"Vitamin S" (Steroids) and Vitamin C for the Treatment of Severe Sepsis and Septic Shock!*

Paul E. Marik, MD, FCCM, FCCP
Division of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School
Norfolk, VA

It has been assumed that severe sepsis and septic shock occur due to immune disequilibrium. Excessive activation of nuclear factor-κB (NF-κB) has been implicated in generation of the "cytokine storm" in the early stages of sepsis. Through a variety of genomic and nongenomic mechanisms, glucocorticoids inhibit NF-κB activation. Therefore, it has been suggested that the immune disequilibrium in the early phase of sepsis results from inadequate endogenous glucocorticoid mediated regulation of NF-κB activation. Inadequate release of cortisol (relative adrenal insufficiency) and/or glucocorticoid tissue resistance have been postulated as the cause of the inadequate glucocorticoid activity; the term "Critical Illness Related Corticosteroid Insufficiency" (CIRCI) has been coined to describe this syndrome (also known colloquially as "vitamin S deficiency") (1). Multiple pathogenic mechanisms have been implicated in the causation of CIRCI. In patients with septic shock, adrenal cells may lose their sensitivity to corticotropin (adrenocorticotropic hormone [ACTH]) (2). Anti-inflammatory cytokines such as interleukin (IL)-10 down-regulate adrenal steroidogenesis (3). Substrate deficiency (high-density lipoprotein) may lead to inadequate cortisol synthesis during acute illness (4). In addition, polymorphisms of the ACTH receptor have been associated with a low cortisol response to stress (5). Tissue corticosteroid resistance is a well-known manifestation of chronic inflammatory diseases. It is likely that patients with acute inflammatory diseases such as sepsis and acute lung injury may develop tissue resistance to glucocorticoids during the course of their disease (6). Alterations in the molecular mechanisms of glucocorticoid receptor (GR) action impair glucocorticoid signal transduction and alter tissue sensitivity to glucocorticoids (6). In a murine *Staphylococcal aureus* sepsis model, Bergquist et al (7) demonstrated markedly decreased GR-α expression and decreased nuclear translocation of the GR complex into the nucleus. These changes in GR number and function occurred in a time-dependent manner. Altered phosphorylation of the GR, altered importin-7 function, or defective dissociation from the chaperon molecules may account for the decreased nuclear translocation of the GR complex. The anti-inflammatory actions of glucocorticoids are more effective in men (8). Estrogens have been suggested to antagonize glucocorticoid action through alterations in phosphorylation of the GR (9). Increased expression of β-isoform of the GR (GR-β) has been demonstrated in sepsis (10). GR-β fails to bind cortisol and activate gene expression and thus functions as a negative inhibitor of GR-α (11). Single nucleotide polymorphisms in the GR gene are associated with varying sensitivity to glucocorticoids (12). 11β-Hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts cortisol to cortisone, its inactive reduced metabolite which is unable to bind to the GR. Increased expression of 11β-HSD2 may result in glucocorticoid resistance.

In this issue of *Critical Care Medicine*, Cohen et al (13) sought to determine glucocorticoid sensitivity in critically ill patients with septic shock when compared with control subjects. Glucocorticoid sensitivity was measured by in vitro suppression of cytokine production from lipopolysaccharide-stimulated leukocytes. Although there was no significant difference in glucocorticoid sensitivity between the groups, there was a greater range in the patients with septic shock. Furthermore, the patients in the lowest quartile of glucocorticoid sensitivity were sicker (higher Acute Physiology and Chronic Health Evaluation II scores) with a trend toward a higher mortality. Expressions of GR-β and 11β-HSD-2 were higher in patients than in controls; however, expression of these genes did not correlate with glucocorticoid sensitivity. Furthermore, there was no difference in glucocorticoid sensitivity between male and female patients. Although this study demonstrates alterations of GR isoform expression and glucocorticoid sensitivity in patients with septic shock, the failure to find a statistically significant difference between the groups may be a consequence of the insensitivity of the assay used. The authors used the inhibitory effects of glucocorticoids on NF-κβ signaling pathways as a surrogate marker of activation of GR target genes. Activation of primary GR target genes would allow more accurate quantification of glucocorticoid activity (14). Nevertheless, this study does support the concept that tissue resistance to glucocorticoids may occur in patients with acute inflammatory conditions such as sepsis. Importantly, this study

*See also p. 1034.

Key Words: Critical Illness Related Corticosteroid Insufficiency; glucocorticoids; septic shock; vitamin C

Dr. Marik disclosed off-label product use (vitamin C: this compound is regarded as generally safe and is exempted from Food and Drug Administration approval).

DOI: 10.1097/CCM.0000000000001684

demonstrates that the standard tests evaluating the integrity of the hypothalamic-pituitary-adrenal axis (total cortisol and ACTH stimulation test) are unable to detect relative adrenal insufficiency (low fee cortisol) or tissue glucocorticoid resistance in acutely ill patients.

Experimental models suggest that exogenous glucocorticoids overcome glucocorticoid resistance; however, this effect appears to be time dependent (7). In addition to down-regulating the proinflammatory response and modulating the anti-inflammatory response, glucocorticoids may have additional beneficial effects in patients with sepsis including increasing adrenergic responsiveness, restoring the tight junctions between endothelial cells, and preserving the endothelial glycocalyx.

Due to changes in GR function, glucocorticoids alone may be insufficient to regulate NF-κβ signaling in patients with sepsis. Reactive oxygen species (ROS) are important activators of NF-κB. ROS are generated following exposure to cytokines and lipopolysaccharide and treatment with antioxidants blocks activation of NF-κB by these stimuli. In experimental and clinical studies, high-dose IV vitamin C has been shown to decrease NF-κβ activation, with a reduction inflammatory markers and organ dysfunction (15, 16). Similar to glucocorticoids, vitamin C may increase vasomotor responsiveness by increasing endogenous synthesis of norepinephrine and vasopressin (17). Glucocorticoids and vitamin C may act synergistically with glucocorticoids inducing the sodium-dependant vitamin C transporter increasing cellular vitamin C uptake (18), whereas vitamin C may restore GR function (19). It should be noted that oral vitamin C has been shown to have steroid-sparing effects in steroid-dependent asthmatics (20). These data suggest that patients with severe sepsis and septic shock may benefit from the early administration of IV glucocorticoids (vitamin S) and vitamin C. Clinical studies are required to test this highly cost effective and "radical" hypothesis.

REFERENCES

1. Marik PE, Pastores SM, Annane D, et al; American College of Critical Care Medicine: Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; 36:1937–1949
2. Keri G, Parameswaran V, Trunkey DD, et al: Effects of septic shock plasma on adrenocortical cell function. *Life Sci* 1981; 28:1917–1923
3. Koldzic-Zivanovic N, Tu H, Juelich TL, et al: Regulation of adrenal glucocorticoid synthesis by interleukin-10: A preponderance of IL-10 receptor in the adrenal zona fasciculata. *Brain Behav Immun* 2006; 20:460–468
4. Polito A, Lorin de la Grandmaison G, Mansart A, et al: Human and experimental septic shock are characterized by depletion of lipid droplets in the adrenals. *Intensive Care Med* 2010; 36:1852–1858
5. Jardine D, Emond M, Meert KL, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: A single nucleotide polymorphism in the corticotropin receptor gene is associated with a blunted cortisol response during pediatric critical illness. *Pediatr Crit Care Med* 2014; 15:698–705
6. Meduri GU, Muthiah MP, Carratu P, et al: Nuclear factor-kappaB- and glucocorticoid receptor alpha- mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. *Neuroimmunomodulation* 2005; 12:321–338
7. Bergquist M, Nurkkala M, Rylander C, et al: Expression of the glucocorticoid receptor is decreased in experimental Staphylococcus aureus sepsis. *J Infect* 2013; 67:574–583
8. Duma D, Collins JB, Chou JW, et al: Sexually dimorphic actions of glucocorticoids provide a link to inflammatory diseases with gender differences in prevalence. *Sci Signal* 2010; 3:ra74
9. Zhang Y, Leung DY, Nordeen SK, et al: Estrogen inhibits glucocorticoid action via protein phosphatase 5 (PP5)-mediated glucocorticoid receptor dephosphorylation. *J Biol Chem* 2009; 284:24542–24552
10. Webster JC, Oakley RH, Jewell CM, et al: Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: A mechanism for the generation of glucocorticoid resistance. *Proc Natl Acad Sci U S A* 2001; 98:6865–6870
11. Oakley RH, Jewell CM, Yudt MR, et al: The dominant negative activity of the human glucocorticoid receptor beta isoform. Specificity and mechanisms of action. *J Biol Chem* 1999; 274:27857–27866
12. Manenschijn L, van den Akker EL, Lamberts SW, et al: Clinical features associated with glucocorticoid receptor polymorphisms. An overview. *Ann N Y Acad Sci* 2009; 1179:179–198
13. Cohen J, Pretorius CJ, Ungerer JPJ, et al: Glucocorticoid Sensitivity Is Highly Variable in Critically Ill Patients With Septic Shock and Is Associated With Disease Severity. *Crit Care Med* 2016; 44:1034–1041
14. Wang JC, Derynck MK, Nonaka DF, et al: Chromatin immunoprecipitation (ChIP) scanning identifies primary glucocorticoid receptor target genes. *Proc Natl Acad Sci U S A* 2004; 101:15603–15608
15. Fisher BJ, Seropian IM, Kraskauskas D, et al: Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Crit Care Med* 2011; 39:1454–1460
16. Fisher BJ, Kraskauskas D, Martin EJ, et al: Attenuation of sepsis-induced organ injury in mice by vitamin C. *JPEN J Parenter Enteral Nutr* 2014; 38:825–839
17. Carr AC, Shaw GM, Fowler AA, et al: Ascorbate-dependent vasopressor synthesis: A rationale for vitamin C administration in severe sepsis and septic shock? *Crit Care* 2015; 19:418
18. Fujita I, Hirano J, Itoh N, et al: Dexamethasone induces sodium-dependant vitamin C transporter in a mouse osteoblastic cell line MC3T3-E1. *Br J Nutr* 2001; 86:145–149
19. Okamoto K, Tanaka H, Makino Y, et al: Restoration of the glucocorticoid receptor function by the phosphodiester compound of vitamins C and E, EPC-K1 (L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl hydrogen phosphate] potassium salt), via a redox-dependent mechanism. *Biochem Pharmacol* 1998; 56:79–86
20. Fogarty A, Lewis SA, Scrivener SL, et al: Corticosteroid sparing effects of vitamin C and magnesium in asthma: A randomised trial. *Respir Med* 2006; 100:174–179

CHEST

How to Give Vitamin C a Cautious but Fair Chance in Severe Sepsis

Heleen M. Oudemans-van Straaten, MD, PhD
Paul W. G. Elbers, ME, PhD
Angélique M. E. Spoelstra-de Man, MD, PhD
Amsterdam, The Netherlands

PODCAST

Overwhelming inflammation and oxidative stress contribute to the high morbidity and mortality of sepsis by causing vasoplegia, capillary leakage, and organ failure. This provided the strong rationale for Paul Marik's[1] group to target both uncontrolled inflammation and oxidative stress in an attempt to improve patient outcome. In their provocative before and after study, they administered a combination of IV vitamin C, hydrocortisone, and thiamine in the early phase of severe sepsis and found a considerable decrease in organ failure and mortality. Results are reported in this issue of *CHEST*.[1]

The study included 47 consecutive patients with a primary diagnosis of severe sepsis or septic shock and a procalcitonin level of 2 ng/mL or higher and compared this cohort with a control cohort from 7 months earlier. The study intervention included IV vitamin C (1.5 g every 6 h) and IV thiamine (200 mg every 12 h) as well as IV hydrocortisone (50 mg every 6 h). During the control period, 60% of patients also received IV hydrocortisone (50 mg every 6 h) but no supplemental vitamin C or thiamine. The study cocktail was administered within 24 h of ICU admission. The hospital mortality was significantly lower in the treatment group (8.5%) than in the control group (40.4%). The propensity adjusted OR of mortality in the study patients was 0.13 (95% CI, 0.04-0.48). The duration of vasopressor support was reduced by two-thirds, the 72-h delta Sequential Organ Failure Assessment score was reduced by 82%, and the need for renal replacement therapy declined from 37% to 10%. None of the patients in the treatment group experienced progressive organ failure.

FOR RELATED ARTICLE SEE PAGE 1229

AFFILIATIONS: Department of Intensive Care, VU University Medical Centre.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Heleen M. Oudemans-van Straaten, MD, PhD, Department of Intensive Care, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands; e-mail: hmoudemans@gmail.com

DOI: http://dx.doi.org/10.1016/j.chest.2017.01.008

Why This Combination?

Hydrocortisone and vitamin C act synergistically on multiple sites in the inflammatory cascade.[1-4] In addition, hydrocortisone facilitates the uptake of vitamin C into the cell by restoring the cytokine-induced downregulation of the vitamin C transporter, whereas vitamin C restores the sensitivity of the glucocorticoid receptor.[1] Thiamine was added to reduce the risk of renal oxalate crystallization (see further on).

The Primary Circulating Antioxidant

During sepsis, reactive oxygen species (ROS) are produced in neutrophils. ROS not only kill invading microorganisms but also cause collateral damage to host cells. Vitamin C is the only antioxidant in plasma able to completely prevent neutrophil-induced lipid oxidation.[5] Vitamin C also prevents the depletion of other circulatory antioxidants such as lipid-soluble vitamin E and glutathione, although this is not the case in reverse. However, when consumed, plasma vitamin C becomes rapidly depleted on neutrophil activation.[4,5] *Early* IV supplementation is therefore needed to limit oxidation of lipids, proteins, and DNA.

Protection of the Circulation

Preclinical and clinical studies have shown that vitamin C protects against the loss of the endothelial barrier and microcirculation.[3,4] In addition, vitamin C may increase vasomotor responsiveness by increasing endogenous synthesis of norepinephrine and vasopressin.[6]

Host Defense and Wound Healing

Although glucocorticoids predominantly have antiinflammatory effects, vitamin C reduces oxidant damage and can increase host defenses by improving macrophage and T-cell function.[2,7] Vitamin C is an

essential cofactor in the biosynthesis of collagen and thereby crucial for the firmness of blood vessels. Moreover, vitamin C facilitates wound healing beyond its role in collagen metabolism and blood supply.[8]

Optimal Dose and Route

The optimal dose of vitamin C in the critically ill population is not known. It also is not known whether we should aim at normal or temporarily supernormal plasma concentrations to achieve more antioxidant effects.[2,7] Pharmacokinetic data in critically ill patients are scarce. However, enteral administration is ineffective during critical illness as shown by persistently subnormal plasma concentrations after administering 600 mg vitamin C daily for 8 days.[9] An IV dose of 2 to 3 g/d seems necessary to reach normal plasma concentrations (50-70 μM),[10-12] whereas super-high plasma concentrations can be obtained with dosages of 200 mg/kg/d[11] or 10 g/d.[12] In a phase I safety trial in patients with sepsis, high plasma concentrations were associated with an earlier decline in the Sequential Organ Failure Assessment score and procalcitonin concentrations.[11] With continuous infusion, urinary vitamin C loss and oxalate excretion seem to be lower, whereas a higher proportion of vitamin C remains in the body.[12] Beneficial effects on organ dysfunction or length of ICU support were reported with IV doses between 1,000 mg and up to 200 mg/kg/d.[4,11] The concomitant use of hydrocortisone generally was not mentioned. Altogether, a dose finding is needed.

Negative Image

Despite a huge amount of evidence on the protective effect of vitamin C,[2-4] the administration of vitamin C in higher than the so-called daily recommended dose is often qualified as quackery. Opponents refer to Linus Pauling, who was Nobel Prize winner twice but later in his life persevered in his beliefs that vitamin C taken daily was a panacea and had the miraculous property to prolong life and that mega doses could cure cancer, negating numerous negative studies. A second objection comes from nephrologists pointing to the renal crystallization of oxalate being produced during vitamin C metabolism. However, whether short-term, high-dose administration in the setting of hemodynamic and fluid monitoring will lead to renal oxalate crystallization has not been investigated. Based on physiological reasoning, Marik et al[1] added thiamine to reduce this risk. Thiamine is a coenzyme to glyoxylate aminotransferase, which promotes the oxidation of glyoxylate (a metabolite of vitamin C) to carbon dioxide (instead of oxalate). *Post aut propter*, Marik et al[1] found renal benefit, not harm.

How to Proceed?

The pathophysiology of sepsis reminds us that high-dose IV vitamin C should probably be limited to the very early phase of severe sepsis or septic shock because in the long run, low levels of ROS are crucial for intracellular signaling. To avoid the Linus Pauling trap, pragmatic multicenter trials are needed to confirm this benefit and to exclude unforeseen harm as was seen in previous sepsis trials using promising drugs. Studies should also determine optimal dose and treatment duration, whether normal or temporarily supernormal plasma concentrations should be obtained, whether intermittent (high peak concentrations) or continuous dosing (less renal excretion of vitamin C and oxalate) performs better, whether coadministration of thiamine reduces oxalate excretion, and finally whether the combination with hydrocortisone acts synergistically.

References

1. 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.
2. Wilson JX. Evaluation of vitamin C for adjuvant sepsis therapy. *Antioxid Redox Signal*. 2013;19(17):2129-2140.
3. May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. *Antioxid Redox Signal*. 2013;19(17): 2068-2083.
4. Oudemans-van Straaten HM, Spoelstra-de Man AM, de Waard MC. Vitamin C revisited. *Crit Care*. 2014;18(4):460.
5. Frei B, Stocker R, England L, Ames BN. Ascorbate: the most effective antioxidant in human blood plasma. *Adv Exp Med Biol*. 1990;264: 155-163.
6. Carr AC, Shaw GM, Fowler AA, Natarajan R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? *Crit Care*. 2015;19:418.
7. Berger MM, Oudemans-van Straaten HM. Vitamin C supplementation in the critically ill patient. *Curr Opin Clin Nutr Metab Care*. 2015;18(2):193-201.
8. Mohammed BM, Fisher BJ, Kraskauskas D, et al. Vitamin C: a novel regulator of neutrophil extracellular trap formation. *Nutrients*. 2013;5(8):3131-3151.
9. van Zanten AR, Sztark F, Kaisers UX, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. *JAMA*. 2014;312(5):514-524.
10. Long CL, Maull KI, Krishnan RS, et al. Ascorbic acid dynamics in the seriously ill and injured. *J Surg Res*. 2003;109(2):144-148.
11. Fowler AA III, Syed AA, Knowlson S, et al. Phase I safety trial of IV ascorbic acid in patients with severe sepsis. *J Transl Med*. 2014;12:32.
12. de Grooth HJ, Choo WP, Spoelstra-de Man AM, Swart EL, Oudemans-van Straaten HM. Pharmacokinetics of four high-dose regimens of IV Vitamin C in critically ill patients [abstract]. *Intensive Care Med Exp*. 2016;4(suppl 1):A52.

CHEST

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

PODCAST

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP

BACKGROUND: The global burden of sepsis is estimated as 15 to 19 million cases annually, with a mortality rate approaching 60% in low-income countries.

METHODS: In this retrospective before-after clinical study, we compared the outcome and clinical course of consecutive septic patients treated with intravenous vitamin C, hydrocortisone, and thiamine during a 7-month period (treatment group) with a control group treated in our ICU during the preceding 7 months. The primary outcome was hospital survival. A propensity score was generated to adjust the primary outcome.

RESULTS: There were 47 patients in both treatment and control groups, with no significant differences in baseline characteristics between the two groups. The hospital mortality was 8.5% (4 of 47) in the treatment group compared with 40.4% (19 of 47) in the control group ($P < .001$). The propensity adjusted odds of mortality in the patients treated with the vitamin C protocol was 0.13 (95% CI, 0.04-0.48; $P = .002$). The Sepsis-Related Organ Failure Assessment score decreased in all patients in the treatment group, with none developing progressive organ failure. All patients in the treatment group were weaned off vasopressors, a mean of 18.3 $\pm$ 9.8 h after starting treatment with the vitamin C protocol. The mean duration of vasopressor use was 54.9 $\pm$ 28.4 h in the control group ($P < .001$).

CONCLUSIONS: Our results suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine, are effective in preventing progressive organ dysfunction, including acute kidney injury, and in reducing the mortality of patients with severe sepsis and septic shock. Additional studies are required to confirm these preliminary findings.

CHEST 2017; 151(6):1229-1238

KEY WORDS: corticosteroid; hydrocortisone; septic shock; thiamine; vitamin C

FOR EDITORIAL COMMENT SEE PAGE 1199

ABBREVIATIONS: AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; D5W = dextrose 5% in water; EHR = electronic health record; LOS = length of stay; PCT = procalcitonin; SOFA = Sepsis-Related Organ Failure Assessment; SVCT2 = sodium-vitamin C transporter-2

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (Drs Marik, Khangoora, and Hooper), Eastern Virginia Medical School; the Department of Pharmacy (Dr Rivera), Sentara Norfolk General Hospital; the School of Medical Diagnostic & Translational Sciences (Dr Catravas), College of Health Sciences, Old Dominion University; and the Department of Medicine and Department of Physiological Sciences (Dr Catravas), Eastern Virginia Medical School, Norfolk, VA.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Paul E. Marik, MD, FCCP, Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, 825 Fairfax Ave, Ste 410, Norfolk, VA 23507; e-mail: marikpe@evms.edu

DOI: http://dx.doi.org/10.1016/j.chest.2016.11.036

The global burden of sepsis is substantial with an estimated 15 to 19 million cases per year; the vast majority of these cases occur in low-income countries.[1] With more timely diagnosis and improvement in supportive care the 28-day mortality from sepsis in high-income countries has declined to about 25%; however, the mortality rate from septic shock remains as high as 50%.[2-5] Moreover, the mortality from sepsis and septic shock in low-income countries is approximately 60%.[6-8] In addition to short-term mortality, septic patients suffer from numerous short- and long-term complications, with reduced quality of life and an increased risk of death up to 5 years following the acute event.[9-11] Over the last 3 decades, more than 100 phase 2 and phase 3 clinical trials have been performed testing various novel pharmacologic agents and therapeutic interventions in an attempt to improve the outcome of patients with severe sepsis and septic shock; all of these efforts ultimately failed to produce a novel pharmacologic agent that improved the outcome of sepsis.[12] New therapeutic approaches to sepsis are desperately required. To impact the global burden of sepsis these interventions should be effective, inexpensive, safe, and readily available.

We were confronted with three patients with fulminant sepsis who were almost certainly destined to die from overwhelming septic shock. On the basis of experimental and emerging clinical data, we decided to administer intravenous vitamin C to these patients as a life-saving measure.[13-17] "Moderate-dose" hydrocortisone was added for its theoretical synergistic benefit. All three of these patients made a dramatic recovery and were discharged from the ICU within days with no residual organ dysfunction. On the basis of this experience and the reported safety and potential benefit of this therapeutic intervention, the combination of intravenous vitamin C and corticosteroid became routinely used as adjunctive therapy for the treatment of severe sepsis and septic shock in our ICU. Patents with sepsis predictably have very low serum vitamin C levels, which can only be corrected with intravenous vitamin C at a dose of more than 3 g/d.[16,18,19] On the basis of published clinical data, vitamin C pharmacokinetic modeling, as well as the package insert, we decided to administer 6 g of vitamin C per day, divided in four equal doses.[16,18-23] This dosage is devoid of any reported complications or side effects. Doses as high as 100 to 150 g have been safely administered to patients with burns and malignancy.[17,24,25] Hydrocortisone was dosed according to the consensus guidelines of the American College of Critical Care Medicine.[26] Intravenous thiamine (vitamin B_1) was added to the vitamin C protocol (see the Discussion section for rationale).[27]

Methods

This study was an electronic health record (EHR)-based retrospective before-after clinical study.[28] The study was approved by our institutional review board (#16-08-WC-0179) and the Sentara Health System Office of Research (16-08-SRC-88) (see study protocol e-Appendix 1). This study was conducted at Sentara Norfolk General Hospital, a tertiary care referral hospital affiliated with Eastern Virginia Medical School and the only tertiary care facility in the Hampton Roads area, serving a population of approximately 1.8 million people. Between January 2016 and July 2016, consecutive patients admitted to the Eastern Virginia Medical School Critical Care Medicine service in the general ICU at Sentara Norfolk General Hospital with a primary diagnosis of severe sepsis or septic shock and a procalcitonin (PCT) level $\geq$ 2 ng/mL were treated with intravenous hydrocortisone, vitamin C, and thiamine (vitamin C protocol) within 24 h of ICU admission (treatment group). PCT is routinely measured in our hospital as a screening tool for sepsis and to monitor the evolution of the disease.[29-32] PCT is measured in our laboratory using the VIDAS B·R·A·H·M·S PCT assay, a one-step immunoassay sandwich method with final fluorescence detection (bioMérieux); the lower limit of PCT detection was 0.05 ng/mL. Septic patients with a PCT level $<$ 2 ng/mL within the first 24 h of ICU admission were not treated with the vitamin C protocol. We used a threshold PCT level of 2 ng/mL to increase the certainty that the patients had severe sepsis and were at risk of developing sepsis-related organ dysfunction.[32-34] Patients $<$ 18 years of age, pregnant patients, and patients with limitations of care were not treated with the vitamin C protocol. The control group consisted of a similar number of consecutive patients admitted to our ICU between June 2015 and December 2015, using the same inclusion and exclusion criteria as the treatment group. During the control period, patients with sepsis did not receive intravenous vitamin C or thiamine. The diagnoses of severe sepsis and septic shock were based on the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions.[35]

We queried our EHRs (Epic Systems) to identify patients who met the inclusion criteria for the treatment and control groups. The patients' clinical and demographic data, including age, sex, admitting diagnosis, comorbidities, requirement for mechanical ventilation, use of vasopressors (and hourly dosages), daily urine output (for the first 4 days), fluid balance after 24 and 72 h, length of ICU stay (LOS), and laboratory data, were abstracted from the EHR. Patients were considered immunocompromised if they were taking more than 10 mg of prednisone-equivalent per day for at least 2 weeks, were receiving cytotoxic therapy, or were diagnosed with acquired immunodeficiency syndrome. The hourly dosage of vasopressors was recorded as the norepinephrine equivalent dosage.[36,37] The serum creatinine, WBC, platelet count, total bilirubin, PCT, and lactate levels were recorded daily for the first 4 days. Acute kidney injury (AKI) was defined on the basis of KDIGO (Kidney Disease: Improving Global Outcomes) criteria; namely, an increase in serum creatinine $>$ 0.3 mg/dL or a level $>$ 1.5 times the baseline value.[38] If the baseline serum creatinine was not known a value $>$ 1.5 mg/dL was assumed to be indicative of AKI. The patient's admission

APACHE (Acute Physiology and Chronic Health Evaluation) II and APACHE IV scores, including the APACHE IV predicted hospital mortality, were recorded. The APACHE II score (incrementing score of 0 to 71) and APACHE IV score (incrementing score of 0 to 286) are standardized measures of disease severity that are used to predict hospital mortality.[39,40] The SOFA (Sepsis-Related Organ Failure Assessment) score was calculated daily for 4 days. The SOFA score was designed to sequentially assess the severity of organ dysfunction in patients who were critically ill from sepsis (incrementing score of 0 to 24).[41] The SOFA scores were calculated 24 h after admission to the ICU and daily thereafter.

ICU Treatment Protocol

The overall treatment of patients with sepsis during the control and treatment periods was similar except for the administration of the combination of vitamin C, hydrocortisone, and thiamine during the treatment period.[42] There were no known significant changes to our ICU protocols, referral patterns, or patient population during the study period. During the control period patients received hydrocortisone (50 mg every 6 h) at the discretion of the attending physician.[26,42,43] As per standard operating procedure in our ICU, all patients with sepsis and septic shock are started empirically on broad-spectrum antibiotics, which are then deescalated according to microbiologic data and clinical progress[44]; are treated according to a conservative, physiologically based fluid and vasopressor strategy[45,46]; and are ventilated according to a lung-protective strategy,[46,47] avoiding hyperoxia[48] and with the limited use of sedative agents (preferred agent, dexmedetomidine).[49] Norepinephrine is the vasopressor of first choice and is titrated to a dose of 20 μg/min, targeting a mean arterial pressure > 65 mm Hg. In patients failing to achieve this target, fixed-dose vasopressin was then added at 0.04 units/min followed by phenylephrine or epinephrine.[42,45] Patients receive enteral nutrition with a whey-based formula (Vital 1.2; Abbott), using an intermittent bolus protocol that is started 24 h after ICU admission; once clinical stability is achieved,[50,51] they receive deep venous thrombosis prophylaxis with both enoxaparin (or heparin in patients with a calculated creatinine clearance < 30 mL/min) and sequential compression, and we allow permissive hyperglycemia.[52] Routine stress ulcer prophylaxis is not administered.[53] During the treatment period consecutive patients with a primary admitting diagnosis of severe sepsis or septic shock and a PCT level > 2 ng/mL were treated with intravenous vitamin C (1.5 g every 6 h for 4 days or until ICU discharge), hydrocortisone (50 mg every 6 h for 7 days or until ICU discharge followed by a taper over 3 days), as well as intravenous thiamine (200 mg every 12 h for 4 days or until ICU discharge). The vitamin C was administered as an infusion over 30 to 60 min and mixed in a 100-mL solution of either dextrose 5% in water (D5W) or normal saline. Intravenous thiamine was given as a piggyback in 50 mL of either D5W or normal saline and was administered as a 30-min infusion. We attempted to determine the vitamin C level prior to the first dose of vitamin C. The vitamin C assay was performed at LabCorp by high-pressure liquid chromatography with electrochemical detection. The specimens were collected in a serum separation gel tube, protected from light, and transported on ice. The specimens were frozen prior to transport to the local reference laboratory (LabCorp).

Data Analysis

The first three "pivotal" patients treated with the vitamin cocktail were excluded from analysis. The patients' deidentified clinical and laboratory data were recorded in an electronic spreadsheet. The primary outcome was hospital survival. Secondary outcomes included duration of vasopressor therapy,[54] requirement for renal replacement therapy in patients with AKI, ICU LOS, and the change in serum PCT and SOFA score over the first 72 h.[30,55-58] The procalcitonin clearance was calculated according to the following formula: initial PCT minus PCT at 72 h, divided by the initial PCT multiplied by 100.[57,59] Summary statistics were used to describe the clinical data and are presented as means ± SD, medians and interquartile range, or percentages as appropriate. χ^2 analysis with Fisher's exact test (when appropriate) and Student's *t* test (Mann-Whitney *U* test for nonnormal distributions) were used to compare data between the treatment and control groups, with statistical significance declared for probability values of 0.05 or less. Logistic discriminant analysis was performed on the entire data set to determine the independent predictors of survival. Statistical analysis was performed with NCSS 11 (NCSS Statistical Software) and SPSS Statistics version 24 (IBM).

To adjust for potential baseline differences between the treatment and control groups, SPSS Statistics was used to generate propensity scores for the patients' likelihood to receive the vitamin C protocol. Factors included in propensity score generation included age, weight, sex, APACHE IV score, need for mechanical ventilation at presentation, use of vasopressor agents at presentation, WBC count at presentation, serum lactate level at presentation, procalcitonin level at presentation, and serum creatinine at presentation (e-Table 1). Binary logistic regression with propensity score adjustment was then performed to assess the odds ratio for mortality by treatment group.[60] This analysis was then repeated with both age and propensity score adjustments to assess the odds ratio for mortality (e-Table 2). The propensity score distribution for the treatment and control groups is presented in e-Figure 1, while the APACHE IV distribution between the treatment and control groups is presented in e-Figure 2.

Results

There were 47 patients in each group. The baseline characteristics of the two groups are presented in Table 1; there were no significant differences in baseline characteristics between the two groups. Most patients had multiple comorbidities, with only two patients in the treatment group and one in the control group being previously "healthy." The distribution of infections was similar between the two groups, with the lung being the most common site of infection. Blood cultures were positive in 13 patients (28%) in each group. *Escherichia coli* (n = 6) and gram-positive organisms (n = 3) were the commonest blood isolates in the treatment group while gram-positive organisms (n = 6) and *E coli* (n = 4) were the commonest isolates in the control group. Correctly timed baseline vitamin C levels were available for 22 patients in the treatment group; the mean level was 14.1 ± 11.8 μM (normal, 40-60 μM), with no patient having a normal level. Twenty-two patients (47%) in each group were treated with vasopressor agents and met the criteria for septic shock. The primary and secondary outcomes are provided in Table 2. The hospital mortality was 8.5% (4 of 47 patients) in the treatment group compared with

TABLE 1] Baseline Characteristics of Treated and Control Patients

Variable	Treated (n = 47)	Control (n = 47)
Age, mean ± SD, y	58.3 ± 14.1	62.2 ± 14.3
Sex, male, No. (%)	27 (57)	23 (49)
Comorbidities, No. (%)		
None	2 (4)	1 (2)
Diabetes	16 (34)	20 (42)
Hypertension	20 (43)	25 (53)
Heart failure	15 (32)	16 (34)
Malignancy	5 (11)	7 (15)
COPD	8 (17)	7 (15)
Cirrhosis	6 (13)	3 (6)
CVA	8 (17)	5 (11)
CRF	7 (15)	8 (17)
Morbid obesity	6 (13)	8 (17)
Immunocompromised[a]	6 (13)	4 (9)
Drug addiction	5 (11)	5 (11)
Primary diagnosis, No. (%)		
Pneumonia	18 (38)	19 (40)
Urosepsis	11 (23)	10 (21)
Primary bacteremia	7 (15)	7 (15)
GI/biliary	6 (13)	6 (13)
Other	5 (11)	5 (11)
Mechanical ventilation, No. (%)	22 (47)	26 (55)
Vasopressors, No. (%)	22 (46)	22 (46)
Acute kidney injury, No. (%)	31 (66)	30 (64)
Positive blood cultures, No. (%)	13 (28)	13 (28)
WBC,[b] mean ± SD, × 10^9	20.6 ± 13.5	17.1 ± 13.4
Lactate, mean ± SD, mM	2.7 ± 1.5	3.1 ± 2.8
Creatinine,[c] mean ± SD, mg/dL	1.9 ± 1.4	1.9 ± 1.1
Procalcitonin, median and IQR, ng/ml	25.8 (5.8-93.4)	15.2 (5.9-39.0)
Day 1 SOFA, mean ± SD	8.3 ± 2.8	8.7 ± 3.7
APACHE II, mean ± SD	22.1 ± 6.3	22.6 ± 5.7
APACHE IV, mean ± SD	79.5 ± 16.4	82.0 ± 27.4
Predicted mortality, mean ± SD	39.7 ± 16.7	41.6 ± 24.2

There were no significant differences in baseline characteristics between groups. APACHE = Acute Physiology and Chronic Health Evaluation; CRF = chronic respiratory failure; CVA = cerebrovascular accident; IQR = interquartile range; SOFA = Sepsis-Related Organ Failure Assessment.
[a]HIV infection, neutropenia, post-transplantation, and so on.
[b]Excluding neutropenic patients.
[c]Excluding patients with chronic renal failure.

40.4% (19 of 47 patients) in the control group ($P < .001$). The predicted and actual mortality for the treatment and control groups is illustrated in Figure 1. Logistic discriminant analysis identified three independent predictors of mortality, namely, treatment with the vitamin C protocol (F value, 17.33; $P < .001$), the APACHE IV score (F value, 13.29; $P < .001$), and need for mechanical ventilation (F value, 3.75; $P = .05$). The propensity adjusted odds of mortality in patients treated with the vitamin C protocol was 0.13 (95% CI, 0.04-0.48; $P = 002$). None of the patients in the treatment group died of complications related to sepsis. All these patients survived their ICU stay, received "comfort care" on the hospital floor, and died of

TABLE 2] Outcome and Treatment Variables

Variable	Treated (n = 47)	Control (n = 47)
Hospital mortality, No. (%)	4 (8.5)	19 (40.4)[a]
ICU LOS, median and IQR, d	4 (3-5)	4 (4-10)
Duration of vasopressors, mean ± SD, h	18.3 ± 9.8	54.9 ± 28.4 [a]
RRT for AKI, No. (%)	3 of 31 (10%)	11 of 30 (33%)[b]
ΔSOFA, 72 h	4.8 ± 2.4	0.9 ± 2.7[a]
Procalcitonin clearance, median % and IQR, 72 h	86.4 (80.1-90.8)	33.9 (−62.4 to 64.3)[a]

AKI = acute kidney injury; LOS = length of stay; RRT = renal replacement therapy; ΔSOFA = change in Sepsis-Related Organ Failure Assessment score. See Table 1 legend for expansion of other abbreviations.
[a]$P < .001$.
[b]$P = .02$.

complications of their underlying disease (advanced dementia, severe heart failure, advanced sarcoidosis, and severe COPD).

Twenty-eight patients (59.6%) in the control group were treated with hydrocortisone. Thirty-one patients (66%) in the treatment group met the criteria for AKI compared with 30 (64%) in the control group (not significantly different). Three patients (10%) with AKI in the treatment group required renal replacement therapy compared with 11 (37%) in the control group ($P = .02$). The 24-h fluid balance was 2.1 ± 3.2 L in the treatment group compared with 1.9 ± 2.7 L in the control group (not significantly different). Similarly, the 72-h fluid balance was 1.9 ± 3.7 L in the treatment group compared with 1.6 ± 3.3 L in the control group. All patients in the treatment group were weaned off vasopressors a mean of 18.3 ± 9.8 h after starting treatment with the vitamin C protocol. The dose of pressors was predictably reduced between 2 and 4 h after the first infusion of vitamin C. The mean duration of vasopressor use was 54.9 ± 28.4 h in the control group ($P < .001$); nine patients in the control group received escalating doses of vasopressors and died of refractory septic shock. The mean duration of vasopressor treatment was 61.4 ± 33.8 h in the control patients who died compared with 38.7 ± 6.5 h in those who survived. The time course of the vasopressor dose (in norepinephrine equivalents)[36,37] in the treatment group, the control patients who died, and the control patients who survived is illustrated in Figure 2. The 72-h ΔSOFA score was 4.8 ± 2.4 in the treatment group compared with 0.9 ± 2.7 in the control group ($P < .001$). None of the patients in the treatment group developed new organ failure (as reflected by an increase in their SOFA score) requiring an escalation of therapy. The time course of the SOFA score in the treatment group, the control patients who died, and the control patients who survived

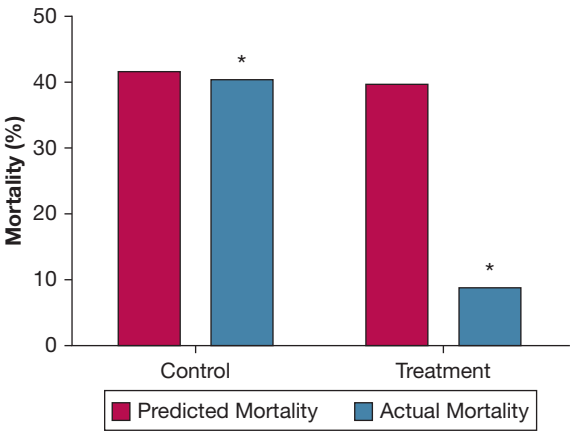


Figure 1 – *Predicted and actual mortality in the treatment and control groups. Predicted mortality was derived from APACHE IV scoring system results. *P < .001 for comparison of treatment group vs control group (see text). APACHE = Acute Physiology and Chronic Health Evaluation.*

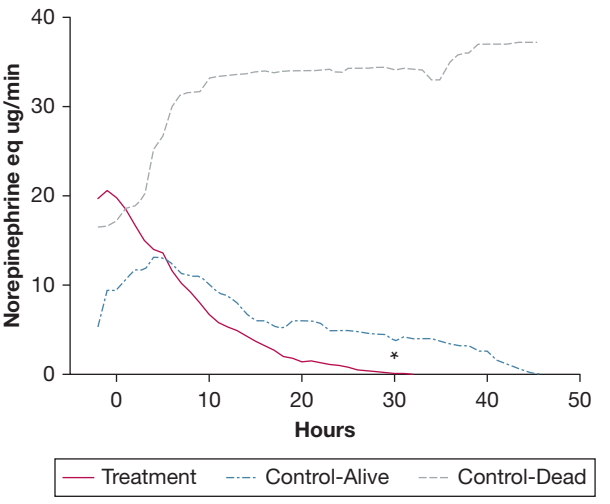


Figure 2 – *Time course of vasopressor dose (in norepinephrine equivalents) in the treatment group and in the control group survivors and nonsurvivors. *P < .001 for comparison of treatment group vs control group (see text).*

is shown in Figure 3. The median 72-h PCT clearance was 86.4% (80.1%-90.8%) in the treatment group compared with 33.9% (–62.4% to 64.3%) in the control group ($P < .001$); the time course of the PCT over the first 4 days is illustrated in Figure 4. The median ICU LOS was 4 (3-5) days in the treatment group compared with 4 (4-10) days in the control group (not significantly different).

Discussion

In this observational study the combination of intravenous vitamin C, moderate-dose hydrocortisone, and thiamine appeared to have a marked effect on the natural history of patients with severe sepsis and septic shock. No patient in the treatment group developed progressive organ failure, and the four deaths in this group were related to the patients' underlying disease; these patients did not die of sepsis-related complications. Our study evaluated the use of intravenous vitamin C, hydrocortisone, and thiamine in a real-world setting where all eligible patients with sepsis were studied. This is important as less than 20% of eligible patients with severe sepsis and septic shock are commonly included in many of the sepsis trials, limiting the applicability and generalizability of the results.[61] Furthermore, we did not test an expensive, proprietary designer molecule, but rather the combination of three inexpensive and readily available agents with a long safety record and in clinical use since 1949.[62,63]

The findings of our study are supported by extensive experimental and clinical studies that have demonstrated

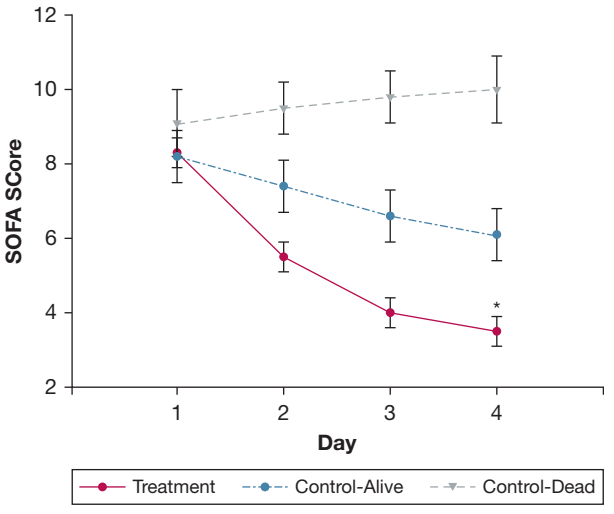


Figure 3 – *Time course of the SOFA score over the 4-day treatment period in the treatment group and in the control group survivors and nonsurvivors. *P < .001 for comparison of treatment group vs control group (see text). SOFA = Sepsis-Related Organ Failure Assessment.*

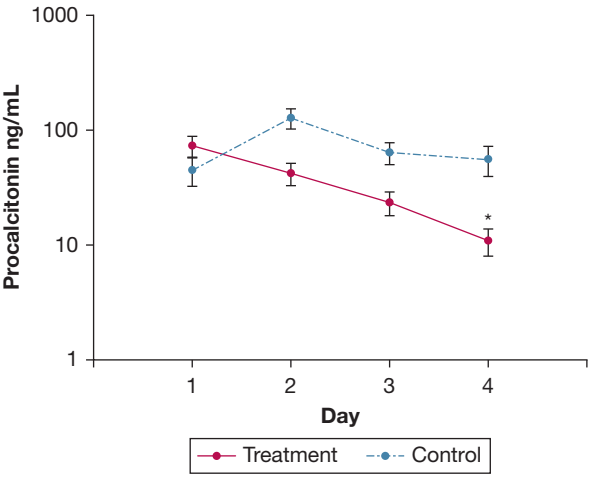


Figure 4 – *Time course of the PCT score over the 4-day treatment period in the treatment group and in the control group plotted on a semilog scale. *P < .001 for comparison of treatment group vs control group (see text). PCT = procalcitonin.*

the safety and potential benefit of moderate-dose hydrocortisone, intravenous vitamin C, and thiamine in critically ill patients.[16,17,21,26,64] However, ours is the first study to evaluate the combination of intravenous vitamin C, hydrocortisone, and thiamine, a combination we believe synergistically reverses the pathophysiologic changes of sepsis. The outcome data are supported by the time course of the PCT levels and SOFA score as well as the rapid decline in vasopressor requirements in the treatment group as compared with the control group. The time course of PCT in patients with severe sepsis and septic shock has been evaluated in a number of studies.[31,32,65] These studies have demonstrated a linear fall in PCT, reaching about 30% of the baseline value in 72 h; a fall of greater than 30% over this time has been shown to indicate the appropriate use of antibiotics and is predictive of survival. In the treatment group, the PCT fell exponentially in all patients, reaching a median of 86% of the baseline value at 72 h. In comparison, the PCT remained relatively unchanged in the control group during this time. This observation is supported by the pilot study of Fowler et al,[16] who in a randomized controlled trial evaluated the clinical response to low-dose (50 mg/kg/d) and high-dose vitamin C (200 mg/kg/d) (without corticosteroids) in 24 patients with sepsis. In this study, the fall of the PCT in the first 72 h was approximately 40% in the low-dose group and 80% in the high-dose group whereas it increased in the control patients. In our study, the mean time to vasopressor independence after starting the vitamin C protocol was 18 h. The mean duration of vasopressor therapy was 54 h in the control group. In the literature, the mean duration of vasopressor dependency in patients with septic shock is

reported to vary between about 72 and 120 h.[37,54] In the VANISH (Vasopressin vs Noradrenaline as Initial Therapy in Septic Shock) trial, the median time to shock reversal was 45 h (interquartile range, 23-75 h).[66] The mean duration of vasopressor dependency in the patients treated with vitamin C in the study by Fowler et al[16] was 86 h. Similarly, in the CORTICUS (Corticosteroid Therapy of Septic Shock) study, the time to vasopressor independence was 79 h.[54] These data support the contention that vitamin C, hydrocortisone, and thiamine have synergistic effects in reversing vasoplegic shock in patients with sepsis. Shortening the duration of vasopressor treatment and preventing dose escalation likely have numerous beneficial effects, including limiting organ and limb ischemia.[66-68] Furthermore, norepinephrine exerts antiinflammatory and bacterial growth-promoting effects, which may potentiate the immunoparesis of sepsis, thereby increasing the susceptibility to secondary infections.[69]

Experimental studies have demonstrated that both vitamin C and hydrocortisone have multiple and overlapping beneficial pathophysiologic effects in sepsis. Vitamin C is a potent antioxidant that directly scavenges oxygen free radicals; restores other cellular antioxidants, including tetrahydrobiopterin and α-tocopherol; and is an essential cofactor for iron- and copper-containing enzymes.[70,71] Both drugs inhibit nuclear factor-κB activation, down-regulating the production of proinflammatory mediators; increase tight junctions between endothelial and epithelial cells; preserve endothelial function and microcirculatory flow; are required for the synthesis of catecholamines; and increase vasopressor sensitivity.[13-15,26,70-75] Vitamin C plays a major role in preserving endothelial function and microcirculatory flow.[70,72] In addition, vitamin C activates the nuclear factor erythroid 2-like 2 (Nrf2)/heme oxygenase (HO)-1 pathway, which plays a critical role in antioxidant defenses and enhances T-cell and macrophage function.[76-78] The explanation as to why the combination of intravenous vitamin C, hydrocortisone, and thiamine appeared to have a marked effect on the course of sepsis, as compared with the myriad of designer molecules that have been evaluated in previous sepsis trials, is likely related to the multiple and overlapping effects of all three agents as compared with drugs that target a single molecule or pathway.[12] Furthermore, we believe that vitamin C and corticosteroids act synergistically.[79] Oxidation of cysteine thiol groups of the glucocorticoid receptor affects ligand and DNA binding, reducing the efficacy of glucocorticoids.[80,81] Vitamin C has been demonstrated to reverse these changes and restore glucocorticoid function.[82] The transport of vitamin C into the cell is mediated by the sodium-vitamin C transporter-2 (SVCT2).[83] Proinflammatory cytokines have been demonstrated to decrease expression of SVCT2.[84] Glucocorticoids, however, have been shown to increase expression of SVCT2.[85] In an experimental model using cultured human lung vascular endothelial cells exposed to endotoxin we have demonstrated that incubation with the combination of vitamin C and hydrocortisone preserved endothelial integrity as compared with either agent alone, the latter being no more effective than placebo.[86] This finding is in keeping with clinical studies suggesting that hydrocortisone and vitamin C alone have little impact on the clinical outcome of patients with sepsis.[16,54] The HYPRESS (Hydrocortisone for Prevention of Septic Shock) study failed to demonstrate an outcome benefit from a hydrocortisone infusion in patients with severe sepsis.[87]

While the dosing strategy for corticosteroids (hydrocortisone) in patients with severe sepsis and septic shock has been well studied,[26,88] that for vitamin C is more uncertain. Critically ill patients have either low or undetectable vitamin C levels (normal serum levels, 40-60 μM).[18,19] Because of the saturable intestinal transporter (sodium-vitamin C transporter-1),[20,83] oral administration of doses as high as 1,500 mg cannot restore normal serum levels.[20] To achieve normal serum vitamin C levels in critically ill patients, a daily dose of more than 3 g is required.[16,18,21] On the basis of pharmacokinetic data and preliminary dose-response data we believe that a daily dose of 6 g combined with hydrocortisone is optimal. When high dosages of vitamin C are given intravenously, metabolic conversion to oxalate increases.[19] Oxalate is normally excreted by the kidney, and serum levels will increase with renal impairment. In patients with renal impairment receiving megadose vitamin C, supersaturation of serum with oxalate may result in tissue deposition as well as crystallization in the kidney.[89,90] Worsening renal function is therefore a concern with megadose vitamin C. It is noteworthy that renal function improved in all the patients with AKI. Glyoxylate, a byproduct of intermediary metabolism, is either reduced to oxalate or oxidized to carbon dioxide by the enzyme glyoxylate aminotransferase; thiamine pyrophosphate is a coenzyme required for this reaction.[91] Thiamine deficiency increases the conversion of glyoxylate to oxalate.[92,93] Thiamine deficiency is common in septic patients and is associated with an increased risk of death.[64]

For these reasons, thiamine was included in our vitamin C protocol.

Our study has several limitations, namely the small sample size, single-center design, and the participation of nonconcurrent control subjects. Furthermore, the treatment and control periods occurred during different seasons. We used propensity score adjustment in an attempt to control for some of these factors. We believe that the data from our study are internally consistent, have a valid mechanistic basis, and are supported by experimental studies. In addition, the safety of hydrocortisone, vitamin C, and thiamine is supported by more than 50 years of clinical experience. Because of the inherent safety of the combination of hydrocortisone, vitamin C, and thiamine we believe that this treatment strategy can be adopted pending the results of further clinical trials. We believe that the results of our study provide sufficient information for the design of an adequately powered, high-quality pragmatic trial to confirm the findings of our study. Because of the lack of clinical equipoise and the ethics of withholding a potentially lifesaving intervention, we were unable to initiate a randomized controlled trial in our center. Furthermore, while our observational study suggests that a 4-day course of vitamin C is optimal, additional studies are required to determine the ideal dosing strategy, and the contributing role of thiamine requires further exploration.

In conclusion, the results of our study suggest that the early use of intravenous vitamin C, together with moderate-dose hydrocortisone and thiamine, may prove to be effective in preventing progressive organ dysfunction, including acute kidney injury, and reducing the mortality of patients with severe sepsis and septic shock. This inexpensive and readily available intervention has the potential to reduce the global mortality from sepsis. Additional studies are required to confirm our preliminary findings.

Acknowledgments

Author contributions: P. M. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. P. M.: Conception of study, literature review, pharmacologic modeling and interpretation, study design, study execution, data collection, data analysis, data interpretation, writing of study. V. K.: Literature review, study design, data analysis, data interpretation, writing of study. R. R.: Pharmacologic modeling and interpretation, formulation of dosing strategy, study execution, data collection, writing of study. M. H.: Interpretation of data, statistical analysis, writing of study. J. C.: Study design, interpretation of data, writing of study.

Financial/nonfinancial disclosures: None declared.

Other contributions: The authors acknowledge the thoughtful comments of Jerry Nadler, MD, FAHA, MACP, Chair of Medicine, and Edward Oldfield, MD, retired Chief of Infectious Diseases, both at Eastern Virginia Medical School.

Additional information: The e-Appendix, e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Adhikari NK, Fowler RA, Bhagwanjee S, et al. Critical care and the global burden of critical illness in adults. *Lancet*. 2010;376(9749):1339-1346.
2. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA*. 2014;311:1308-1316.
3. Gaieski DF, Edwards JM, Kallan MJ, et al. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med*. 2013;41:1167-1174.
4. Kadri SS, Rhee C, Strich JR, et al. Estimating ten-year trends in septic shock incidence and morality in United States Academic Medical Centers using clinical data. *Chest*. 2017;151(2):278-285.
5. Marik PE, Linde-Zwirble WT, Bittner EA, et al. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database [published online ahead of print January 27, 2017]. *Intensive Care Med*. http://dx.doi.org/10.1007/s00134-016-4675-y.
6. Silva E, de Almeida Pedro M, Beltrami Sogayar AC, et al. Brazilian Sepsis Epidemiological Study (BASES study). *Crit Care*. 2004;8(4):R251-R260.
7. Sales JA, David CM, Hatum R, et al; Sepsis Brazil Study. Sepse Brasil: Estudo Epidemiologico da Sepse em Unidades de Terapia Intensiva Brasileiras [An epidemiological study of sepsis in intensive care units]. *Rev Bras Ter Int*. 2006;18:9-17.
8. World Health Organization. The top 10 causes of death: the 10 leading causes of death by country income group 2012. WHO fact sheet. http://www.who.int/mediacentre/factsheets/fs310/en/index1.html. Published 2016. Accessed December 15, 2016.
9. Karlsson S, Ruokonen E, Varpula T, et al. Long-term outcome and quality-adjusted life years after severe sepsis. *Crit Care Med*. 2009;37(4):1268-1274.
10. Yende S, Austin S, Rhodes A, et al. Long-term quality of life among survivors of severe sepsis: analyses of two international trials. *Crit Care Med*. 2016;44(8):1461-1467.
11. Ou SM, Chu H, Chao PW, et al. Long-term mortality and major adverse cardiovascular events in sepsis survivors: a nationwide population-based study. *Am J Respir Crit Care Med*. 2016;194(2):209-217.
12. Artenstein AW, Higgins TL, Opal SM. Sepsis and scientific revolutions. *Crit Care Med*. 2013;41(12):2770-2772.
13. Fisher BJ, Kraskauskas D, Martin EJ, et al. Attenuation of sepsis-induced organ injury in mice by vitamin C. *JPEN*. 2014;38(7):825-839.
14. Fisher BJ, Seropian IM, Masanori Y, et al. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Crit Care Med*. 2011;39(6):1454-1460.
15. Zhou G, Kamenos G, Pendem S, et al. Ascorbate protects against vascular leakage in cecal ligation and puncture-induced septic peritonitis. *Am J Physiol Regulatory Integrative Comp Physiol*. 2012;302(4):R409-R416.
16. Fowler AA, Syed AA, Knowlson S, et al. Phase 1 safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med*. 2014;12:32.
17. Tanaka H, Matsuda T, Miyagantani Y, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch Surg*. 2000;135(3):326-331.
18. Long CL, Maull KL, Krishman RS, et al. Ascorbic acid dynamics in the seriously ill and injured. *J Surg Res*. 2003;109(2):144-148.

19. de Grooth HJ, Choo WP, Spoelstra-de Man AM, et al. Pharmacokinetics of four high-dose regime[n]s of intravenous vitamin C in critically ill patients [abstract]. *Intensive Care Med Exp*. 2016;4(suppl 1):A52.

20. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med*. 2004;140(7):533-537.

21. Nathens AB, Neff MJ, Jurkovich GJ, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Ann Surg*. 2002;236(6):814-822.

22. Zabet MH, Mohammadi M, Ramezani M, et al. Effect of high-dose ascorbic acid on vasopressor requirement in septic shock. *J Res Pharm Pract*. 2016;5(2):94-100.

23. Ascorbic acid injection. Torrance Company. http://medlibrary.org/lib/rx/meds/ascorbic-acid-5/. Updated November 18, 2016. Accessed December 15, 2016.

24. Ohno S, Ohno Y, Suzuki N, et al. High-dose vitamin C (ascorbic acid) therapy in the treatment of patients with advanced cancer. *Anticancer Res*. 2009;29(3):809-815.

25. Stephenson CM, Levin RD, Spector T, et al. 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.

26. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(6):1937-1949.

27. Marik PE. "Vitamin S" (steroids) and vitamin C for the treatment of severe sepsis and septic shock! *Crit Care Med*. 2016;44(6):1228-1229.

28. Fiore LD, Lavori PW. Integrating randomized comparative effectiveness research with patient care. *N Engl J Med*. 2016;374(22):2152-2158.

29. Wacker C, Prkno A, Brunkhorst FM, et al. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(5):426-435.

30. Schuetz P, Maurer P, Punjabi V, et al. Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. *Crit Care*. 2013;17(3):R115.

31. Charles PE, Tinel C, Barbar S, et al. Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and outcome. *Crit Care*. 2016;13(2):R38.

32. Reynolds SC, Shorr AF, Muscedere J, et al. Longitudinal changes in procalcitonin in a heterogeneous group of critically ill patients. *Crit Care Med*. 2012;40(10):2781-2787.

33. Arora S, Singh P, Singh PM, et al. Procalcitonin levels in survivors and non survivors of sepsis: systematic review and meta-analysis. *Shock*. 2015;43(3):212-221.

34. Kutz A, Briel M, Christ-Crain M, et al. Prognostic value of procalcitonin in respiratory tract infections across clinical settings. *Crit Care*. 2015;19:74.

35. Society of Critical Care Medicine Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20(6):864-874.

36. Mancl EE, Muzevich KM. Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. *JPEN*. 2013;37(5):641-651.

37. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-887.

38. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care*. 2013;17(1):204.

39. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-828.

40. Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med*. 2006;34(5):1297-1310.

41. Vincent JL, Moreno R, Takala J, et al; Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-Related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22(7):707-710.

42. Marik PE. Early management of severe sepsis: current concepts and controversies. *Chest*. 2014;145(6):1407-1418.

43. Siemieniuk RA, Meade MP, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163(7):519-528.

44. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, et al. De-escalation of emperical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med*. 2014;40(1):32-40.

45. Marik P, Bellomo R. A rational apprach to fluid therapy in sepsis. *Br J Anaesth*. 2016;116(3):339-349.

46. Marik PE. Fluid responsiveness and the six guiding principles of fluid resuscitation. *Crit Care Med*. 2016;44(10):1920-1922.

47. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.

48. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA*. 2016;316(15):1583-1589.

49. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306.

50. Marik PE. Feeding critically ill patients the right "whey": thinking outside of the box: a personal view. *Ann Intensive Care*. 2015;5(1):51.

51. Marik PE. Is early starvation beneficial for the critically ill patient? *Curr Opin Clin Nutr Metab Care*. 2016;19(2):155-160.

52. Marik PE. Tight glycemic control in acutely ill patients: low evidence of benefit, high evidence of harm! *Intensive Care Med*. 2016;42(9):1475-1477.

53. Marik PE. Stress ulcer prophylaxis de-adoption: what is the barrier? *Crit Care Med*. 2016;44(10):1939-1941.

54. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.

55. Karlsson S, Heikkinen M, Pettila V, et al. Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study. *Crit Care*. 2010;14(6):R205.

56. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286(14):1754-1758.

57. de Azevedo JR, Torres OJ, Beraldi RA, et al. Prognostic evaluation of severe sepsis and septic shock: procalcitonin clearance vs Δ Sequential Organ Failure Assessment. *J Crit Care*. 2015;30(1):219-212.

58. Guan J, Lin Z, Lue H. Dynamic change of procalcitonin, rather than concentration itself, is predictive of survival in septic shock patients when beyond 10 ng/mL. *Shock*. 2011;36(6):570-574.

59. Ruiz-Rodriguez JC, Caballero J, Ruiz-Sanmartin A, et al. Usefulness of procalcitonin clearance as a prognostic biomarker in septic shock: a prospective pilot study. *Medicina Intensiva*. 2012;36(7):475-480.

60. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.

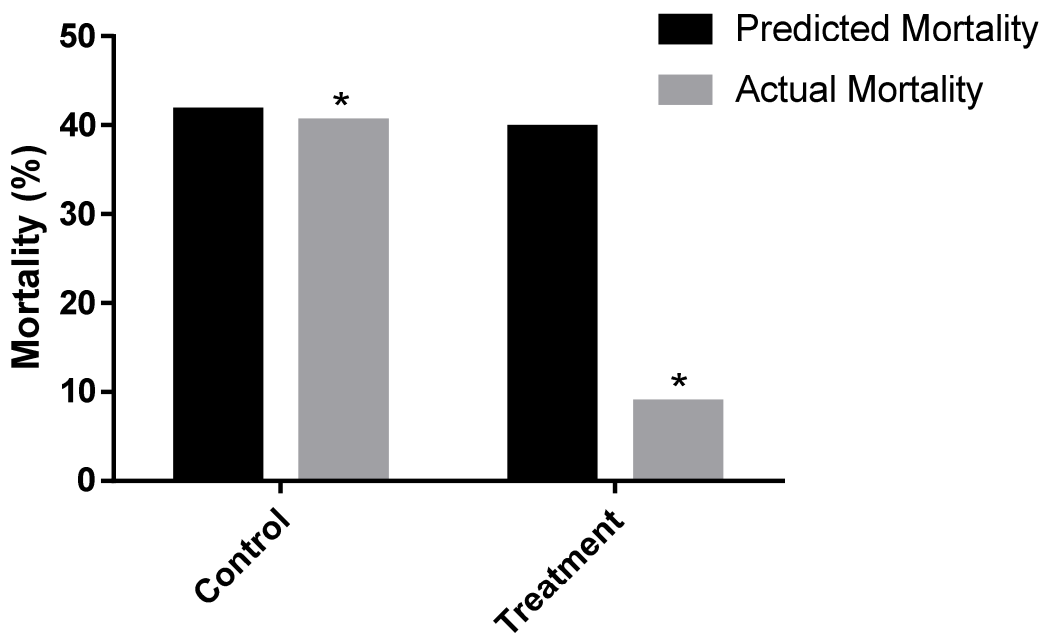
61. Marik PE, Pastores SM, Kavanaugh BP. Selection bias negates conclusions from the CORTICUS study? *N Engl J Med*. 2008;358:2069-2070.

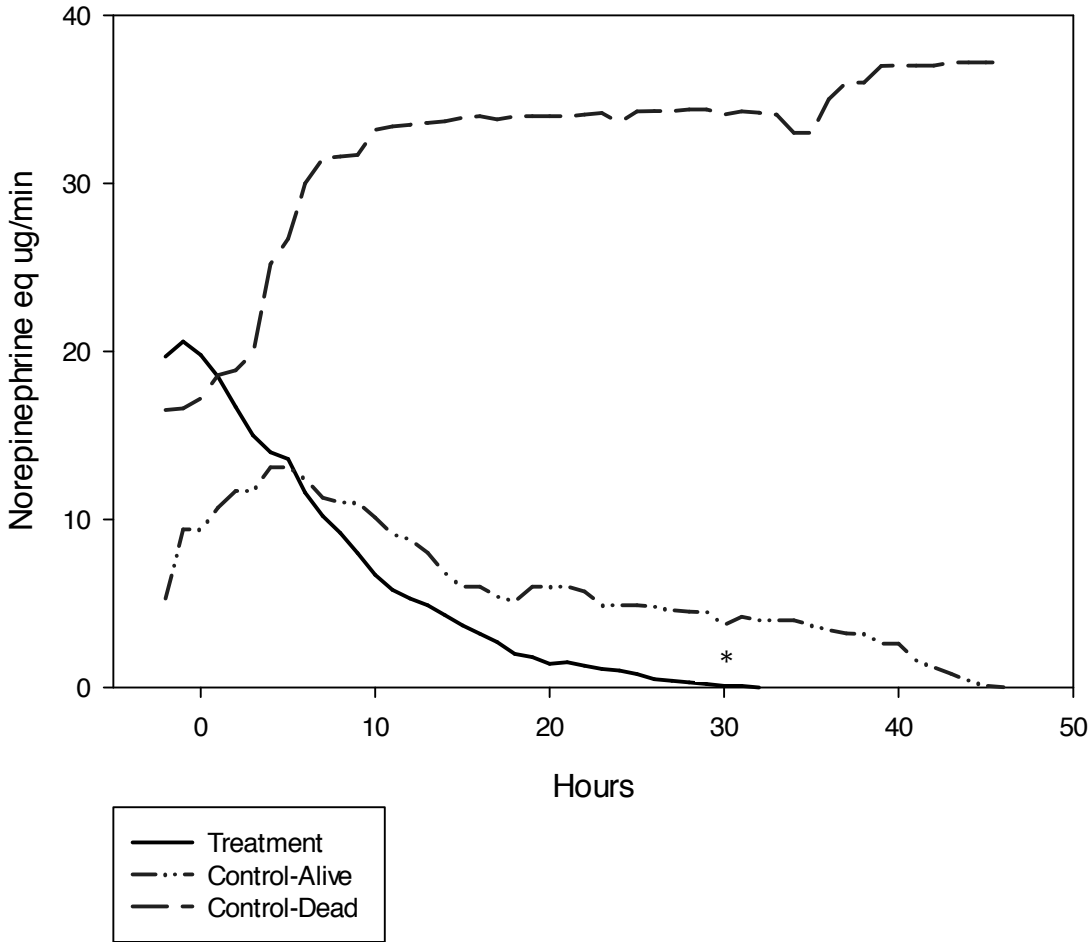
62. Klenner FR. The treatment of poliomyelitis and other virus diseases with vitamin C. *South Med Surg*. 1949;111(7):209-214.

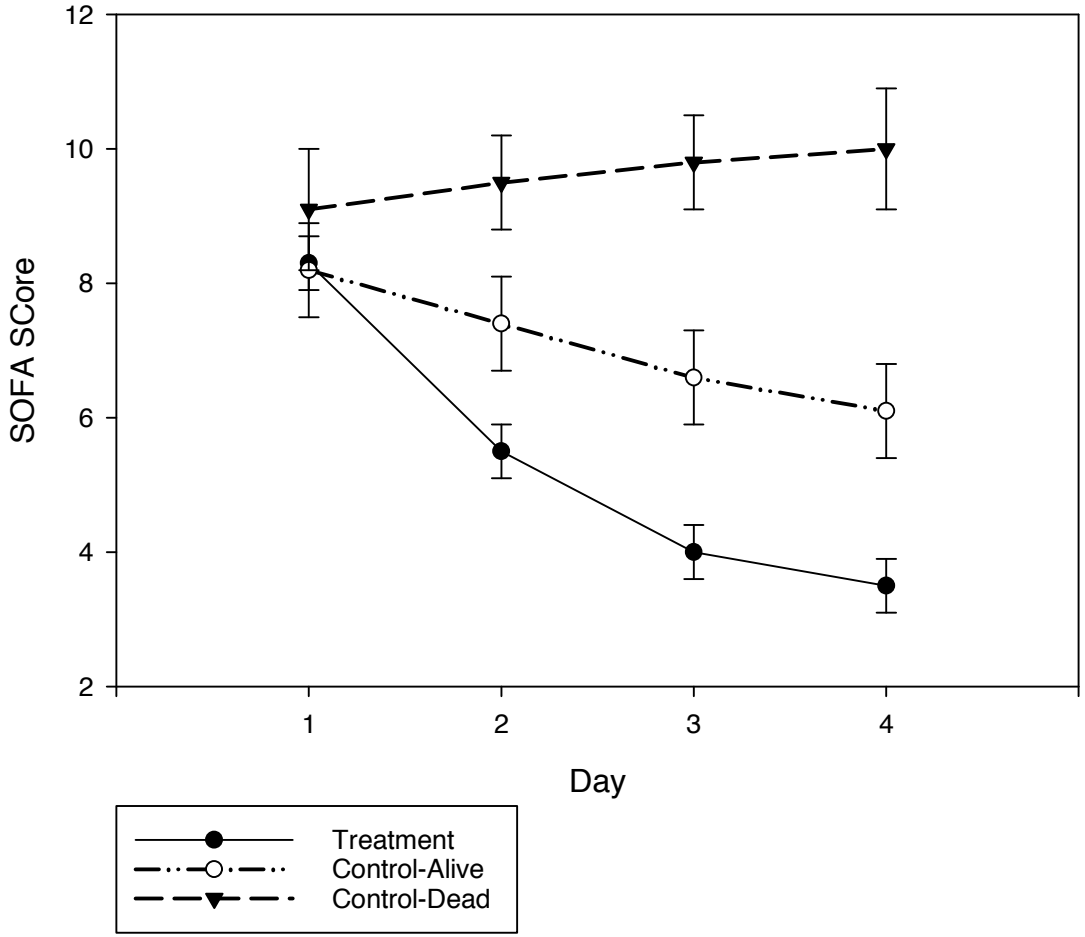
63. Hench PS, Kendall EC, Slocumb CH, et al. The effect of a hormone of the adrenal

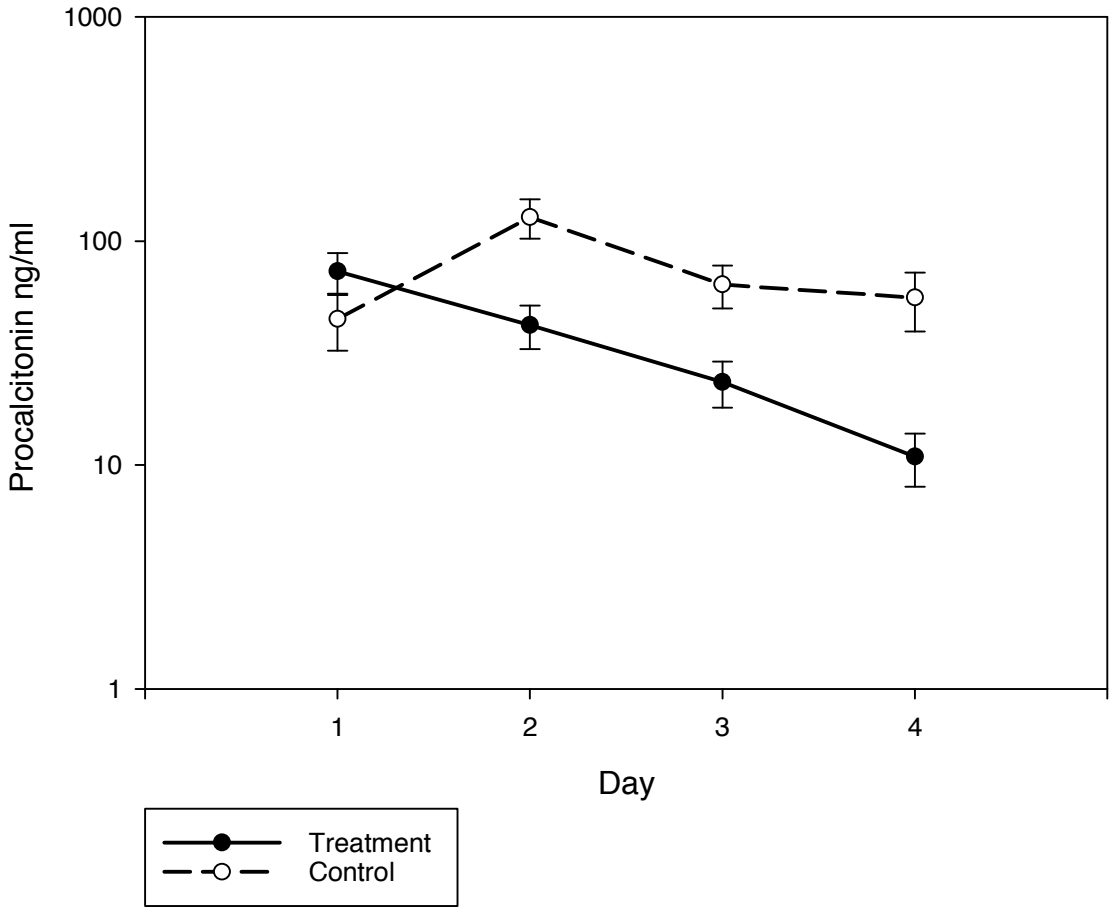
cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and the pituitary adenocorticotrophic hormone on rheumatoid arthritis: preliminary report. *Ann Rheum Dis*. 1949;8(2):97-104.

64. Donnino MW, Andersen LW, Chase M, et al. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. *Crit Care Med*. 2016;44(2):360-367.
65. Gibot S, Cravoisy A, Kolopp-Sarda MN, et al. Time-course of sTREM (soluble triggering receptor expressed on myeloid cells)-1, procalcitonin, and C-reactive protein plasma concentrations during sepsis. *Crit Care Med*. 2005;33(4):792-796.
66. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. *JAMA*. 2016;316(5):509-518.
67. Hayes MA, Yau EH, Hinds CJ, et al. Symmetrical peripheral gangrene: association with noradrenaline administration. *Intensive Care Med*. 1992;18(7):433-436.
68. Dunser MW, Wenzel V, Hasibeder WR. Ischemic skin lesions and microcirculatory collapse during vasopressin therapy: a possible role of the microcirculation? *Acta Anaesthesiol Scand*. 2006;50(5):637-638.
69. Stolk RF, van der Poll T, Angus DC, et al. Potentially inadvertant immunomodulation: norepinephrine use in sepsis. *Am J Respir Crit Care Med*. 2016;194(5):550-558.
70. May JM. Role of vitamin C in the function of the vascular endothelium. *Antioxid Redox Signal*. 2013;19(17):2068-2083.
71. Wilson JX. Evaluation of vitamin C for adjuvant sepsis therapy. *Antioxid Redox Signal*. 2013;19(17):2129-2140.
72. Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. *Biofactors*. 2009;35(1):5-13.
73. Han M, Pendem S, Teh SL, et al. Ascorbate protects endothelial barrier function during septic insult: role of protein phosphatase type 2A. *Free Radic Biol Med*. 2010;48(1):128-135.
74. Dillon PF, Root-Bernstein RS, Lieder CM. Antioxidant-independent ascorbate enhancement of catecholamine-induced contractions of vascular smooth muscle. *Am J Physiol Heart Circ Physiol*. 2004;286(6):H2353-H2360.
75. Marik PE. Critical illness related corticosteroid insufficiency. *Chest*. 2009;135(1):181-193.
76. Kalden JR. Prolonged skin allograft survival in vitamin C-deficient guinea-pigs: preliminary communication. *Eur Surg Res*. 1972;4(2):114-119.
77. Kim SR. Ascorbic acid reduces HMGB1 secretion in lipopolysaccharide-activated RAW 264.7 cells and improves survival rate in septic mice by activation of Nrf2/HO-1 signals. *Biochem Pharmacol*. 2015;95(4):279-289.
78. Manning J, Mitchell B, Appadurai DA, et al. Vitamin C promotes maturation of T-cells. *Antioxid Redox Signal*. 2013;19(17):2054-2067.
79. Fogarty A, Scrivener SL, Antoniak M, et al. Corticosteroid sparing effects of vitamin C and magnesium in asthma: a randomised trial. *Respir Med*. 2006;100(1):174-179.
80. Bodwell JE, Holbrook NJ, Munck A. Sulfhydryl-modifying reagents reversibly inhibit binding of glucocorticoid-receptor complexes to DNA-cellulose. *Biochemistry*. 1984;23(7):1392-1398.
81. Okamoto K, Tanaka H, Ogawa H, et al. Redox-dependent regulation of nuclear import of the glucocorticoid receptor. *J Biol Chem*. 1999;274(15):10363-10371.
82. Okamoto K, Tanaka H, Makino Y, et al. Restoration of the glucocorticoid receptor function by the phosphodiester compound of vitamins C and E, EPC-K1 (l-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-yl hydrogen phosphate] potassium salt), via a redox-dependent mechanism. *Biochem Pharmacol*. 1998;56(1):79-86.
83. Burzle M, Hediger MA. Functional and physiological role of vitamin C transporters. *Curr Top Membr*. 2012;70:357-375.
84. Seno T, Inoue N, Matsui K, et al. Functional expression of sodium-dependent vitamin C transporter 2 in human endothelial cells. *J Vasc Res*. 2004;41(4):345-351.
85. Fujita I, Hirano J, Itoh N, et al. Dexamethasone induces sodium-dependant vitamin C transporter in a mouse osteoblastic cell line MC3T3-E1. *Br J Nutr*. 2001;86(2):145-149.
86. Barabutis N, Khangoora V, Marik PE, et al. Hydrocortisone and ascorbic acid synergistically protect against LPS-induced pulmonary endothelial barrier dysfunction. *Chest*. In press.
87. Keh D, Trips E, Marx G, et al; SepNet-Critical Care Trials Group. Effect of hydrocortisone on development of shock among patients with severe sepsis: the HYPRESS Randomized Clinical Trial. *JAMA*. 2016;316(17):1775-1785.
88. Minneci PC, Deans KJ, Eichacker PQ, et al. The effects of steroids during sepsis depend on dose and severity of illness: an updated meta-analysis. *Clin Microbiol Infect*. 2009;15(4):308-318.
89. Massey LK. Ascorbate increases human oxaluria and kidney stone risk. *J Nutr*. 2005;135(7):1673-1677.
90. Wandzilak TR. Effect of high dose vitamin C on urinary oxalate levels. *J Urol*. 1994;151(4):834-837.
91. Hoppe B, Beck BB, Milliner D. The primary hyperoxalurias. *Kidney Int*. 2009;75(12):1264-1271.
92. Sidhu H, Gupta R, Thind SK, et al. Oxalate metabolism in thiamine-deficient rats. *Ann Nutr Metab*. 1987;31(6):354-361.
93. Ortiz-Alvarado O, Muyaoka R, Kriedberg C, et al. Pyridoxine and dietary counseling for the management of idiopathic hyperoxaluria in stone-forming patients. *Urology*. 2011;77(5):1054-1058.









3. Yanke G, Rady MY, Verheijde JL. In re guardianship of Hailu: The Nevada Supreme Court casts doubt on the standard for brain death diagnosis. *Med Sci Law*. 2017;57(2):100-102.
4. Machado C, Perez-Nellar J, Estevez M, et al. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2011;76(3):307-309.
5. Wijdicks EF. The case against confirmatory tests for determining brain death in adults. *Neurology*. 2010;75(1):77-83.

Response

To the Editor:

As we have presented, because there are numerous reasons why consent should not be required prior to an evaluation for brain death (BD), Nevada revised its Uniform Determination of Death Act (UDDA) to stipulate that consent is not needed to conduct a BD evaluation.[1,2] Rady et al[3] argue that this is constitutionally problematic.

The revisions to Nevada's UDDA stem from the response of the Supreme Court of Nevada to the case of Aden Hailu, a woman whose father requested continuation of organ support after she was declared brain dead using the practice parameter for determination of BD from the American Academy of Neurology (AANPP).[4] The AANPP was originally written in 1995 in response to concerns raised by the authors of the UDDA and was updated in 2010.[5] The Court found that organ support should be continued because the hospital did not provide sufficient evidence or expert testimony that the AANPP is the accepted criteria for determination of BD in the medical community. Notably, the Court stated that their ruling was not an attempt to "set in stone certain medical criteria for determining BD," but rather that it was based on the "undeveloped record before [them]."[4]

The Nevada Assembly sought to avoid future confusion about the criteria needed to determine BD, so they proposed revisions to their UDDA to clearly state that BD determination in an adult must be made in accordance with the AANPP.[2] Additionally, because questions about the need for consent prior to the determination of BD were raised in recent lawsuits in other states, the Assembly specified in the revised UDDA that BD determination is a clinical decision and therefore does not require consent. The determination is not based on "battery" as Rady et al[3] claim but rather on a neurologic examination that is similar to, but more detailed than, the routine examination performed multiple times a day on comatose patients around the world.[1-3] The AANPP provides: (1) clear instructions about performing the examination and apnea testing, (2) stipulations on how to avoid complications during the evaluation, and (3) indications to abort apnea testing.[5]

We applaud Nevada for revising their UDDA in response to these recent lawsuits. Although claims have been made that determination of BD in the absence of consent violates a patient's freedom of religion and privacy, determination of death should not be a negotiated standard or choice.[1,6] Nonetheless, determination of whether or not Nevada's UDDA revision is constitutionally problematic is outside the purview of physicians.

Ariane Lewis, MD
New York, NY
David Greer, MD
Boston, MA

AFFILIATIONS: From the Division of Neurocritical Care (Dr Lewis), Departments of Neurology and Neurosurgery, NYU Langone Medical Center; and the Department of Neurology (Dr Greer), Boston University Medical Center.

FINANCIAL/NONFINANCIAL DISCLOSURES: See earlier cited article for author conflicts of interest.

CORRESPONDENCE TO: Ariane Lewis, MD, Division of Neurocritical Care, Department of Neurology, NYU Langone Medical Center, 530 First Ave, HCC-5A New York, NY 10016; e-mail: ariane.kansas.lewis@gmail.com

DOI: http://dx.doi.org/10.1016/j.chest.2017.06.051

References

1. Lewis A, Greer D. Point: Should informed consent be required for apnea testing in patients with suspected brain death? No. *Chest*. 2017;152(4):700-702.
2. An Act Relating to the Determination of Death, 2017 Nevada Acts ch. 315 (A.B. 424), effective Oct 1, 2017.
3. Rady MY, Verheijde JL, Yanke G. Nonconsensual determination of neurologic (brain) death: Is it a violation of constitutional rights? *Chest*. 2017;152(4):903-904.
4. In Re: Guardianship of Hailu. 2015.
5. Wijdicks EFM, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2010;74(23):1911-1918.
6. Alameda Superior Court Case No. RP 13–707598.

Vitamin C and Sepsis
Framing the Postpublication Discussion

To the Editor:

We read with interest the recent study by Marik et al[1] published in the June 2017 issue of *CHEST*. The trial has many notable limitations, which, in our opinion, render

its findings hypothesis generating. However, given the long history of frustrated attempts to identify novel pharmacotherapies for patients with sepsis, efforts to advance the care of critically ill patients should be applauded.

Our concern centers on efforts by the investigators to leverage the lay press and medical education blogs to frame their findings as revolutionary. In a press release filed jointly by Eastern Virginia Medical School and Sentara Healthcare, the study's lead author Dr Marik states, "my intention was never to discover the cure for sepsis, it just kind of happened by mistake."[2] This message has been emphasized by Dr Marik on popular medical education blogs (which are read by thousands of trainees and practicing physicians in internal medicine and emergency medicine) stating, "there can be no question of doubt that we have changed the natural history and disease progression of patients with sepsis."[3]

The leap from retrospective single-center data to unequivocal proclamations of safety and efficacy is a startling one. Aggressive nutritional supplementation in the early stages of critical illness has repeatedly been shown not to benefit patients. Vitamin C supplementation in critical illness has been studied in high-quality trials without any signal of benefit. In a recent multicenter randomized trial of high-protein enteral nutrition enriched with immune-modulating nutrients including vitamin C, patients in the intervention arm actually had increased adjusted mortality at 6 months compared with patients who received standard high-protein enteral nutrition.[4] Arguing, as the study authors do, that high-dose IV supplementation is not only more efficacious but also unquestionably safe ignores high-quality trials of other antioxidant therapy. Glutamine, an amino acid felt to have many of the same immunomodulatory properties as vitamin C, although no better than placebo at moderate doses,[5] increased rates of death when given at high doses.[6]

These studies do not refute Marik et al's findings. They do, however, highlight the need for caution and humility when extrapolating the results of a single-center study to scores of critically ill patients. Without ingenuity and persistence in the face of repeated failures, medical breakthroughs would not be possible. However, when in the desperate hope for discovery we greet the fantastic with unblinking acceptance, we risk becoming unmoored from the principles that have guided steady advances in the care of critically ill patients.

James M. Walter, MD
Benjamin D. Singer, MD
Chicago, IL

AFFILIATIONS: Division of Pulmonary and Critical Care, Department of Medicine, Northwestern University Feinberg School of Medicine.

CORRESPONDENCE TO: James M. Walter, MD, Division of Pulmonary and Critical Care, Department of Medicine, Northwestern University Feinberg School of Medicine, 240 E Huron, McGaw M-300, Chicago, IL 60611; e-mail: james.walter@northwestern.edu

DOI: http://dx.doi.org/10.1016/j.chest.2017.06.038

References

1. 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.
2. EVMS Magazine. A cure for sepsis? http://www.evms.edu/about_evms/administrative_offices/marketing_communications/publications/issue_9_4/sepsis.php?utm_source=digital_magazine&utm_medium=web&utm_campaign=sepsis_resources&utm_content=media - media-professional. Accessed April 25, 2017.
3. PulmCrit/EMCrit. Metabolic sepsis resuscitation: the evidence behind Vitamin C. https://emcrit.org/pulmcrit/metabolic-sepsis-resuscitation/. Accessed April 25, 2017.
4. van Zanten AR, Sztark F, Kaisers UX, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. *JAMA*. 2014;312(5):514-524.
5. Andrews PJ, Avenell A, Noble DW, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. *BMJ*. 2011;342:d1542.
6. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med*. 2013;368(16):1489-1497.

Response

To the Editor:

We thank Drs Walter and Singer for their comments regarding our study.[1] However, we believe that a number of the quoted statements have been taken out of context or misinterpreted. It is true that we did not expect our therapy to have a dramatic impact on the initial treated patients and we did not expect to see the dramatic impact on mortality that we witnessed vs historical control subjects. Although the standards for applying the term cure are different in the lay press, we were responding to the apparent size of the effect from our intervention. Furthermore, it is true that we believe that the treatment was effective for patients with sepsis. This strong belief was the reason that we applied the therapy to additional patients and why we analyzed those results after the fact. We agree that additional well-designed studies are necessary to convince the medical community of the efficacy of this treatment.

and Bolukbas), University Hospital Wuppertal, University Witten/Herdecke.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Michael Eberlein, MD, PhD, University of Iowa, 200 Hawkins Dr, C-33-GH, Iowa City, IA 52242; e-mail: michael-eberlein@uiowa.edu

DOI: http://dx.doi.org/10.1016/j.chest.2017.03.060

References

1. Dugan KC, Laxmanan B, Murgu S, Hogarth DK. Management of persistent air leaks. *Chest*. 2017;152(2):417-423.
2. Petrella F, Rizzo S, Radice D, et al. Predicting prolonged air leak after standard pulmonary lobectomy: computed tomography assessment and risk factors stratification. *Surgeon*. 2011;9(2):72-77.
3. Liang S, Ivanovic J, Gilbert S, et al. Quantifying the incidence and impact of postoperative prolonged alveolar air leak after pulmonary resection. *J Thorac Cardiovasc Surg*. 2013;145(4):948-954.
4. Chahla M, Larson CD, Parekh KR, et al. Transpleural ventilation via spiracles in severe emphysema increases alveolar ventilation. *Chest*. 2016;149(6):e161-e167.
5. Khauli S, Bolukbas S, Reed RM, Eberlein M. Interlobar collateral ventilation in severe emphysema. *Thorax*. 2016;71(12):1168-1169.

Response

To the Editor:

We thank Drs Eberlein, Reed, Redwan, and Bolukbas for their insightful comments on our recent article in *CHEST* regarding the relationship between collateral ventilation and persistent air leaks (PALs).[1] As they pointed out in their letter, emphysema has been identified as a significant risk factor for the development of PALs following surgery. Indeed, collateral ventilation is more prevalent in patients with emphysema and incomplete fissures and would not only put these patients at risk for a PAL but likely make management more challenging.[2] When endobronchial valves (EBVs) have been used for bronchoscopic lung volume reduction, the researchers found a lack of significant improvement in patients with incomplete fissures, arguing that collateral ventilation can complicate EBV placement by allowing air to bypass the pathway of greater resistance.[3] Anecdotally, as hypothesized in the letter, we have seen evidence of this phenomenon when placing EBVs in patients with emphysema and a PAL. Typically, occluding only one airway does not resolve the air leak (despite proper localization using the endobronchial balloon technique), and multiple valves may need to be placed, sometimes in more than one lobe. Thus, on average, three valves are typically required to control each PAL.[4] The Valves Against Standard Therapy (VAST) study is ongoing, comparing EBVs with standard care for PALs.[5] We hope that this study will allow a further analysis of fissure integrity (as assessed by using chest CT scans) and the success of EBVs for patients experiencing PALs.

Karen C. Dugan, MD
Balaji Laxmanan, MD
Septimiu Murgu, MD, FCCP
D. Kyle Hogarth, MD, FCCP
Chicago, IL

AFFILIATIONS: From the Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago.

FINANCIAL/NONFINANCIAL DISCLOSURES: See earlier cited article for author conflicts of interest.

CORRESPONDENCE TO: D. Kyle Hogarth, MD, FCCP, University of Chicago, Department of Medicine, Section of Pulmonary and Critical Care, 5841 S Maryland Ave, Chicago, IL 60637; e-mail: dhogarth@uchicago.edu

DOI: http://dx.doi.org/10.1016/j.chest.2017.04.165

References

1. Dugan KC, Laxmanan B, Murgu S, Hogarth DK. Management of persistent air leaks. *Chest*. 2017;152(2):417-423.
2. Terry PB, Traystman RJ, Newball HH, et al. Collateral ventilation in man. *N Engl J Med*. 1978;298(1):10-15.
3. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med*. 2010;363(13):1233-1244.
4. Travaline JM, McKenna RJ, De Giacomo T. Treatment of persistent pulmonary air leaks using endobronchial valves. *Chest*. 2009;136(2):355-360.
5. Spiration Valves Against Standard Therapy (VAST). 2015. NLM identifier NCT02382614. https://clinicaltrials.gov/ct2/show/NCT02382614. Accessed June 13, 2017.

Vitamin C in Sepsis

When It Seems Too Sweet, It Might (Literally) Be

To the Editor:

We read with great interest the paper by Marik et al[1] published in *CHEST* (June 2017). The authors described their experience using a vitamin C-containing regimen as adjunctive therapy in sepsis. Whether this approach is prime for clinical practice is open to debate; however, we wish to issue a cautionary note to clinicians who may adopt this approach regarding the "fictitious hyperglycemia" that has been described with the use of vitamin C in the population of burn patients.[2] Significant discrepancies between point-of-care (POC) and central laboratory-analyzed blood glucose values have been previously reported in burn patients receiving high-dose vitamin C (mean of 225 mg/dL vs 138 mg/dL, respectively).[2] These discrepancies are often inconsistent over time and can range from 10 to 200 units.[3] A falsely

elevated POC blood glucose measurement may result in overly aggressive insulin therapy, resulting in iatrogenic hypoglycemia, and reportedly has been attributed to patient mortality in at least one case.[2] Thus, if appropriate precautions are not in place, the regimen may not be "devoid of… side effects," as the authors assert, when implemented into clinical practice.[1]

This directly impacts centers using glucose-dehydrogenase-pyrroloquinoline quinone amperometric methods (or similar technology), a technology commonly used in POC testing.[2,4] In a comparative assessment of various POC devices, ascorbic acid concentrations falsely increased glucose readings > 30% in commonly used POC technologies, including Accu-Chek (Roche Diagnostic) and Optium (Abbott Diabetes Care) (but not StatStrip; Nova Biomedical), underpinning the importance of awareness regarding an ICU's POC technology.[4] Although other types of POC testing modalities may not be as susceptible to the effects of vitamin C, clinical evidence is lacking.[3]

Based on the mechanism by which vitamin C oxidizes at the electrode, releases an electron, and creates additional negative charges measured at the electrode, it seems logical that this effect would be dose dependent. Although this phenomenon has mostly been observed with higher doses of vitamin C (66 mg/kg/h for 18-24 hours) than used in the present study (1.5 g every 6 hours), caution remains warranted.[1,2] Extrapolated from phase I data, the anticipated blood levels of ascorbic acid used in the present study are likely to yield concentrations in the range shown to interfere with POC testing.[1,4,5] As vitamin C continues to be studied in a research fashion or implemented clinically, it seems prudent to adopt recommendations from the burn literature and avoid reliance on POC testing to monitor blood glucose and titrate insulin during vitamin C therapy and for up to 24 hours following completion of therapy.[2]

Alexander H. Flannery, PharmD, BCCCP, BCPS
Melissa L. Thompson Bastin, PharmD, BCPS
Carolyn A. Magee, PharmD
Eric S. Bensadoun, MD, MPH, FCCP
Lexington, KY

AFFILIATIONS: From the Department of Pharmacy Services (Drs Flannery, Bastin, and Magee), University of Kentucky HealthCare, University of Kentucky College of Pharmacy; Division of Pulmonary, Critical Care, and Sleep Medicine (Dr Bensadoun), Department of Internal Medicine, University of Kentucky College of Medicine.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Alexander H. Flannery, PharmD, BCCCP, BCPS, 800 Rose St, H110, Lexington, KY 40536; e-mail: alex.flannery@uky.edu

DOI: http://dx.doi.org/10.1016/j.chest.2017.05.023

References

1. 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.
2. Kahn SA, Lentz CW. Fictitious hyperglycemia: point-of-care glucose measurement is inaccurate during high-dose vitamin C infusion for burn shock resuscitation. *J Burn Care Res*. 2015;36(2):e67-e71.
3. Sartor Z, Kesey J, Dissanaike S. The effects of intravenous vitamin C on point-of-care glucose monitoring. *J Burn Care Res*. 2015;36(1):50-56.
4. Ceriotti F, Kaczmarek E, Guerra E, et al. Comparative performance assessment of point-of-care testing devices for measuring glucose and ketones at the patient bedside. *J Diabetes Sci Technol*. 2015;9(2):268-277.
5. Fowler AA 3rd, Syed AA, Knowlson, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med*. 2014;12:32.

Response

To the Editor:

We appreciate the correspondence of Flannery et al regarding their concerns regarding point-of-care (POC) glucose testing in patients receiving IV vitamin C.[1] We are aware of this potential interaction. Vitamin C and glucose have very similar molecular structures, both being six-carbon molecules, with glucose-6-phospate being the precursor molecule of vitamin C. Spuriously elevated POC glucose levels have been reported in patients with burns who have received large pharmacologic doses of vitamin C (in excess of 50 g/d).[2,3] This phenomenon has been reported with vitamin C and other compounds with POC glucose devices that incorporate the glucose-dehydrogenase-pyrroloquinoline quinone amperometric method of testing. The pharmacologic doses of vitamin C used in patients with burns[2,3] and those with malignancy[4-6] result in concentrations of vitamin C in the mmol/L range. Our dosing strategy (1.5 g IV every 6 hours) will result in blood vitamin C levels that are in the 200 μmol/L range, which should not cause a significant cross reaction with blood glucose concentrations that are in the mmolar range (6-11 mmol). To validate this, we have measured blood glucose levels with POC testing (Accu-Chek Inform, Roche) and simultaneously with our central laboratory at the end of the vitamin C infusion and have noted minimal differences in the measured

elevated POC blood glucose measurement may result in overly aggressive insulin therapy, resulting in iatrogenic hypoglycemia, and reportedly has been attributed to patient mortality in at least one case.[2] Thus, if appropriate precautions are not in place, the regimen may not be "devoid of… side effects," as the authors assert, when implemented into clinical practice.[1]

This directly impacts centers using glucose-dehydrogenase-pyrroloquinoline quinone amperometric methods (or similar technology), a technology commonly used in POC testing.[2,4] In a comparative assessment of various POC devices, ascorbic acid concentrations falsely increased glucose readings > 30% in commonly used POC technologies, including Accu-Chek (Roche Diagnostic) and Optium (Abbott Diabetes Care) (but not StatStrip; Nova Biomedical), underpinning the importance of awareness regarding an ICU's POC technology.[4] Although other types of POC testing modalities may not be as susceptible to the effects of vitamin C, clinical evidence is lacking.[3]

Based on the mechanism by which vitamin C oxidizes at the electrode, releases an electron, and creates additional negative charges measured at the electrode, it seems logical that this effect would be dose dependent. Although this phenomenon has mostly been observed with higher doses of vitamin C (66 mg/kg/h for 18-24 hours) than used in the present study (1.5 g every 6 hours), caution remains warranted.[1,2] Extrapolated from phase I data, the anticipated blood levels of ascorbic acid used in the present study are likely to yield concentrations in the range shown to interfere with POC testing.[1,4,5] As vitamin C continues to be studied in a research fashion or implemented clinically, it seems prudent to adopt recommendations from the burn literature and avoid reliance on POC testing to monitor blood glucose and titrate insulin during vitamin C therapy and for up to 24 hours following completion of therapy.[2]

Alexander H. Flannery, PharmD, BCCCP, BCPS
Melissa L. Thompson Bastin, PharmD, BCPS
Carolyn A. Magee, PharmD
Eric S. Bensadoun, MD, MPH, FCCP
Lexington, KY

AFFILIATIONS: From the Department of Pharmacy Services (Drs Flannery, Bastin, and Magee), University of Kentucky HealthCare, University of Kentucky College of Pharmacy; Division of Pulmonary, Critical Care, and Sleep Medicine (Dr Bensadoun), Department of Internal Medicine, University of Kentucky College of Medicine.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Alexander H. Flannery, PharmD, BCCCP, BCPS, 800 Rose St, H110, Lexington, KY 40536; e-mail: alex.flannery@uky.edu

DOI: http://dx.doi.org/10.1016/j.chest.2017.05.023

References

1. 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.
2. Kahn SA, Lentz CW. Fictitious hyperglycemia: point-of-care glucose measurement is inaccurate during high-dose vitamin C infusion for burn shock resuscitation. *J Burn Care Res*. 2015;36(2):e67-e71.
3. Sartor Z, Kesey J, Dissanaike S. The effects of intravenous vitamin C on point-of-care glucose monitoring. *J Burn Care Res*. 2015;36(1):50-56.
4. Ceriotti F, Kaczmarek E, Guerra E, et al. Comparative performance assessment of point-of-care testing devices for measuring glucose and ketones at the patient bedside. *J Diabetes Sci Technol*. 2015;9(2):268-277.
5. Fowler AA 3rd, Syed AA, Knowlson, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med*. 2014;12:32.

Response

To the Editor:

We appreciate the correspondence of Flannery et al regarding their concerns regarding point-of-care (POC) glucose testing in patients receiving IV vitamin C.[1] We are aware of this potential interaction. Vitamin C and glucose have very similar molecular structures, both being six-carbon molecules, with glucose-6-phospate being the precursor molecule of vitamin C. Spuriously elevated POC glucose levels have been reported in patients with burns who have received large pharmacologic doses of vitamin C (in excess of 50 g/d).[2,3] This phenomenon has been reported with vitamin C and other compounds with POC glucose devices that incorporate the glucose-dehydrogenase-pyrroloquinoline quinone amperometric method of testing. The pharmacologic doses of vitamin C used in patients with burns[2,3] and those with malignancy[4-6] result in concentrations of vitamin C in the mmol/L range. Our dosing strategy (1.5 g IV every 6 hours) will result in blood vitamin C levels that are in the 200 µmol/L range, which should not cause a significant cross reaction with blood glucose concentrations that are in the mmolar range (6-11 mmol). To validate this, we have measured blood glucose levels with POC testing (Accu-Chek Inform, Roche) and simultaneously with our central laboratory at the end of the vitamin C infusion and have noted minimal differences in the measured

levels. We therefore believe that in the dosage used in our study, the interaction between vitamin C and POC glucose testing is not a clinically significant problem.

Paul E. Marik, MD, FCCP
Racquel Rivera, PharmD
Michael H. Hooper, MD
Vikramjit Khangoora, MD
John Catravas, PhD, FCCP
Norfolk, VA

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (Drs Marik, Hooper, and Khangoora), and the Departments of Medicine and Physiological Sciences (Dr Catravas), Eastern Virginia Medical School; the Department of Pharmacy (Dr Rivera), Sentara Norfolk General Hospital; and the School of Medical Diagnostic and Translational Sciences (Dr Catravas), College of Health Sciences, Old Dominion University.

FINANCIAL/NONFINANCIAL DISCLOSURES: See earlier cited article for author conflicts of interest.

CORRESPONDENCE TO: Paul E. Marik, MD, FCCP, 825 Fairfax Ave, Ste 410, Norfolk VA 23507; e-mail: marikpe@evms.edu

DOI: http://dx.doi.org/10.1016/j.chest.2017.05.028

References

1. Marik PE, Khangoora V, Rivera R, et al. 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.
2. Kupfer DJ, Ehlers CL, Pollock BG, et al. Clomipramine and EEG sleep in depression. *Psychiatry Res*. 1989;30(2):165-180.
3. Sartor Z, Kesey J, Dissanaike S. The effects of intravenous vitamin C on point-of-care glucose monitoring. *J Burn Care Res*. 2015;36(1):50-56.
4. Chen Q, Espey MG, Krishna MC, et al. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. *Proc Natl Acad Sci U S A*. 2005;102(38):13604-13609.
5. Hoffer LJ, Robitaille L, Zakarian R, et al. High-dose intravenous vitamin C combined with cytotoxic chemotherapy in patients with advanced cancer: a phase I-II clinical trial. *PloS One*. 2015;10(4):e0120228.
6. Yun J. Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. *Science*. 2015;350(6266):1391-1396.