Critical Review Form
Therapy

PGY-3

Venkatesh B, Finfer S, Cohen J, et al; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med. 2018 Mar 1;378(9):797-808.

Objectives: **"to test the hypothesis that hydrocortisone results in lower mortality than placebo among patients with septic shock." (p. 798)**

Methods: **This international, double-blind, randomized controlled trial was conducted in 69 ICUs in Australia (45 sites), the UK (12 sites), New Zealand (8 sites), Saudi Arabia (3 sites), and Denmark (1 site) between March 2013 and April 2017. Adult patients aged 18 years or older with sepsis (presumed infection with two or more SIRS criteria) requiring mechanical ventilation and treatment with either vasopressors or inotropic agents for at least 4 hours were eligible for inclusion. Patients requiring glucocorticoids for another indication, patients who received etomidate during the hospitalization, those likely to die within 90 days from a pre-existing condition or who treatment limitations in place, and patients who met all inclusion criteria for > 24 hours prior to randomization were excluded.**

Patients were randomized to receive either hydrocortisone (continuous IV infusion of 200 mg per day for a maximum of 7 days or until ICU discharge or death) or matching placebo. The primary outcome was death from any cause at 90 days. Secondary outcomes included 28-day mortality, time to resolution of shock, recurrence of shock, ICU length of stay, hospital length of stay, frequency and duration of mechanical ventilation and renal replacement therapy, new-onset bacteremia or fungemia between 2 and 14 days after randomization, and need for blood transfusion in the ICU.

Out of 5501 eligible patients, 3800 were enrolled. A total of 114 patients were excluded (primarily due to withdrawing consent) and 28 were lost to follow-up, leaving 3658 in the final analysis (1832 in the hydrocortisone group and 1826 in the placebo group).

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 receive either hydrocortisone or placebo. Randomization was stratified by study center and according to medical vs. surgical admission.
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. "We concealed the randomized trial-group assignments using a minimization algorithm by means of a password-protected, encrypted, Web-based interface." (p. 799)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All the analyses were conducted on an intention-to-treat basis with no imputation of missing data." (p. 800) Adherence was excellent, with 99.8% and 99.7% of patients in the hydrocortisone and placebo groups receiving the assigned treatment, respectively. Mean rate of adherence to the dosing protocol was 95.2% and 94.9%, respectively. Open label glucocorticoids were received by 8.8% of patients in the placebo group.
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, median APACHE II scores, percent of patients with surgical and medical admission, primary site of infection, therapies provided (e.g. mechanical ventilation, vasopressor therapy), and time from onset of shock. The article does not provide baseline measures of organ dysfunction (i.e. SOFA scores).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "Blinding regarding the trial regimen was ensured by the supply of hydrocortisone and placebo in identical, masked vials... The patients, treating clinicians, and trial personnel were unaware of the trial-group assignments and sequence." (p. 799)
2.	Were clinicians aware of group	See above.

	allocation?	
3.	Were outcome assessors aware of group allocation?	See above.
4.	Was follow-up complete?	Yes. Only 28 patients (0.8%) were lost to follow-up, resulting in a low risk of attrition bias.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• 90-day all-cause mortality was similar between the groups: 27.9% in the hydrocortisone group vs. 28.8% in the placebo group (OR 0.95, 95% CI 0.82-1.10). • There was no significant difference in 28-day all-cause mortality (OR 0.89, 95% CI 0.76-1.03). • Median time to resolution of shock was faster in the hydrocortisone group: 3 vs. 4 days; hazard ratio (HR) 1.32, 95% CI 1.23-1.41). • Recurrence of shock occurred slightly less frequently in the hydrocortisone group: OR 1.07, 95% CI 0.94-1.22. • Time to discharge from the ICU was shorter in the hydrocortisone group (10 vs. 12 days; HR 1.14, 95% CI 1.06-1.23) as was time to cessation of mechanical ventilation (6 vs. 7 days; HR 1.13, 95% CI 1.05-1.22). • There was no difference hospital length of stay, need for renal replacement therapy, or new-onset bacteremia.
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?	No. Although this was an international study with no US sites, only patients with septic shock were included and would hence likely be similar to such patients seen at our institution. It would seem reasonable to generalize the results to a similar group of patients in our institution (external validity), except that the authors excluded patients who had received etomidate. As the majority of patients being intubated in our ED receive etomidate during RSI, these results would not be generalizable to a large

		proportion of our patients.
2.	Were all clinically important outcomes considered?	Yes. The most clinically relevant patient-centered outcomes were considered, including short and long-term mortality, ICU and hospital length of stay, need for renal replacement therapy, and 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 (which is of unclear clinical benefit). The study was limited in part because they did not specify how longer after onset of shock patients could be enrolled, and in fact only enrolled patients who had been on pressors for at least four hours. It is possible that earlier administration of steroids would result in improved outcomes (as observed in the Annane trial).

Limitations:

1. **The trial excluded those who had received etomidate, an anesthetic with some adrenal suppression. Given that most patients intubated for sepsis in our ED likely receive etomidate, this study would not be generalizable to our population (external validity).**

2. **The article does not provide baseline measures of organ dysfunction (i.e. SOFA scores).**

3. **This study utilized a continued infusion of hydrocortisone rather than bolus dosing. It is possible that a slower infusion may have delayed onset of action of the medication, hence reducing any possible benefit.**

4. **The study enrolled patients who had been on pressors for up to 24 hours. It is possible that earlier administration of steroids would result in improved outcomes (as observed in the Annane trial).**

Bottom Line:

This large multicenter, randomized controlled trial evaluated the efficacy of a continuous infusion of hydrocortisone in mechanically ventilated patients requiring vasopressor infusion. While there was no effect on mortality, patients receiving hydrocortisone did have a shorter median time to resolution of shock (4 vs. 3 days). The clinical significance of this is unclear. Given that the study excluded patients receiving etomidate, it may be difficult to apply the results to our patient population.