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**Reference Article:** 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), doi: 10.1016/j.chest.2016.11.036.

**Questions:** Does a combination of hydrocortisone, vitamin C, and thiamine improve mortality in septic patients?

**Introduction:** The diagnosis of sepsis and the appropriate treatment of sepsis and septic shock is an evolving and highly researched area of medicine. It has become a highly discussed area more recently, especially in emergency medicine and critical care medicine. Clinicians are constantly balancing appropriate fluid resuscitation, antibiotic therapy, and vasopressor therapy to appropriately treat these patients. In addition, CMS guidelines are now calling for strict adherence to 30 cc/kg fluid resuscitation and antibiotics within 3 hrs of patient triage and within 1 hour of severe sepsis/septic shock recognition. Despite the amount of attention sepsis has received, the understanding of this area in medicine continues to grow and treatment modalities are in flux to a certain extent. The mantra of medicine currently calls for fluids, antibiotics, and vasopressors/inotropes. Other adjuvant therapies have also been examined in sepsis which have included the use of stress dose steroids and more recently vitamin C. The purpose of this study was to examine the treatment effects of a combination of vitamin c, hydrocortisone, and thiamine in the treatment of sepsis compared to standard sepsis/septic shock treatment.

**Methods:** This was a single centered retrospective before/after study that looked at a control group from June 2015 to December 2015 vs a treatment group from January 2016 until July 2016 that were each diagnosed with severe sepsis or septic shock. Inclusion criteria included adult patients with a primary diagnosis of severe sepsis or septic shock and a procalcitonin level > 2.0. Exclusion criteria included patients < 18 yrs old, pregnant patients, and patients with limitations of care. The control group was provided with IV fluids, broad spectrum antibiotics, and vasopressors per hospital protocol. The first line vasopressor in all patients was norepinephrine followed by vasopressin as second line which was followed by either phenylephrine or epinephrine. If intubated they were placed on lung protective ventilation strategies. Some patients (56.9%) in control group also received hydrocortisone at discretion of the clinician at 50 mg q6h. Those in the treatment group were provided with same interventions as the control but were also provided with hydrocortisone 50 mg q6h for 7 days (or until ICU discharge) followed by 3 day taper, vitamin C 1.5 gm q6h for 4 days or until ICU discharge, and thiamine 200 mg q12h for 4 days or until ICU discharge. A total of 47 patients were placed in each group. Primary endpoint was hospital survival. Secondary outcomes included duration of vasopressor therapy, ICU length of stay, need for renal replacement therapy for AKI, change in SOFA score at 72 hrs, and procalcitonin clearance.

**Results:** The hospital mortality in treatment group was 8.5% (4/47 patients) in the treatment group compared to 40.4% (19/47 patients) in the control group ( $p < 0.001$ ). Three patients (10%) in treatment group required RRT for AKI vs 11 patients (37%) in the control group ( $p=0.02$ ). The mean duration of vasopressor use in the treatment group was 18.3 hrs vs 54.9 hrs in the control group ( $p<0.001$ ). The 72 hour delta SOFA score was 4.8 in treatment group vs 0.9 in the control group ( $p<0.001$ ). The procalcitonin clearance was 86.4% in the treatment group vs 33.9% in the control group ( $p<0.001$ ).

**Discussion:** The optimal treatment of sepsis and septic shock is ever evolving area in medicine. Previous studies have demonstrated low vitamin C levels and low thiamine levels in septic patients. Furthermore, other studies have suggested a possible benefit of vitamin C therapy and hydrocortisone therapy in septic

shock. This study attempted to look at the benefits of a combined hydrocortisone, vitamin C, and thiamine treatment plan added to the normal treatment modalities of fluids, antibiotics, and vasopressors in septic shock/severe sepsis patients. The data is certainly intriguing and suggests a benefit from the combined therapy. The study did do an excellent job at matching patients at baseline. However, this was a single centered study that is retrospective in nature. Furthermore, the treatment group was given three separate interventions making it impossible to comment on which intervention could be providing the proposed benefit. The low sample size is also an issue with the study with only an N of 47 per group. Despite the shortcomings of the study it certainly promotes discussion of these interventions in septic patients and warrants a randomized controlled trial. From a practice perspective I certainly think that while caring for ICU patients I will push for the administration of vitamin C. Although the overall benefit has not been convincingly demonstrated I don't see a downside to this medication intervention. Overall, the study certainly has the world of medicine talking and clamoring for further follow up studies.

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