

EDITORIAL

Open Access



# Doctor—your septic patients have scurvy!

Paul E. Marik\* and Michael H. Hooper

See related research by Carr et al., <https://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1891-y>.

Scurvy is a disease of antiquity described in Egyptian Hieroglyphics and responsible for the deaths of thousands of sailors during the Renaissance. Today, clinicians consider scurvy a very rare disease seen only in patients with extreme dietary deficiencies. They would undoubtedly be shocked to learn that about 40% of the patients in their ICU with septic shock have serum levels of vitamin C supporting a diagnosis of scurvy (<11.3 u/mol/l). The remainder of their patients with sepsis are likely to have hypovitaminosis C (serum level < 23 u/mol/l). Half of their nonseptic ICU patients also have hypovitaminosis C. These are the findings recently reported by Carr et al. [1]. Surprisingly, these astonishing observations are not new. It has been known for over two decades that acute illness results in an acute deficiency of vitamin C with low serum and intracellular levels [2–4]. Low plasma concentrations of vitamin C are associated with more severe organ failure and increased risk of mortality [5]. The most likely explanation for the acute vitamin C deficiency (acute scurvy) in patients with sepsis (and other critical illnesses) is a consequence of metabolic consumption [1]. The fall in serum and cellular levels occurs too rapidly to be explained by decreased gastrointestinal absorption or increased urinary losses. Indeed, in a guinea pig model, myocardial ascorbate was depleted within hours of endotoxin administration [6].

Most clinicians are likewise unaware that primates and guinea pigs are the only mammals that are unable to synthesize vitamin C (in their livers) and that all other mammals increase the synthesis of vitamin C during stress (vitamin C is a true stress hormone). Anthropoid primates and guinea pigs have lost the ability to synthesize vitamin C due to mutations in the L-gulonolactone oxidase (GULO) gene which codes for the enzyme responsible for catalyzing the last step of vitamin C biosynthesis [7]. The inability to synthesize vitamin C may partly explain why humans and guinea pigs have an increased vulnerability to sepsis and to dying from sepsis [8].

The inability to generate vitamin C makes humans very susceptible to dysfunction in a variety of biochemical pathways that are vital for surviving a critical illness such as sepsis. In experimental models of sepsis, treatment with vitamin C limited the deleterious consequences of sepsis by multiple mechanisms, including attenuation of the proinflammatory response, enhancement of the endothelial and epithelial barrier function, and prevention of sepsis-associated coagulation abnormalities [9, 10]. Sepsis is characterized by the excessive production of reactive oxygen species (ROS) by the induction of enzymes such as nicotinamide adenine dinucleotide phosphate-oxidase (NOX) and the uncoupling of mitochondrial oxidative phosphorylation and inducible nitric oxide synthetase [11]. Vitamin C is a key cellular antioxidant which counteracts these ROS. In addition, vitamin C recycles other antioxidants including  $\alpha$ -tocopherol (vitamin E) and tetrahydrobiopterin (BH<sub>4</sub>). BH<sub>4</sub> plays a critical role in the function of endothelial nitric oxide synthase (eNOS). Vitamin C deficiency results in the incomplete regeneration of BH<sub>4</sub> resulting in the uncoupling of eNOS and the generation of superoxide and peroxynitrite [11]. Vitamin C inhibits activation of nuclear factor kappa-B (NF- $\kappa$ B), a major nuclear transcription factor involved in release of numerous proinflammatory mediators [12]. Vitamin C is an essential cofactor for the activity of monoxygenase and dioxygenase enzymes, including those enzymes required for the synthesis of catecholamines and vasopressin [13]. In addition, vitamin C binds adrenergic receptors increasing catecholamine sensitivity (acts like a vasopressor agent).

These facts provide the scientific underpinning for treating septic patients with intravenous vitamin C. Due to severe total body depletion of vitamin C, the need for rapid correction, and limited gastrointestinal absorption (due to the saturable vitamin C transporter), vitamin C must be given intravenously in an adequate dose [14]. Based on our experience in treating over 300 patients with severe sepsis and septic shock, we believe that a dose of 1.5 g every 6 hours is adequate. In our experience, this dose is remarkably safe without any discernible side effects [1]. We routinely monitor serum oxalate

\* Correspondence: [marikpe@evms.edu](mailto:marikpe@evms.edu)

Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, 825 Fairfax Av, Suite 410, Norfolk, VA 23507, USA



in high-risk patients (kidney transplant, patients with kidney stones, etc); two patients were noted to have increased baseline oxalate levels, both of which fell during treatment with intravenous vitamin C. We ascribe this finding to improved renal function as well as the effect of thiamine on oxalate metabolism. We believe the clinical benefit of vitamin C in patients with sepsis is synergistically enhanced with the addition of low-dose corticosteroids and thiamine [15, 16]. This novel therapeutic intervention is being tested prospectively in a number of ongoing randomized controlled trials (ClinicalTrials.gov NCT03333278, NCT03335124, NCT03258684, NCT 03380507). In addition, VICTAS (Vitamin C, Thiamine and Steroids in Sepsis: A Randomized, Double-Blind, Parallel Group Study in Critically Ill Patients with Sepsis) is a large multicenter study being conducted in the USA that should elucidate the potential benefit of this treatment strategy.

#### Acknowledgements

None.

#### Funding

None.

#### Availability of data and materials

Not applicable.

#### Authors' contributions

PEM drafted the original version of the manuscript. MHH reviewed and revised the manuscript. Both authors read and approved the final manuscript.

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Both authors have reviewed the final version of the manuscript and approve the manuscript for publication.

#### Competing interests

The authors declare that they have no competing interests.

#### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 7 December 2017 Accepted: 9 January 2018

Published online: 29 January 2018

#### References

- Carr AC, Rosengrave PC, Bayer S, et al. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. *Crit Care*. 2017;21:300.
- Borrelli E, Roux-Lombard P, Grau GE, et al. Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. *Crit Care Med*. 1996;24:392–7.
- Victor VM, Guayerbas N, Puerto M, et al. Changes in the ascorbic acid levels of peritoneal lymphocytes and macrophages of mice with endotoxin-induced oxidative stress. *Free Radic Res*. 2001;35:907–16.
- Evans-Olders R, Eintracht S, Hoffer LJ. Metabolic origin of hypovitaminosis C in acutely hospitalized patients. *Nutrition*. 2010;26:1070–4.
- De Grooth HM, Spoeistra-de Man AM, Oudermans-van Straaten HM. Early plasma vitamin C concentration, organ dysfunction and ICU mortality. *Intensive Care Med*. 2014;40:S199.
- Rojas C, Cadenas S, Herrero A, et al. Endotoxin depletes ascorbate in the guinea pig heart. Protective effects of vitamins C and E against oxidative stress. *Life Sci*. 1996;59:649–57.
- Drouin G, Godin JR, Page B. The genetics of vitamin C loss in vertebrates. *Current Genomics*. 2011;12:371–8.
- Fuller RN, Henson EC, Shannon EL, et al. Vitamin C deficiency and susceptibility to endotoxin shock in guinea pigs. *Arch Pathol Lab Med*. 1971;92:239–43.
- Fisher BJ, Kraskauskas D, Martin EJ, et al. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. *Am J Physiol Lung Cell Mol Physiol*. 2012;303:L20–32.
- Fisher BJ, Kraskauskas D, Martin EJ, et al. Attenuation of sepsis-induced organ injury in mice by vitamin C. *JPEN*. 2014;38:825–39.
- May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. *Antioxid Redox Signal*. 2013;19:2068–83.
- Carcamo JM, Pedraza A, Borquez-Ojeda O, et al. Vitamin C suppresses TNF-alpha induced NFkB activation by inhibiting IκB-alpha phosphorylation. *Biochem*. 2002;41:12995–3002.
- Carr AC, Shaw G, 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.
- Long CL, Maull KL, Krishnan RS, et al. Ascorbic acid dynamics in the seriously ill and injured. *J Surg Res*. 2003;109:144–8.
- 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;151:1229–38.
- Barabutis N, Khangoora V, Marik PE, et al. Hydrocortisone and ascorbic acid synergistically protect and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. *Chest*. 2017;152:954–62.