"Hydrocortisone therapy for patients with septic shock."
NEJM, 2008; 358:111-24.

Background

- Steroid therapy in patients with septic shock has been widely used despite a survival benefit demonstrated only in patients with hypotension refractory to fluid and vasopressor resuscitation *and* who lacked an appropriate rise in cortisol serum levels after a corticotropin stimulation test.
- High dose corticosteroid treatment became an accepted therapy in 1976 after Schumer showed a significant mortality decrease with septic shock patients.
- A prior study (Annane et al.) demonstrated decreased risk of death in nonresponders to ACTH with septic shock after a 7 day treatment of low dose hydrocortisone and fludrocortisone
- A 1984 study by Sprung et al., showed an increased incidence of reversal of shock and improved survival in patients who received high-dose steroid treatment within 4 hours

Hypothesis

- The use of hydrocortisone therapy should improve morbidity and mortality rates in patients with sepsis who did have a response to corticotropin stimulation testing, the CORTICUS trial (Corticosteroid Therapy of Septic Shock study)

Study Design

Study type: Double-blinded, RCT
Setting: Intensive care units at 52 participating medical centers
Time period: Patients recruited from 3/02 until 11/05
Inclusion Criteria:

- Clinical evidence of infection within the preceding 72 hours
- Evidence of systemic response to infection within the preceding 24 hours
- Onset of shock within the preceding 72 hours
- Informed consent

Exclusion Criteria: Pregnancy, Age < 18 years old, underlying disease or cancer with prognosis of survival <3 months, CPR within the preceding 72 hours, drug-induced immunosuppression including chemotherapy and/or radiation within the preceding 4 wks, use of chronic steroids within the last 6 months or the acute use of steroids within the past 4 weeks, HIV, presence of a DNR order, acute MI or PE, participation in another experimental drug study within the last 30 days, patients likely to die within 24 hours, patients treated in the ICU for >2 months
Randomization: N = 500, were randomized into two groups (one patient withdrew consent). Fifteen patients (8 in hydrocortisone group, 7 in placebo group were excluded based on exclusion criteria).
The groups were further sub-divided into patients who did and did not respond appropriately to an ACTH stimulation test (response was determined positive if cortisol levels increased by 9mcg/dL one hour after administration of cosyntropin).

- Hydrocortisone (N = 251): Received hydrocortisone 50mg iv q6hr x5days, then tapered to 50mg iv q12hr for Day 6-8, then 50mg iv daily for Days 9-11 (total 29 doses).
    - Responders: (N=118)
    - Non-responders: (N=125)
- Placebo (N = 248): Received placebo medication 50mg iv q6hr x5days, then tapered to 50mg iv q12hr for Day 6-8, then 50mg iv daily for Days 9-11 (total 29 doses).
    - Responders: (N=136)
    - Non-responders: (N=108)

Patient characteristics: Characteristics between groups were similar. Average age of patients 63 years old. Patients were also evaluated for similarities in previous disease states, sex, race, and admission category. Patients were also similar in current severity of illness, as evaluated by vital signs and SAPS II and SOFA scores. Additionally, the use of vasopressors, antibiotics, and etomidate were included in the demographic data.
Outcomes:

- Primary Outcome: Mortality = rate of death at 28 days
- Secondary Outcome: Reversal of Shock

The evidence

	Controls		Cases		Relative Risk (RR)		Relative Risk Reduction (RRR)		Absolute Risk Reduction (ARR)		Number Needed to Treat (NNT)	
	Control Event Rate (CER)		Experimental Event Rate (EER)		EER/CER		1 – RR		CER – EER		1/ARR	
	Res	Non	Res	Non	Res	Non	Res	Non	Res	Non	Res	Non
Mortality at 28 d	39/136 (28.7%)	39/108 (36.1%)	34/118 (28.8%)	49/125 (39.2%)	1.00	1.09	0	-0.1	0	0	∞	∞
Reversal of Shock	104/136 (76.5%)	76/108 (70.4%)	100/118 (84.7%)	95/125 (76.0%)	1.11	1.08	-0.1	-0.1	0	0	∞	∞

Comments

- Hydrocortisone therapy showed no significant effect on the rate of death in patients with septic shock regardless of patients' adrenal responsiveness.
- Hydrocortisone did, however, hasten shock reversal in those in whom shock was reversed, although the number of people in whom shock was reversed was unaffected.
- In the hydrocortisone group there was an increase in super infection, including new episodes of sepsis and septic shock.
- Of note there was an increase rate of death in patients who received etomidate in both groups, rate of death with etomidate 45.1% (steroid) and 40% (placebo) vs. 31.5.% (steroid) and 29.6% (placebo) p=0.03
- Limitations of CORTICUS trial include the lack of statistical power since a sample size of 800 was needed to achieve a statistical power of 80%

References

Schumer W. Steroids in the treatment of clinical septic shock. Ann Surg 1976;184:333-41

Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. N Engl J Med 1984;311:1137-43

Annane S, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71