

Hydrocortisone therapy for patients with septic shock

In patients with septic shock, the administration of corticosteroids leads to faster resolution of shock but has no effect on mortality at 28 days or at one year.

Level of evidence: 1* (RCT with a low risk of bias)

Appraised by: Kevin Sim

Citation: Sprung CL, Annane D, Keh D *et al.* Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358: 111-24.

Lead author: Charles L Sprung

Three-part clinical question:

Patients: Patients with septic shock.

Intervention: Corticosteroids.

Outcome: (Primary) 28-day mortality, (Secondary) one-year mortality, superinfection rates, time to reversal of shock.

Search terms: Septic shock; corticosteroids.

The study: Double-blinded randomised controlled trial with intention-to-treat analysis.

The study patients: Adults (18 years and over) with onset of

septic shock within the previous 72 hours and hypoperfusion or organ dysfunction due to sepsis. (Septic shock defined as: infection with SIRS and systolic BP <90 mm Hg despite adequate fluid replacement or a need for vasopressors for at least one hour). It is important to note that these inclusion criteria differ from those used by Annane (*JAMA*, 2002).

Control group (N=248; 248 analysed): Placebo was an identical white powder made up in identical ampoules of injectable water and was indistinguishable from active drug.

Experimental group (N=251; 251 analysed): Hydrocortisone 50 mg.

Active drug and placebo were given as a bolus every six hours for five days, then every 12 hours for days 6 to 8, then every 24 hours on days 9 to 11 and then stopped.

The evidence:

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
28-day mortality	28 days	0.315	0.343	-9%	-0.028	-36
		95% confidence intervals:		ns	ns	ns
One-year mortality	one year	0.512	0.546	-7%	-0.034	-29
		95% confidence intervals:		ns	ns	ns
Superinfection	variable	0.246	0.311	-26%	-0.065	-15
		95% confidence intervals:		ns	ns	ns

Non-event outcomes	Time to outcome/s	Control group	Experimental group	P-value
Time to resolution of shock	variable	5.8 days (95% CI 5.2 to 6.9)	3.3 days (95% CI 2.9 to 3.9)	<0.001

Results in non responders to corticotropin 250 micrograms (defined as an increase of less than 248 nmol/L)

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
28-day mortality	28 days	0.361	0.392	-9%	-0.031	ns
		95% confidence intervals:		ns	ns	ns
One-year mortality	one year	0.556	0.584	-5%	-0.028	ns
		95% confidence intervals:		ns	ns	ns

Non-event outcomes	Time to outcome/s	Control group	Experimental group	P-value
Time to resolution of shock	variable	6.0 (95% CI 4.9 to 9.0)	3.9 (95% CI 3.0 to 5.2)	<0.001

Results in responders to corticotropin 250 micrograms (defined as an increase of more than 248 nmol/L)

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
28-day mortality	28 days	0.287	0.288	0%	-0.001	ns
		95% confidence intervals:		ns	ns	ns
One-year mortality	one year	0.493	0.517	-5%	-0.024	ns
		95% confidence intervals:		ns	ns	ns

Non-event outcomes	Time to outcome/s	Control group	Experimental group	P-value
Time to resolution of shock	variable	5.8 (95% CI 5.2 to 6.9)	2.8 (95% CI 2.1 to 3.3)	<0.001

EBM comments:

1. *Do the methods allow accurate testing of the hypothesis?* **Yes.** This is a well designed, well conducted clinical trial, however slow recruitment led to it being relatively underpowered with only 500 patients recruited when the target had been 800.
2. *Do the statistical tests correctly test the results to allow differentiation of statistically significant results?* **Yes.**
3. *Are conclusions valid in light of the results?* **Yes.** The authors conclude that hydrocortisone cannot be recommended as general adjuvant therapy for septic shock, nor can corticotropin testing be recommended to determine which patients should receive hydrocortisone therapy.
4. *Did results get omitted, and why?* **Yes.** One patient withdrew consent and was not analysed.
5. *Did they suggest areas of further research?* **No.**
6. *Did they make any recommendations based on the results and were they appropriate?* **No.**
7. *Is the study relevant to my clinical practice?* **Yes.** The patients recruited appear to be representative of a typical cohort of patients with septic shock that may be found in Scottish ICUs.
8. *What level of evidence does this study represent?* **1+**
9. *What grade of recommendation can I make on this result alone?* **B**
10. *What grade of recommendation can I make when this study is considered along with other available evidence?* **B**
11. *Should I change my practice because of these results?* **Yes.** In view of the lack of efficacy and possible increase in adverse effects, if you currently use corticosteroids routinely in patients with septic shock or following a synacthen test you should review your practice. It may be appropriate to continue using steroid therapy "in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy" as stated in the surviving sepsis criteria. This would match the patient sub group identified as benefiting from steroids by Annane (JAMA, 2002).
12. *Should I audit my current practice because of these results?* **Yes.** If you use corticosteroids in septic shock you should audit your rate of complications associated with this.

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