

## What are the next steps for vitamin C in sepsis?

Andrew Udy, Tomoko Fujii and Nora Luethi

Severe sepsis accounts for more than 10% of intensive care unit admissions in Australia and New Zealand,<sup>1</sup> and although outcomes have improved over the past decade, hospital mortality in patients with septic shock remains as high as 22%.<sup>1</sup> Indeed, ever since Hippocrates described sepsis nearly 2500 years ago, clinicians and researchers have relentlessly attempted to understand the underlying pathophysiological mechanisms to provide more specific therapies. As sepsis has been characterised by a dysregulated host response to infection, numerous adjunctive therapies targeting the inflammatory cascade have been explored.<sup>2-4</sup>

A recent before-and-after observational study comparing standard care with a combination of vitamin C, thiamine and hydrocortisone in patients with severe sepsis reported a dramatic reduction in mortality and organ failure in patients treated with metabolic resuscitation.<sup>5</sup> These results have created intense debate in both the lay and medical community, sparking renewed interest in the role of vitamin C in the treatment of critically ill patients with sepsis and establishing a seemingly unrealistic therapeutic expectation. Clearly, with the inherent limitations of this study design, a large number of clinical trials are now underway in an attempt to reproduce these data.

In the current issue of *Critical Care and Resuscitation*, McNamara and colleagues<sup>6</sup> present a brief review outlining the biochemical roles of vitamin C in the human body, the consequences of vitamin C deficiency, vitamin C pharmacokinetics, and the possible dosage of parenteral ascorbate (vitamin C) during acute inflammatory conditions. The authors concisely summarise the underlying mechanisms and provide a rationale for the potential use of parenteral ascorbate. During critical illness and acute inflammation, reduced intake and increased oxidative consumption can lead to a rapid fall of plasma ascorbate levels, and a recent study has found that more than 80% of patients with sepsis have some form of hypovitaminosis C.<sup>7,8</sup>

Vitamin C is an essential water-soluble vitamin that humans are not able to store or synthesise *in vivo*. It plays an extensive role as an antioxidant, electron donor, and cofactor for many enzymes and proteins.<sup>8,9</sup> When depleted, the interendothelial electrical coupling of nitric oxide synthase is reduced, and this impairment accelerates the inflammatory cascade, increasing microvascular dysfunction and endothelial permeability.<sup>10-12</sup> The authors suggest that, due to the oxidative environment in acute inflammation, greater parenteral doses of vitamin C might be needed to

replace any deficit in ascorbate metabolism. Furthermore, the synergistic effect of hydrocortisone and vitamin C may also be partly explained by their capacity to reduce the oxidative environment,<sup>13</sup> with vitamin C helping to restore the function of glucocorticoid receptors,<sup>14</sup> and glucocorticoids inducing the expression of a key vitamin C transporter.<sup>15</sup>

However, despite having an appealing model of pathogenesis, the effectiveness of vitamin C administration in sepsis to restore intracellular ascorbate levels, counteract the adverse inflammatory reactions and improve clinical outcomes is yet to be determined.

What are then the next steps for vitamin C in sepsis? Any clinical trial that aims to examine the efficacy or effectiveness of an intervention should be based on an adequate rationale and inherent clinical equipoise. Given that we still have limited knowledge about vitamin C therapy in critical illness, a systematic approach is clearly required before considering a large pragmatic effectiveness trial exploring any reduction in mortality. This would aim to clarify the biological mechanisms supporting the utility of vitamin C in critical illness, and the implications of organ dysfunction on the pharmacokinetics and pharmacodynamics of this agent. Gaining insight into the implementation and feasibility of such an intervention in multiple different centres is similarly a key step.

Fundamental logistic and practical issues concerning vitamin C preparation and stability also need to be addressed before moving to a large pragmatic trial. The Technical Report by Carr and colleagues<sup>16</sup> in this issue of the Journal, describing the stability of vitamin C solutions up to 96 hours after preparation, is therefore very timely. In demonstrating that the prepared vitamin C infusions remain stable in ambient light, the authors provide a crucial piece of information for planning future blinded trials. In Australia and New Zealand, a vital phase 2 study (the Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock [VITAMINS] trial; ClinicalTrials.gov identifier: NCT03333278) is actively recruiting. This randomised open-label controlled clinical trial is comparing vitamin C (6 g/day), thiamine (400 mg/day) and hydrocortisone (200 mg/day) with hydrocortisone monotherapy in critically ill patients with septic shock. The aim is to determine the synergistic effects of metabolic resuscitation on vasopressor requirements and organ dysfunction, while also informing future studies about effect size and feasibility. A smaller substudy will also

explore changes in vitamin C pharmacokinetics in these patients.

As outlined, numerous steps are required in preparing for a definitive effectiveness trial of vitamin C in severe sepsis in order to ensure that the intervention has biological plausibility and is being delivered optimally and at an ideal dose. The articles published in this issue of *Critical Care and Resuscitation* promote this agenda and, along with the future results of the VITAMINS trial, place the Australian and New Zealand intensive care community in an ideal position to ultimately answer this clinical question.

### Competing interests

None declared.

### Author details

Andrew Udy<sup>1,2</sup>

Tomoko Fujii<sup>1,3</sup>

Nora Luethi<sup>1</sup>

1 Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Vic, Australia.

2 Department of Intensive Care and Hyperbaric Medicine, Alfred Hospital, Melbourne, Vic, Australia.

3 Department of Epidemiology and Preventive Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

**Correspondence:** nora.luethi@monash.edu

### References

- 1 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: 1308-16.
- 2 Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; 378: 797-808.
- 3 Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358: 111-24.
- 4 Eisen DP, Reid D, McBryde ES. Acetyl salicylic acid usage and mortality in critically ill patients with the systemic inflammatory response syndrome and sepsis. *Crit Care Med* 2012; 40: 1761-7.
- 5 Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock. *Chest* 2017; 151: 1229-38.
- 6 McNamara R, Deane AM, Anstey J, Bellomo R. Understanding the rationale for parenteral ascorbate (vitamin C) during an acute inflammatory reaction: a biochemical perspective. *Crit Care Resusc* 2018; 20: 174-9.
- 7 Amrein K, Oudemans-van Straaten HM, Berger MM. Vitamin therapy in critically ill patients: focus on thiamine, vitamin C, and vitamin D. *Intensive Care Med* 2018. doi: 10.1007/s00134-018-5107-y [Epub ahead of print]
- 8 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.
- 9 Carr A, Frei B. Does vitamin C act as a pro-oxidant under physiological conditions? *FASEB J* 1999; 13: 1007-24.
- 10 Wilson JX. Evaluation of vitamin C for adjuvant sepsis therapy. *Antioxid Redox Signal* 2013; 19: 2129-40.
- 11 Parker WH, Qu ZC, May JM. Intracellular ascorbate prevents endothelial barrier permeabilization by thrombin. *J Biol Chem* 2015; 290: 21486-97.
- 12 Tymi K. Vitamin C and microvascular dysfunction in systemic inflammation. *Antioxidants (Basel)* 2017; 6: E49.
- 13 Barabutis N, Khangoora V, Marik PE, Catravas JD. Hydrocortisone and ascorbic acid synergistically prevent and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. *Chest* 2017; 152: 954-62.
- 14 Okamoto K, Tanaka H, Makino Y, Makino I. 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.
- 15 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: 145-9.
- 16 Carr A, Wohlrab C, Young P, Bellomo R. Stability of intravenous vitamin C solutions: a technical report. *Crit Care Resusc* 2018; 20: 180-1.