Critical Review Form
Therapy

PGY-1

Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008 Jan 10;358(2):111-24.

Objectives: **To evaluate "the efficacy and safety of low-dose hydrocortisone therapy in a broad population of patients with septic shock — in particular, patients who had had a response to a corticotropin test, in whom a benefit was unproven." (p. 112)**

Methods: **This international, multi-center, prospective, randomized controlled trial was conducted at 52 intensive care units (ICUs) between March 2002 and November 2005. Patients 18 years of age or older with clinical evidence of infection with a systemic response, onset of shock within the previous 72 hours, and hypoperfusion or organ dysfunction were eligible. Shock was defined as a systolic blood pressure (SBP) < 90 mm Hg despite adequate fluid resuscitation or need for vasopressors for at least one hour. Exclusion criteria were underlying disease with poor prognosis, life expectancy < 24 hours, immunosuppression, and long-term steroid use.**

Patients were randomized in a 1:1 fashion to receive either hydrocortisone (50 mg IV bolus every 6 hours for 5 days, followed by a taper over the next 6 days) or placebo. The primary endpoint was death at 28 days in patients who did not have a response to corticotropin on stimulation testing. Secondary endpoints included death at 28 days in patients who did have a response to corticotropin, death at 28 days in all patients, rates of death in the ICU and in-hospital, rates of death at one year, reversal of organ system failure and shock, and duration of stay in the ICU and in the hospital. Adverse events, including superinfection, were monitored.

A total of 500 patients were enrolled, though one patient in the hydrocortisone group was excluded due to withdrawal of consent. Of the remaining 499 patients, 251 were assigned to receive hydrocortisone (125 with no response to corticotropin) and 248 were assigned to receive placebo (108 with no response to corticotropin). The median age in both groups was 63 years and 66% and 67% were male in the hydrocortisone and placebo groups, respectively.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	

1.	Were patients randomized?	Yes Patients were randomized in a 1:1 fashion to either hydrocortisone or placebo.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Randomization...was stratified according to study center in blocks of four with the use of a computerized random-number generator list provided by a statistician who was not involved in the determination of eligibility, administration of a study drug, or an assessment of outcomes." (p. 112) This should be sufficient to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. This was an intention to treat analysis. "Eighty-seven percent of patients in both the hydrocortisone group and the placebo group received at least 90% of the doses of a study drug." (p. 114) Those patients who did not receive all of the study drug were still analyzed in their allocation groups.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, previous medical history, admission type (medical vs. surgical), baseline vital signs, SOFA score, and type of vasopressor administered.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "In each center, the study drug (hydrocortisone or placebo) was sealed in sequentially numbered, identical boxes that contained the en- tire treatment for each patient to be administered sequentially." (p. 112) "All patients, medical and nursing staff members, pharmacists, investigators, and members of the monitoring board remained unaware of study-group assignments throughout the study period." (pp. 112-113)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	No. See above.

4.	Was follow-up complete?	Uncertain. The authors do not mention any loss to follow-up, but also do not specify how one-year follow-up occurred. Follow-up data should have been available for all other ICU- and hospital-based outcomes.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• There was no significant difference in 28-day mortality among patients who did not respond to corticotropin (39.2% in the hydrocortisone group vs. 36.1% in the placebo group; RR 1.09, 95% CI 0.77 to 1.52). • There was also no significant difference in 28-day mortality among those who responded to corticotropin (RR 1.00, 95% CI 0.68 to 1.49) or among all patients (RR 1.09, 95% CI 0.84 to 1.41). • Similarly, rates of death in the ICU, death during hospitalization, and death at one year were similar between the two treatment groups when looking at those who responded, those who did not respond, and all patients. • ICU length of stay was similar between hydrocortisone and placebo groups: median 17±19 days vs. 17±17 days among non-responders; 18±22 vs. 19±16 days among responders; and 19±31 vs. 18±17 days among all patients. Hospital length of stay was also similar in all scenarios. • While reversal of shock occurred at a similar rate among patients receiving hydrocortisone and placebo in all three subgroups, the duration of time until reversal was shorter among patients receiving hydrocortisone among all patients ($p < 0.001$) and among those who responded to corticotropin ($p < 0.001$).
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Likely yes. Although this was an international study, only patients with septic shock were included and would hence likely be similar to such patients seen at our institution. The study also began 16 years ago, and there may be some

		changes in the management of septic shock (including treatment algorithms, use of lung protective ventilation, and antibiotic choices) that could affect outcomes in general (external validity).
2.	Were all clinically important outcomes considered?	No. The most clinically relevant patient-centered outcomes were considered, including short and long-term mortality. The authors did not address other potential complications of sepsis and need for vasopressor therapy, including limb ischemia, need for renal replacement therapy, or duration of mechanical ventilation.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. Based on this study, hydrocortisone did not improve mortality when used in a broad cohort of patients with septic shock, though it did reduce the duration of shock. The study was limited in part because they allowed enrollment up to 72 hours after onset of shock; it is possible that earlier administration of steroids would result in improved outcomes (as observed in the Annane trial).

Limitations:

1. **Although the authors calculated a target sample size of 800 patients in their power calculations, only 499 (62%) were included in the final analysis. The study may hence have been underpowered to detect a clinically meaningful improvement in outcomes.**

2. **Patients were enrolled up to 72 hours after onset of shock; it is possible that earlier administration of steroids would result in improved outcomes (as observed in the Annane trial).**

3. **This study enrolled overall less sick patients than the Annane study, which only enrolled patients with persistent hypotension. In that study, the SAPS II score was higher and mortality in the placebo group was twice that observed in this study.**

4. **One quarter of culture-positive patients in the study did not receive appropriate antibiotics (Daley 2008).**

Bottom Line:

This international, multicenter trial evaluating the efficacy of hydrocortisone in patients with septic shock found decreased time to reversal of shock with no improvements in rate of reversal or shock or mortality. The clinical significance of this reduction in duration of septic shock is unclear. This study overall enrolled less

sick patients compared to prior studies, and allowed patients to be enrolled up to 72 hours after onset of shock, potentially missing a benefit when steroids are administered earlier in the course of illness.