Critical Review Form
Therapy

PGY-4

Annane D, Renault A, Brun-Buisson C, et al; CRICS-TRIGGERSEP Network. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. N Engl J Med. 2018 Mar 1;378(9):809-818.

Objectives: **"to test the hypothesis that hydrocortisone-plus-fludrocortisone therapy or drotrecogin alfa (activated) would improve the clinical outcomes of patients with septic shock." (p. 810)**

Methods: **This placebo-controlled trial was conducted at 34 centers from September 2, 2008 to June 23, 2015 and initially included four parallel groups using a 2-by-2 factorial design, but continued only two parallel groups when drotrecogin alfa was removed from the market in 2011. Patients in intensive care units (ICUs) with "indisputable or probable" septic shock (infection plus a SOFA score of 3 or 4 for at least 2 organs for at least 6 hours AND use of vasopressor therapy for at least 6 hours) were eligible for enrollment. Patients with septic shock for 24 hours or more, high risk of bleeding, pregnancy (or lactation), underlying conditions that could affect short-term survival, previous treatment with corticosteroids, or known hypersensitivity to drotrecogin alfa were excluded. All patients underwent corticotropin stimulation testing prior to randomization.**

Patients were randomized to receive hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa, the combination of the three drugs, or their respective placebo. Hydrocortisone was given as a 50 mg IV bolus every 6 hours and fludrocortisone was given as a 50 µg tablet once daily, each for 7 days.

The primary outcome was 90-day all-cause mortality. Secondary outcomes included (among others) ICU mortality, in-hospital mortality, 28-day mortality, 180-day mortality; proportion of patients weaned from vasopressors at days 28 and 90 and time to weaning of vasopressors; proportion of patients weaned from mechanical ventilation at days 28 and 90 and time to weaning of mechanical ventilation; and ventilator-free and pressor-free days by day 28 and 90. Several safety outcomes were evaluated as well (including superinfection, GI bleeding, and neurologic sequelae).

At total of 1241 patients were included in the analysis, with 627 assigned to placebo and 614 assigned to hydrocortisone plus fludrocortisone (HF group). The median age was 66 years, 66.6% were male, and 81.7% were admitted from a medical ward.

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 randomly assigned in permuted blocks of eight to receive hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa, the combination of the three drugs, or their respective placebo." (p. 811)
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?	Uncertain. The authors do not provide details on how group allocation was achieved and any methods used to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "An intention-to-treat analysis was planned to be performed after all the participants had completed the 180-day follow-up and according to the 2-by-2 factorial design...The analysis compared all the patients assigned to receive hydrocortisone plus fludrocortisone with those assigned to receive the corresponding placebos." (p.812)
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, admission origin (medical vs. surgical), baseline SAPS II and SOFA scores, infectious site, vasopressor use, and baseline need for mechanical ventilation and renal replacement therapy.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. "Placebos of French commercial forms of hydrocortisone and fludrocortisone were manufactured for the requirements of the trial. Active agents and placebos had similar appearances (checked and certified by qualified persons for each batch..." (p. 811)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	Uncertain. While the method of outcome investigation and blinding of outcome assessors were not specified, the outcomes were mostly objective (specifically mortality) and hence should not be subject to observer bias.

4.	Was follow-up complete?	Uncertain. The authors do not specify how many patients were lost to follow-up for each of the outcomes.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• 90-day all-cause mortality was lower in the HF group (43.0%) compared to the placebo group (49.1%): RR 0.88, 95% CI 0.78-0.99. • Mortality at ICU discharge was lower in the HF group compared to the placebo group (RR 0.86, 95% CI 0.75 to 0.99) as was in-hospital mortality (RR 0.86, 95% CI 0.76-0.98) and 180-day mortality (RR 0.89, 95% CI 0.79-0.99). • Duration of mechanical ventilation was shorter in the HF group ($p = 0.0006$), but mean number of ventilator-free days was not significantly different (10 in the placebo group vs. 11 in the HF group, $p = 0.07$). • Duration of vasopressor therapy was shorter in the HF group ($p < 0.001$) with more vasopressor free days noted (mean of 17 vs. 15 days, $p < 0.001$). • Patients in the HF group had significantly more organ-failure free days than those in the placebo group (mean of 14 vs. 12 days, $p = 0.003$). • The risk of serious adverse events was similar between the HF and placebo groups (53.1% vs. 58.0%, $p = 0.008$).
2.	How precise was the estimate of the treatment effect?	See above. The confidence intervals are fairly narrow given the large sample size and high frequency of outcomes.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Not entirely. While this study included patients with septic shock, who would likely be similar in most respects to patients were see with septic shock, the use of drotrecogin alfa in a significant number of patients may affect the outcomes. While initial studies demonstrated some benefit from its use in septic shock, later studies found no reduction in mortality, and some have demonstrated a significant risk of bleeding. Aside from the use of drotrecogin alfa in the initial years of the study, the cohort does seem to represent a generalizable group of patients with septic shock.

2.	Were all clinically important outcomes considered?	Yes. The authors considered mortality, duration of mechanical ventilation, duration of vasopressor use, and organ failure.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study did demonstrate a decrease in mortality with the use of hydrocortisone and fludrocortisone, these results contradict the results of several other randomized controlled trials (HYPRESS, ADRENAL). Given the methodological issues encountered in this trial, primarily the conversion of the study from a four-parallel-group trial to a two-group trial and the fact that the study was suspended twice during the data collection, it may be difficult to trust these results. Having said that, administration of steroids to patients with septic shock who still require vasopressors after 6 hours seems reasonable. The addition of fludrocortisone to any treatment regimen is likely of little benefit.

Limitations:

1. **The authors do not specify how group allocation was achieved and do not provide any details regarding what methods were used to maintain allocation concealment.**

2. **The method of outcome investigation and blinding of outcome assessors were not specified. Despite this, the outcomes were mostly objective (specifically mortality) and hence should not be subject to observer bias.**

3. **The study was initially designed to have four parallel groups in an attempt to study the effects of both steroids and drotrecogin alfa in septic shock. Part of the way through the study drotrecogin alfa was removed from the market due to lack of efficacy and the study was converted to a two-group parallel design.**

4. **This trial was conducted over a rather long period of time (nearly seven years) during which several high-profile studies concerning sepsis were completed (see Journal Club July 2015, Journal Club October 2010) that have altered our management.**

Bottom Line:

This large, multicenter, randomized controlled trial attempted to evaluate the efficacy of combined hydrocortisone-fludricortisone therapy and drotrecogin alfa in the management of septic shock. When drotrecogin alfa was removed from the market, the design was adjusted to solely evaluate steroid efficacy. The results demonstrated a decrease in mortality with a NNT of ~17 with decreased duration of

mechanical ventilation and vasopressor therapy and an increase in the number of days free of organ failure. Despite these positive results, this study is hampered by the fairly large adjustment in study protocol and by the suspension of the study for a combined two years. The fact these results do not agree with the results of other large, methodologically sound trials is also concerning.