

# Additional Trials of Vitamin C in Septic Shock

## A Bag of Mixed Fruit

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As highlighted by a recent report on the worldwide burden of sepsis, life-threatening infection is a growing global health issue.<sup>1,2</sup> Indeed, it has been estimated that 11 million deaths in 2017 were sepsis related, with the burden being greater in developing regions.<sup>2</sup> As such, there is a clear need for more effective and affordable interventions for sepsis; a single-center before-after study that was published in the June 2017 issue of *CHEST* attracted substantial attention from the medical community.<sup>3</sup> This article suggested a strong association between combination therapy that consists of vitamin C 6 g/d, thiamine 400 mg/d, and hydrocortisone 200 mg/d and decreased mortality rates and more rapid liberation from vasopressors.<sup>3</sup> The reported effects were dramatic; hence, they prompted a number of randomized clinical trials (RCT).

Critically, any trial of combination therapy requires careful design, particularly when one of the therapeutic components has an established impact on the outcomes of interest. Otherwise, the effect of combination therapy may be over-estimated. In this circumstance, hydrocortisone is included as part of combination therapy, which has been demonstrated repeatedly to shorten the duration of vasopressor dependency in

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septic shock.<sup>4</sup> Thus, the design of clinical trials that assess the effect of vitamin C combination therapy ideally should account for such confounding, particularly the hemodynamic effects of hydrocortisone.<sup>5</sup>

In this issue of *CHEST*, results from two further RCTs of vitamin C combination therapy in sepsis, combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock (HYVCTTSSS) and outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis (ORANGES), are reported.<sup>6,7</sup>

HYVCTTSSS was a single-center RCT conducted in an ICU in China.<sup>6</sup> The trial was designed to assess the effect of vitamin C combination therapy (for 7 days) compared with placebo in 140 patients with sepsis or septic shock. The trial was terminated after patients were enrolled because of a significantly higher incidence of severe hyponatremia in the intervention arm (13 patients vs 3 patients).

Data from these 80 patients did not demonstrate any benefit in 28-day mortality rate (27.5% vs 35.0%), duration of vasopressor therapy, duration of mechanical ventilation, ICU length of stay, clearance of lactate and procalcitonin, and newly diagnosed acute kidney injury.<sup>6</sup> The change in sepsis-related organ failure assessment (SOFA) score over 72 hours was statistically greater in the intervention group (3.5 vs 1.8); however, patients in the control group did not receive hydrocortisone. As such, it is uncertain whether the observed effect on SOFA scores is due to “combination” therapy.

Of particular interest is the early termination of a trial that investigated vitamin C therapy, in which this intervention has been considered widely to be safe. The investigators considered that the salt-retaining property of hydrocortisone might be responsible<sup>6</sup>; although because commercially available vitamin C products are prepared with the use of sodium ascorbate, high doses of vitamin C may also be implicated. Notably, this is not the first time that hyponatremia has been reported in patients who undergo vitamin C therapy.<sup>8</sup>

ORANGES was a double-blind RCT conducted in two ICUs in the United States, where 137 adult patients with sepsis or septic shock within 12 hours of ICU admission

were allocated randomly to vitamin C combination therapy (for 4 days) or placebo.<sup>7</sup> The investigators reported duration of vasopressor dependency and change in SOFA score (over 4 days) to be primary outcomes. Of the two outcomes, the duration of vasopressor dependency was significantly shorter in those who received vitamin C combination therapy (27 vs 53 hours), albeit what specifically constituted “shock resolution” is not well defined. Moreover, there was no significant difference in SOFA score (2.9 vs 1.9) and secondary outcomes; mortality rate, procalcitonin clearance, ICU and hospital length of stay, ventilator-free days, and acute kidney injury did not differ between the two groups.

The investigators conducted an additional analysis adjusting for hydrocortisone use in the control group (which occurred in 41%), whereby the beneficial effect of combination therapy on shock resolution persisted. However, the lack of any favorable effect on any of the other outcomes, including SOFA scores (where the cardiovascular component should reflect the observed hemodynamic effect) remains unexplained.

Of note, ORANGES was first registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT 03422159) in January 2018, with recruitment commencing in February the same year. Recruitment appears to have stopped in April 2019; albeit in June 2019, the primary outcome was changed from hospital mortality rate to time-to-vasopressor independence and change in SOFA score.<sup>9</sup> Critically, hospital mortality rate is the most distant outcome measure reported in the article, and changing the primary outcome after completing patient follow up does raise some concerns. As such, one has to consider whether the primary study findings are based on a chance result, which has been over emphasized.

A recently published RCT assessed the effect of vitamin C combination therapy compared with hydrocortisone monotherapy in 216 patients with septic shock.<sup>10</sup> The primary outcome was time alive and free of vasopressors; secondary outcomes included death, organ dysfunction, artificial organ support, and ICU and hospital length of stay. The trial found that vitamin C combination therapy did not shorten the duration of septic shock. The trial reported a greater decrease in SOFA score with the intervention; however, no beneficial effect was seen in any of the other outcomes.

Inconsistent findings from these trials can be attributed to study design. Indeed, uncontrolled use of hydrocortisone in the comparator group of HYVCTTSSS and ORANGES confounds the

interpretation of their results. As such, future research must be cognizant of including a valid comparison and should be conducted and reported in a transparent manner. In addition, all of the existing literature concerning vitamin C combination therapy is underpowered with respect to mortality rate and insufficient to prompt widespread practice change. Finally, although the clinical community is particularly interested in novel, inexpensive, and effective therapies for sepsis, the mixed findings from these trials remind clinicians of the importance of focusing on basic strategies, such as focused resuscitation, early antibiotic administration, and source control.

Several RCTs on vitamin C combination therapy are currently ongoing and will hopefully provide more conclusive answers. However, in an effort to avoid more inconclusive trials, future work must focus on patient-centered outcomes and be reported in combination with republished study protocols and statistical analysis plans.

## References

1. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority - a WHO resolution. *N Engl J Med*. 2017;377(5):414-417.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990 – 2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200-211.
3. 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;151(6):1229-1238.
4. Rygård SL, Butler E, Granholm A, Møller MH, Cohen J, Finfer S, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2018;44(7):1003-1016.
5. Fujii T, Udy AA, Venkatesh B. Comparing apples and oranges: the vasoactive effects of hydrocortisone and studies investigating high dose vitamin C combination therapy in septic shock. *Crit Care Resusc*. 2019;21(3):152-155.
6. Chang P, Liao Y, Guan J, et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. *Chest*. 2020;158(1):174-182.
7. Iglesias J, Vassallo A, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES trial. *Chest*. 2020;158(1):164-173.
8. Stephenson CM, Levin RD, Spector T, Lis CG. Phase I clinical trial to evaluate the safety, tolerability, and pharmacokinetics of high-dose intravenous ascorbic acid in patients with advanced cancer. *Cancer Chemother Pharmacol*. 2013;72(1):139-146.
9. National Institutes of Health Clinical Center. Metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in sepsis. (ORANGES). NCT03422159. [ClinicalTrials.gov](https://clinicaltrials.gov). Bethesda, MD: National Institutes of Health; 2018. <https://clinicaltrials.gov/ct2/show/NCT03422159>. Updated September 3, 2019.
10. Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. *JAMA*. 2020;323(5):423-431.