be greater in patients with a higher risk of death. The absolute harm (such as neuromuscular weakness) will also be greater in sicker patients.

The analysis of a subgroup effect showed no convincing evidence of such an effect. Based on published criteria for credible subgroup effects,²² in the absence of a subgroup

HOW THIS RECOMMENDATION WAS CREATED

Our international panel included sepsis survivors, family caregivers of patients who had sepsis, intensivists, internists, nurses, an endocrinologist, physiotherapists, trialists, and methodologists (see appendix 1 on bmj.com). They decided on the scope of the recommendation and the outcomes that are most important to patients. The panel judged death and quality of life to be the most important outcomes. Myocardial infarction, stroke, duration of stay in hospital and in the intensive care unit (ICU), superinfections, and neuromuscular weakness (such as ICU-acquired weakness) were also identified as important outcomes for patients.

Surrogate outcomes such as time to shock reversal, organ dysfunction measured by the sepsis-related organ failure assessment (SOFA) score, hyperglycaemia, and hypervolaemia were less important to the panel. This view is consistent with GRADE recommendations to focus on patient-important outcomes rather than surrogates.²⁹

Subgroups of interest—The panel wanted to know whether the effect of corticosteroids differed in people with sepsis, compared with people who had septic shock, pneumonia, acute respiratory distress syndrome, or were at higher risk of death.³⁰ They also wanted to know whether the type of corticosteroid or its dose influenced outcomes.

The panel met by videoconference to discuss the evidence and formulate a recommendation. No panel member had financial conflicts of interest; intellectual and professional conflicts were minimised and managed (see appendix 2 on bmj.com).

The panel requested a systematic review of randomised controlled trials on the impact of corticosteroid therapy for patients who have sepsis, including those who have septic shock.³ This review examines the two latest, as well as previous studies, on corticosteroids in sepsis. The aim was to resolve apparently conflicting evidence.

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,³¹ including using the GRADE approach to critically appraise the evidence and create recommendations (see appendix 3 on bmj.com).³² The panel considered the balance of benefits, harms, and burdens of corticosteroids, the quality of the evidence for each outcome, expected variations in patient values and preferences, and acceptability of corticosteroids.³³ Determining patient values and preferences occurred before the panel received the results of the meta-analysis to reduce the risk that opinions regarding outcome importance will be data driven. According to the GRADE approach, recommendations can be strong or weak and for or against a course of action.³³ High quality evidence of an effect on surrogate outcomes do not trigger strong recommendations.

effect, the interpretation of the effect of corticosteroids in any particular subgroup should be guided by the effect in the overall population of septic patients.

Several trials of corticosteroids for pneumonia or acute respiratory distress syndrome have enrolled patients who did not have sepsis; we did not consider these trials. Therefore, clinicians treating these conditions should also consider evidence^{23 24} and guidelines¹² applicable to patients who have pneumonia and acute respiratory distress syndrome.

Patient values and preferences

Fully informed patients who place a higher value on avoiding death than on quality of life and function

would be more likely to choose to receive corticosteroids. We heard from our patient partners that most patients will want to reduce their risk of death, even if this reduction is small and uncertain. This view is consistent with the experiences of the rest of the panel. Most patients will likely be willing to accept a small increased risk of weakness.

Patients (or their care givers and surrogate decision-makers) will probably vary in how they would weigh the balance of expected desirable and undesirable consequences from corticosteroids. We assume that most patients want to avoid death and will value even a small, uncertain reduction in mortality. We judge that they will be less concerned about the possible increase in weakness among survivors. There is also likely to be a sizeable minority of patients who would place a large value on avoiding a very uncertain but possible decline in quality of life and functional abilities even at the cost of a small increase in risk of death.²⁵ Shared decision making conversations about specific interventions in patients with sepsis may not always be feasible, and could delay care. However, clinicians should do their best to elicit each patient's values and preferences. For example, they could talk about the patient's goals of care with the patient, their family, and friends.

Practical considerations

Figure 3 outlines the key practical issues for patients and clinicians discussing corticosteroid treatment for sepsis.

The optimal corticosteroid drug, dose, and duration of treatment are uncertain. Hydrocortisone was the most commonly used corticosteroid in the RCTs and is therefore a reasonable choice. Differences among corticosteroids, if they do exist, are probably small; dexamethasone, methylprednisolone, and prednisolone were also studied and produced similar results. Adding an agent that has additional mineralocorticoid activity, such as fludrocortisone, could be helpful, but that is highly speculative.

The typical hydrocortisone dose for an adult in the RCTs was 200-300 mg/day, given either as an infusion or as boluses every six hours.²⁶ If an infusion is chosen, a bolus of 50-100 mg can be given before the infusion. In the RCTs the duration of treatment was typically 7-14 days, or less for those who were rapidly improving.

Inflammation may recur after discontinuing corticosteroid therapy,²⁷ especially when it is stopped abruptly.²⁸ Clinicians should carefully monitor all patients after discontinuing corticosteroids. In patients who deteriorate after stopping corticosteroids (such as development of shock or need for mechanical ventilation), reinitiating corticosteroid therapy could be helpful, although this is highly speculative. Whether corticosteroids should be tapered rather than stopped abruptly is unclear. Corticosteroid induced adrenal suppression is probably duration dependent, and so patients who receive longer courses of corticosteroids (such as >14 days) might be particularly likely to benefit from a taper before discontinuing and an evaluation of hypothalamo-pituitary-adrenal axis function if in doubt.¹²

PRACTICAL ISSUES








	Corticosteroids	No corticosteroids
 MEDICATION ROUTINE	<ul style="list-style-type: none"> Infusion or intermittent bolus dosing Intravenous dosing initially; can change to oral dosing when stable May require short or long tapering doses before stopping 	
 MONITORING	<ul style="list-style-type: none"> Monitor and treat hyperglycaemia, hypernatraemia, and hypokalaemia Monitor for recurrence of inflammation and signs of adrenal insufficiency after stopping corticosteroids Routine sepsis monitoring including bloodwork 	<ul style="list-style-type: none"> Routine sepsis monitoring including bloodwork
 PREGNANCY	<ul style="list-style-type: none"> FDA Class C: possible increase in cleft lip, low birth weight, and neonatal adrenal insufficiency 	
 EMOTIONAL WELL-BEING	<ul style="list-style-type: none"> Can cause insomnia and lead to psychiatric adverse effects in some people, including mania and psychosis in some predisposed individuals 	
 COSTS & ACCESS	<ul style="list-style-type: none"> Inexpensive, widely available The corticosteroid drugs evaluated in RCTs are all considered essential medications by the World Health Organization Impact on healthcare costs remain unclear 	
 FOOD & DRINK	<ul style="list-style-type: none"> Can be given with or without food When taken orally, corticosteroids should be taken with food when possible 	
 RECOVERY	<ul style="list-style-type: none"> Consider early physical therapy 	<ul style="list-style-type: none"> Consider early physical therapy

Fig 3 | Practical issues about use of corticosteroids for treatment of sepsis

Costs

Corticosteroids are typically inexpensive and widely available. The impact of corticosteroids on the overall costs to patients and to health systems is uncertain and would be driven mostly by ICU and hospital lengths of stay or prolonged periods of rehabilitation.

Future research

With the exception of the awaited analysis of quality of life in the ADRENAL trial, there are currently no planned or ongoing RCTs in patients who have sepsis that are likely to substantively change the overall effect estimates for the key outcomes. Given remaining uncertainty regarding the

New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

effect of corticosteroids in different subgroups, additional analyses of existing data to explore heterogeneity of treatment effects are logical next steps before more patients are enrolled in similar trials. Such work mandates individual patient-data meta-analyses that rely on investigators sharing the data from their RCTs and cooperation among research networks.

It is possible that additional adaptive RCTs could help to resolve remaining uncertainty. Key research questions to inform decision makers and future guidelines are:

- What is the impact of corticosteroid therapy on quality of life in the short and long term?
- What is the impact of corticosteroid therapy on functional recovery?
- What is the impact of corticosteroid therapy on healthcare costs?
- Are there subgroups of patients with sepsis who benefit more or less from corticosteroid therapy?
- Are there differences between bolus and infusion dosing?
- Does the addition of fludrocortisone improve outcomes?

Updates to this article

The final table shows evidence that has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

Competing interests: All authors have completed the *BMJ* Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 2 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

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Transparency: R A C Siemieniuk affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

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