BMJ Rapid Recommendation: Corticosteroids for sepsis

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A BMJ Rapid Recommendation on corticosteroids for sepsis.

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Sections

Summary of recommendations

1 - Corticosteroids for sepsis

Weak Recommendation

In patients with sepsis, we suggest corticosteroid therapy rather than no corticosteroid therapy.

1 - Corticosteroids for sepsis

A *BMJ* Rapid Recommendation

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Weak Recommendation

In patients with sepsis, we suggest corticosteroid therapy rather than no corticosteroid therapy.

Practical Info

The optimal corticosteroid drug, dose, and duration of treatment are not known. 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. The effect of adding an agent that has additional mineralocorticoid activity such as fludrocortisone remains speculative. A typical hydrocortisone dose for an adult is 200 to

300mg/day, given either as an infusion or as boluses every 6 hours. If an infusion is chosen, a bolus of 50-100mg can be given before the infusion. A reasonable duration of therapy is similar to that used in the RCTs, which was typically 7 to 14 days, with a shorter course in those who were rapidly improving.

Key Info

Benefits and harms

Small net benefit, or little difference between alternatives

Corticosteroids may reduce short-term and longer-term mortality by approximately 2%. The increased risk of neuromuscular weakness may be approximately 5%. Corticosteroids probably reduce intensive care unit and hospital length of stay, on average, by less than one day.

Quality of evidence

Very Low

Quality of evidence is lower for most outcomes because of imprecision: although there are many patients and randomised trials, the confidence intervals include a very small unimportant effect, or no effect at all for almost all of the critical patient-important outcomes. For short-term mortality, there was borderline inconsistency (some studies reported an effect while others showed no effect) and we therefore further rated down the quality of evidence to low. For neuromuscular weakness, there was indirectness: studies used different measurement tools and it is not clear whether or not the magnitude of impact would lead to patient-important harm or not.

There is no evidence to inform the effect of corticosteroids on quality of life.

Preference and values

Substantial variability is expected or uncertain

Most patients are likely to place a high value on avoiding death, even if the reduction in the risk of death is small and uncertain, and place a smaller value on possible increase in functional deficits from 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.

Resources and other considerations

Important issues, or potential issues not investigated

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.

Rationale

Most patients are likely to place a high value on avoiding death, even if the reduction in the risk of death is small and uncertain, and place a smaller value on possible increase in functional deficits from weakness among survivors. Thefore, we suggest using corticosteroids in most patients, despite the fact that we are not sure that corticosteroids do in fact reduce the risk of death. However, there is probably substantial variability among patients and their caregivers in how they would weigh the balance of expected desirable and unseriable consequences. Therefore, the recommendation is weak rather than strong.

Clinical Question/ PICO

Population: Patients with sepsis
Intervention: Corticosteroids
Comparator: No corticosteroids

Summary

Corticosteroids may reduce mortality in the first month after ICU admission by approximately 2%, but certainty that corticoteroids confer a short-term mortality reduction is low. The effect on longer-term mortality (ie., 90 days to 1 year) was

similar to short-term mortality, except that the results were consistent and therefore certainty in evidence is moderate. However, no RCT has yet reported quality of life outcomes at any time point. Corticosteroids may increase the risk of neuromuscular weakness by a small amount (low certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No corticosteroids	Corticosteroids	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Mortality Longer term (60 days to 1 year)	Relative risk 0.94 (CI 95% 0.89 - 1) Based on data from 6,438 patients in 9 studies. (Randomized controlled) Follow up 60 days-1 year	**371** per 1000	**349** per 1000 Difference: **22 fewer** per 1000 (CI 95% 41 fewer - 0 fewer)	**Low** Due to serious imprecision and indirectness [1]	Corticosteroids possibly achieve a small reduction in long-term mortality.
Mortality Short term (28-31 days)	Relative risk 0.93 (CI 95% 0.84 - 1.03) Based on data from 9,433 patients in 36 studies. (Randomized controlled) Follow up 14-30 days	**254** per 1000	**236** per 1000 Difference: **18 fewer** per 1000 (CI 95% 41 fewer - 8 more)	**Low** Due to serious imprecision; borderline inconsistency and publication bias. [2]	Corticosteroids may achieve a small or no reduction in short-term mortality.
Shock reversal 1 week	Relative risk 1.26 (CI 95% 1.12 - 1.42) Based on data from 2,802 patients in 13 studies. (Randomized controlled) Follow up 7 days	**464** per 1000	**585** per 1000 Difference: **121 more** per 1000 (CI 95% 56 more - 195 more)	**High**	Corticosteroids increase the chance of shock reversal in the first week.
Neuromuscular weakness	Relative risk 1.21 (CI 95% 1.01 - 1.45) Based on data from 6,178 patients in 7 studies. (Randomized controlled)	**250** per 1000	**303** per 1000 Difference: **53 more** per 1000 (CI 95% 3 more - 113 more)	**Low** Due to serious imprecision and indirectness and borderline inconsistency. [3]	Corticosteroids may increase the risk of neuromuscular weakness.
Gastrointestinal bleeding	Relative risk 1.09 (CI 95% 0.86 - 1.38) Based on data from 4,243 patients in 17 studies. (Randomized controlled)	**35** per 1000	**38** per 1000 Difference: **3 more** per 1000 (CI 95% 5 fewer - 13 more)	**Low** Due to serious indirectness and imprecision. [4]	Corticosteroids may have little or no difference on gastrointestinal bleeding

Neuropsychiatric events	Relative risk 0.58 (CI 95% 0.33 - 1.03) Based on data from 1,004 patients in 5 studies. (Randomized controlled)	**59** per 1000	**34** per 1000	Difference: **25 fewer** per 1000 (CI 95% 40 fewer - 2 more)	**Low** Due to serious imprecision and serious indirectness. [5]	Corticosteroids may achieve a small reduction in neuropsychiatric events.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies. (Randomized controlled)	**36** per 1000	**59** per 1000	Difference: **23 more** per 1000 (CI 95% 12 more - 37 more)	**Moderate** Due to serious indirectness [6]	Corticosteroids probably increase the risk of hypernatremia.
Superinfection	Relative risk 1.02 (CI 95% 0.89 - 1.18) Based on data from 4,519 patients in 21 studies. (Randomized controlled)	**161** per 1000	**164** per 1000	Difference: **3 more** per 1000 (CI 95% 18 fewer - 29 more)	**Low** Due to serious imprecision and serious indirectness [7]	Corticosteroids may have little or no difference on superinfection.
Stroke	Relative risk 2.07 (CI 95% 0.45 - 9.61) Based on data from 1,105 patients in 3 studies. (Randomized controlled)	**5** per 1000	**10** per 1000	Difference: **5 more** per 1000 (CI 95% 3 fewer - 43 more)	**Very Low** Due to serious indirectness and very serious imprecision [8]	Whether or not corticosteroids impact the risk of stroke is uncertain.
Myocardial infarction	Relative risk 0.91 (CI 95% 0.45 - 1.82) Based on data from 1,080 patients in 3 studies. (Randomized controlled)	**30** per 1000	**27** per 1000	Difference: **3 fewer** per 1000 (CI 95% 16 fewer - 25 more)	**Very Low** Due to serious indirectness and very serious imprecision [9]	Whether or not corticosteroids impact the risk of myocardial infarction is uncertain.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.24) Based on data from 7,563 patients in 15 studies. (Randomized controlled)	**181** per 1000	**210** per 1000	Difference: **29 more** per 1000 (CI 95% 14 more - 43 more)	**Moderate** Due to serious indirectness. [10]	Corticosteroids probably increase the risk of hyperglycaemia.
ICU length of stay	Measured by: days Based on data from: 7,463 patients in 20 studies. (Randomized controlled)	**13.13** days (Mean)	**12.4** days (Mean)	Difference: **MD 0.73 fewer** (CI 95% 1.78 fewer - 0.31 more)	**Moderate** Due to serious imprecision [11]	Corticosteroids probably achieve a small reduction in the duration of initial ICU stay.
Hospital length of stay	Measured by: days	**32.03**	**31.3**		**Moderate** Due to serious	Corticosteroids probably achieve a small reduction

	Based on data from: 7,706 patients in 18 studies. (Randomized controlled)	days (Mean)	days (Mean)	imprecision [12]	in the duration of hospitalization.
		Difference: **MD 0.73 fewer** (CI 95% 2.06 fewer - 0.6 more)			
Organ dysfunction 1 week	Measured by: Sepsis-related organ failure assessment (SOFA) score Scale: 0-24 Lower better Based on data from: 1,986 patients in 9 studies. (Randomized controlled) Follow up 7 days	**7.61** points (Mean)	**6.22** points (Mean)	**High**	Corticosteroids decrease organ dysfunction at 7 days.
		Difference: **MD 1.39 lower** (CI 95% 1.88 lower - 0.89 lower)			
Quality of Life 9 Critical					Not reported in any of the included studies.

Practical issues	No corticosteroids	Corticosteroids	Both
 Medication routine Dosing regimen		Can be given as a continuous infusion or intermittent dosing 1 to 6 times per day.	
 Medication routine Administration route		Administered intravenously or intramuscularly initially; can be changed to oral administration afterwards.	
 Medication routine Stopping		Can sometimes be stopped abruptly. May need to be tapered over days to weeks or months.	
 Tests and visits Corticosteroid effects		Monitor for hyperglycaemia, hypernatraemia, and hypokalaemia	

	Tests and visits Monitoring after treatment		Monitor closely for recurrence of inflammation and signs of adrenal insufficiency after stopping corticosteroids
	Tests and visits Monitoring	Routine sepsis monitoring including regular bloodwork	Routine sepsis monitoring including regular bloodwork
	Pregnancy and nursing Safety in pregnancy		FDA Class C: possible increase in cleft lip, low birth weight, and neonatal adrenal insufficiency
	Emotional well-being Emotional well-being		Can cause insomnia and lead to psychiatric adverse effects in some people, including mania and psychosis in some predisposed individuals
	Costs and access		Inexpensive, widely available. They are considered essential medications by the World Health Organization
	Food and drinks Dosing and food		Can be given with or without food. When taken orally, corticosteroids should be taken with food when possible.
	Recovery and adaptation Recovery	Consider early physical therapy.	Consider early physical therapy.

1. **Risk of bias: No serious .** Note that all studies that reported 90 day to 1 year mortality also reported 28-30 day mortality: the CI 95% around the pooled effect for short term mortality also excludes no effect: RR 0.91 (CI 95% 0.84 - 0.98). ; **Inconsistency: No serious . Indirectness: Serious .** Only a small proportion of studies reported longer-term mortality. ; **Imprecision: Serious .** Confidence interval includes no effect. ; **Publication bias: No serious .**
2. **Inconsistency: No serious .** There is borderline inconsistency (I2=37%). Fixed effect analysis: risk ratio 0.93 (CI 95% 0.88 - 0.99). ; **Indirectness: No serious . Imprecision: Serious . Publication bias: Serious .** There was also borderline publication bias (some visual

asymmetry in the funnel plot, but statistical tests (Egger's test and the Trim and Fill method) did not detect statistically significant small study effects (P=0.12). ;

3. **Inconsistency: No serious . Indirectness: Serious .** Variable time of assessment. Variable assessment tool utilized. ; **Imprecision: Serious .** Confidence interval includes no difference. ; **Publication bias: No serious .**
4. **Inconsistency: No serious . Indirectness: Serious .** Variable definition of GI bleeding. Varying magnitude/clinical significance of GI bleeding. All decrease our certainty in this effect estimate. ; **Imprecision: Serious .** Confidence interval includes no difference. ; **Publication bias: No serious .**
5. **Inconsistency: No serious . Indirectness: Serious .** Variable time of assessment. Variable assessment tool utilized. Varying magnitude. All decrease our certainty in this effect estimate. ; **Imprecision: Serious .** Confidence interval includes no difference. ; **Publication bias: No serious .**
6. **Inconsistency: No serious . Indirectness: Serious .** Variable time of assessment. Variable assessment tool utilized. Varying magnitude. All decrease our certainty in this effect estimate. ; **Imprecision: No serious . Publication bias: No serious .**
7. **Inconsistency: No serious . Indirectness: Serious .** Variable time of assessment. Variable assessment tool utilized. Varying magnitude. All decrease our certainty in this effect estimate. ; **Imprecision: Serious .** Confidence interval includes important harm. ; **Publication bias: No serious .**
8. **Inconsistency: No serious . Indirectness: Serious .** Unclear how this outcome was abstracted or ascertained. Unclear clinical impact of these stroke or MI events. ; **Imprecision: Very Serious .** Very few events and only 2 studies. ; **Publication bias: No serious .**
9. **Inconsistency: No serious . Indirectness: Serious .** Unclear how this outcome was abstracted or ascertained. Unclear clinical impact of these stroke or MI events. ; **Imprecision: Very Serious .** Very few events and only 1 study. ; **Publication bias: No serious .**
10. **Inconsistency: No serious . Indirectness: Serious .** Variable time of assessment. Variable assessment tool utilized. Varying magnitude. All decrease our certainty in this effect estimate. ; **Imprecision: No serious . Publication bias: No serious .**
11. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious .** Confidence interval includes no difference. ; **Publication bias: No serious .**
12. **Inconsistency: No serious . Indirectness: No serious . Imprecision: Serious . Publication bias: No serious .**

References