Critical Review Form
Therapy

Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest. 2017 Jun;151(6):1229-1238.

Objectives: **To evaluate the efficacy of a combined therapy with IV vitamin C, hydrocortisone, and thiamine in the management of severe sepsis and septic shock.**

Methods: **This retrospective, before-and-after study was conducted at Santara Norfolk General Hospital, a tertiary care hospital associated with Eastern Virginia Medical School. Consecutive patients with severe sepsis and septic shock with a procalcitonin level ≥ 2 ng/mL, admitted to the ICU between January 2016 and July 2016, comprised the treatment group. Exclusion criteria included age < 18, pregnancy, or limitation of care. The control group consisted of consecutive patients admitted to the ICU between June 2015 and December 2015, using the same inclusion and exclusion criteria.**

Patients in the treatment group received IV vitamin C (1.5 g every 6 hours for 4 days or until ICU discharge), hydrocortisone (50 mg every 6 hours for 7 days or until ICU discharge, followed by a taper over 3 days), and thiamine (200 mg every 12 hours for 4 days or until ICU discharge). The control group did not receive IV vitamin C, but hydrocortisone was given at clinician discretion. A total of 28 patients in the group (out of 47) received hydrocortisone.

There were 47 patients enrolled in each group, of whom 22 (47%) in each group received vasopressors and met criteria for septic shock. The mean age in the treatment group was 58 and the mean age in the control group was 62.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. This was a quasi-experimental before and after trial, subject to all of the inherent biases associated with such study design. In particular, it is impossible to control for all other potential changes in patient management over time, and some of these changes could affect the outcomes being studied.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the	N/A. This was not a randomized trial. Patient allocation was based on when the patient was admitted to the ICU.

	randomization process to ensure that a patient would be "randomized" to a particular group?	
3.	Were patients analyzed in the groups to which they were randomized?	Yes. Although there was no randomization, patients were analyzed according to which time frame their presentation occurred in, regardless of whether or not they received intervention being study (intention to treat analysis). It seems that all patients in the treatment group received the study intervention. In addition, 28 patients (59.6%) in the control group received IV hydrocortisone.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients appear to be similar with respect to age, medical comorbidities, infectious source, need for mechanical ventilation, need for vasopressors, baseline labs, and illness severity scores (APACHE II, APACHE IV, and SOFA).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes and no. There was no blinding involved in this study, but as all enrolled patients were critically ill and nearly half were intubated, it is unlikely that they would be aware of group allocation or intervention. It is unlikely that there would be any risk of performance bias on the part of the patients.
2.	Were clinicians aware of group allocation?	Yes. This was a non-blinded, before and after study, and clinicians were aware of group allocation. It is possible (though unlikely) that performance bias on the part of the clinicians could have affected outcomes.
3.	Were outcome assessors aware of group allocation?	Uncertain (but likely yes). There is no mention of blinding of outcome assessors or chart reviewers (although the authors also do not specifically state who assessed patients for the documented outcomes).
4.	Was follow-up complete?	Yes. All outcomes were assessed during the hospitalization, and hence outcome data was available for all enrolled patients.
II.	**What are the results?**	
1.	How large was the treatment effect?	• Mortality was much lower in the treatment group than it was in the control group: 8.5% vs. 40.4% (RR 0.21, 95% CI 0.077 to 0.57). ○ The propensity adjusted odds ratio for mortality was 0.13 (95% CI 0.04 to 0.48). • Acute kidney injury occurred with similar

		frequency in the treatment and control groups (66% vs. 64%), but significantly fewer patients in the treatment group required renal replacement therapy (6.4% vs. 23.4%). • Patients in the treatment group were all weaned off of vasopressors, with a mean duration of treatment of 18.3 hours. The mean duration of vasopressor use in the control group was 54.9 hours. • The change in the mean SOFA score at 72 hours was 4.8 ± 2.4 in the treatment group and 0.9 ± 2.7 in the control group. • The median ICU length of stay was similar in the treatment group (4 days) and the control group (4 days).
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?	Presumably yes. This study was conducted at a tertiary care referral center and the patients enrolled had a wife range of medical comorbidities, similar to what we see in our institution. We may see more patients with immunosuppression (given our large associated cancer center), which may result in a sicker population, but overall I would expect our patients to be similar.
2.	Were all clinically important outcomes considered?	Yes. The authors considered mortality, vasopressor use, kidney injury, need for renal replacement therapy, and ICU length of stay.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study suggests significant benefit from the combined therapy of IV vitamin C, hydrocortisone, and thiamine in patients with severe sepsis and septic shock, this study has several limitations. This was a retrospective before and after study with several potential sources of bias. It was a single center trial with a small number of patients enrolled, and should be replicated in multiple settings with more patients. Additionally, the reported mortality among patients with severe sepsis and septic shock in the treatment group was only 8.5%. This is very low mortality, and it is difficult to attribute such a massive reduction in mortality to the treatment being studied. Again, further studies should be conducted to confirm these findings.

Limitations:

1. **This was not a randomized controlled trial, but was an observational study utilizing a before and after study design, in which it is impossible to control for simultaneous interventions that could affect the outcomes (i.e. changes in methods of sedation, sepsis management protocols, or use of blood products).**

2. **The authors provide very limited details regarding the chart review methods (Gilbert 1996 and Worster 2004).**

3. **No primary outcome was defined a priori.**

4. **Multiple interventions were studied at the same time, making it impossible to determine whether any single intervention was beneficial or if there was truly a synergistic effect.**

5. **Given the nature of the study, clinicians were not blinded, which could lead to significant performance bias.**

Bottom Line:

This single-center, before and after study demonstrated a rather large reduction in morality among patients with severe sepsis and septic shock treated with IV vitamin C, hydrocortisone, and thiamine. The results of this study are quite profound, and hence should be confirmed with additional prospective, randomized controlled trials. If this intervention is truly this beneficial, and truly reduces mortality to less than 10% in this patient population, routine use of this therapy should be initiated immediately.