Critical Review Form
Therapy

PGY-2

Keh D, Trips E, Marx G, et al; SepNet–Critical Care Trials Group. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. JAMA. 2016 Nov 1;316(17):1775-1785.

Objectives: **To evaluate the hypothesis that "early hydrocortisone administration might prevent shock development...in patients with severe sepsis presenting without shock." (p. E2)**

Methods: **This multicenter, placebo-controlled, double-blind randomized controlled trial was conducted at 34 sites in Germany between January 13, 2009 and August 27, 2013. Adult patients aged 18 years or older in an intensive care unit (ICU) or intermediate care unit with sepsis (evidence of infection and at least 2 SIRS criteria) and evidence of organ dysfunction but without septic shock (hypotension despite adequate volume resuscitation or use of vasopressors) for no more than 48 hours were eligible for enrollment. Exclusion criteria were known hypersensitivity to hydrocortisone or mannitol, use of a glucocorticoid medication with need for continuation of therapy, or other indications for treatment with glucocorticoids.**

Patients were randomized to hydrocortisone (50 mg IV bolus followed by a continuous infusion of 200 mg per day for 5 days, 100 mg on days 6 and 7, 50 mg on days 8 and 9, and 25 mg on days 10 or 11) or placebo (mannitol). The primary endpoint was occurrence of septic shock within 14 days or until discharge from the ICU. Secondary endpoints included time until development of septic shock or death, mortality, "vital status" at days 28, 90, and 180, length of ICU and hospital stay, duration of mechanical ventilation, and need for renal replacement therapy.

A total of 9953 patients with severe sepsis or septic shock were screened, of whom 380 were randomized. One hundred and ninety patients were randomized to each group. Twenty-seven patients (14 in the placebo group and 13 in the hydrocortisone group) were excluded, primarily due to issues with consent, leaving 353 patients in the intention to treat analysis (176 in the placebo group and 177 in the hydrocortisone group). The mean age was 65 years and 64.9% were male. There were 322 patients included in the per protocol analysis.

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. "Randomization was stratified by participating center and sex. It was performed with an internet-based computerized randomization tool that uses a modified version of the Pocock minimization algorithm with a random component to generate balanced 1:1 randomization in the strata at any time." (p. E2)
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. The use of an internet-based randomization tool should keep randomization allocation concealed, although the exact mechanism of medication box delivery was not detailed.
3.	Were patients analyzed in the groups to which they were randomized?	Mostly yes. In the flow sheet provided, 3 patients are reported as being excluded in the hydrocortisone group because they did not receive the study medication. Otherwise, all patients in the intention to treat analysis were analyzed according to their group allocation. A secondary per protocol analysis was also conducted.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to gender, age, type of admission (surgical vs. medical), baseline SOFA and APACHE II scores, organ dysfunction, and administration of etomidate. Pneumonia was the source of infection more often in the placebo group compared to the hydrocortisone group (53.4% vs. 37.6%).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "The study medication (hydrocortisone and placebo) was produced and released by BAG Health Care GmbH. The medication was delivered in boxes, each containing 17 brown glass vials for 1 patient. Each vial contained 100 mg of lyophilized hydrocortisone hydrogen succinate or the same amount of lyophilized mannitol as placebo, which was indistinguishable from hydrocortisone." (p. E3) "All patients, study personnel, sponsors, medical staff, and nursing staff were blinded regarding the allocation of study medication throughout the entire

		study period." (pp. E2-3)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	Uncertain. The authors do not specifically mention blinding of outcome assessors, though it seems likely that they would be blinded.
4.	Was follow-up complete?	No. Nine patients (~5%) were lost to follow-up in each group. Six of those, in each group, were lost to follow-up by day 28. This is still good follow-up.
II.	**What are the results ?**	

1.	How large was the treatment effect?	• There was no significant difference in rates of progression to septic shock between hydrocortisone and placebo groups:
		  ○ In the ITT analysis, rates were 21.2% vs. 22.9%, absolute risk reduction (ARR) of -1.8% (95% CI -10.7% to 7.2%).
		  ○ In the per protocol analysis, rates were 18.7% vs. 21.2%, absolute risk reduction (ARR) of -2.4% (95% CI -11.5% to 6.6%).
		  ○ There was no difference in time to development of shock among those patients who did develop septic shock.
		• There were no differences in 28-day, 90-day, 180-day, ICU, or in-hospital mortality.
		• There was no difference in ICU or hospital length of stay, mechanical-ventilation free days, or need for renal replacement therapy.
		• A per protocol analysis found no difference in secondary endpoints between the groups.
		Adverse events:
		• Hyperglycemia occurred more frequently in the hydrocortisone group compared to the placebo group: 90.9% vs. 81.5%; difference 9.4%, 95% CI 2.4% to 16.4%. There was no difference in the total amount of insulin administered between the groups.
		• Secondary infections, weaning failure, and muscle weakness occurred with similar rates between the groups.

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 study was conducted in Germany, only patients with severe sepsis were included and would hence likely be similar to such patients seen at our institution. It seems reasonable to generalize the results to a similar group of patients in our institution (external validity).
2.	Were all clinically important outcomes considered?	Yes. The authors considered rates of progression to shock, time to onset of shock, mortality, length of stay in the ICU and hospital, duration of mechanical ventilation, and need for renal replacement therapy.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. Based on this study, routine administration of hydrocortisone to patients with severe sepsis without shock did not reduce the rates of progression to shock or mortality.

Limitations:

1. **In their sample size calculation, the authors presumed a rate of progression to septic shock of 40% in the placebo group. The actual rate was much lower (23% in the ITT population), increasing the risk of a type II error in this study.**

2. **Patients who developed septic shock early may have been missed, because consent was required prior to enrollment.**

3. **Patients in the placebo arm were more likely to have received glucocorticoids prior to randomization and at higher doses (3.4% vs 1.7%).**

4. **There were 3 patients reported as being excluded in the hydrocortisone group because they did not receive the study medication, hence this was not a true intention to treat analysis.**

Bottom Line:

This multicenter, placebo-controlled, double-blind randomized controlled trial conducted in Germany demonstrated no reduction in the rate of progression to septic shock or mortality with administration of IV hydrocortisone to patients with severe sepsis but without septic shock.