

# To C or not to C? Designing a Pragmatic Trial to Deploy a Novel Immunomodulatory Therapy to Fight Organ Dysfunction in Sepsis

Varun M Angadi<sup>1</sup>, Atul Jindal<sup>2</sup>

**Keywords:** Immunomodulation, Organ dysfunction, Sepsis, Vitamin C.  
*Indian Journal of Critical Care Medicine* (2024): 10.5005/jp-journals-10071-24636

## Dear Editor,

We read the article by Venkataraman et al.,<sup>1</sup> on the usefulness of intravenous vitamin C in lessening organ dysfunction in critically ill adult patients with sepsis. The paradigm shift in viewing sepsis as an entity of 'dysregulated immune response' and not merely an ill-effect of the invading micro-organism has opened up new opportunities in research to look for immune-modulating interventions.<sup>2</sup> Vitamin C, being one such tested intervention with equivocal results is being put to test in the index study and we attempt to critically analyze this topic in the light of available evidence.<sup>3,4</sup>

Starting with the baseline characteristics, the author has provided a comparison of the physiological scores of the patients enrolled in the two groups. However, it would've been prudent to use inferential statistics instead of descriptive statistics for such a comparison where the variables of interest (organ dysfunction scores at admission) are likely to have an impact on the outcome of interest persistent organ dysfunction (POD) in the study. It is impractical to deduce the impact of admission APACHE-II and SOFA scores (with interquartile range) on POD merely based on median values.

The 'Use of corticosteroids' – an intervention carried out at the discretion of the treating physician in this study is an important confounding factor in critically ill patients with sepsis. Significant mortality benefits and a decrease in organ dysfunction have been noted by the use of corticosteroids in patients with sepsis.<sup>5</sup> To negate such confounding effects, a pragmatic study design would be one using matched controls or providing comparative analysis using inferential statistics.

As a process variable, adherence to protocol is the only parameter put to the test. However, a better design would incorporate an objective measure assessing the adequacy of supplementation. Serum levels of vitamin C or a suitable surrogate marker should've been used in this trial before deriving any conclusions regarding its impact on morbidity and mortality.<sup>6,7</sup>

The authors' efforts in designing the trial to test a novel therapy and ensuring complete adherence to the protocol amidst the pandemic are commendable. Though this pilot trial couldn't produce results favoring vitamin C role in sepsis, it is a pioneer to drive concerted efforts in this direction. With a more pragmatic design, more trials testing the benefits of immunomodulation shall come up in this cohort of patients.

## ORCID

Varun M Angadi  <https://orcid.org/0009-0001-0148-1526>  
 Atul Jindal  <https://orcid.org/0000-0002-0504-1077>

<sup>1,2</sup>Department of Pediatrics, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India

**Corresponding Author:** Varun M Angadi, Department of Pediatrics, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India, Phone: +91 9538636135, e-mail: angadi.varun@gmail.com

**How to cite this article:** Angadi VM, Jindal A. To C or not to C? Designing a Pragmatic Trial to Deploy a Novel Immunomodulatory Therapy to Fight Organ Dysfunction in Sepsis. *Indian J Crit Care Med* 2024;28(3):311.

**Source of support:** Nil

**Conflict of interest:** None

## REFERENCES

- Venkataraman R, Sprague S, Ramakrishnan N, Ramachandran P, Jayakumar D, Vijayaraghavan BKT, et al. A pilot feasibility randomized controlled trial of intravenous vitamin C in adults with sepsis in the intensive care unit: The lessening organ dysfunction with vitamin C-India (LOVIT-India) trial. *Indian J Crit Care Med* 2023;27(12):910–916. DOI: 10.5005/jp-journals-10071-24587.
- Toft P, Tønnesen E. Immune-modulating interventions in critically ill septic patients: Pharmacological options. *Expert Rev Clin Pharmacol* 2011;4(4):491–501. DOI: 10.1586/ecp.11.25.
- Fowler AA, Truitt JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. Effect of vitamin c infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: The CITRIS-ALI randomized clinical trial. *JAMA* 2019;322(13):1261–1270. DOI: 10.1001/jama.2019.11825.
- Lamontagne F, Masse MH, Menard J, Sprague S, Pinto R, Heyland DK, et al. Intravenous vitamin c in adults with sepsis in the intensive care unit. *N Engl J Med* 2022;386(25):2387–2398. DOI: 10.1056/NEJMoa2200644.
- Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018;378(9):809–818. DOI: 10.1056/NEJMoa1705716.
- Collie JTB, Greaves RF, Jones OAH, Eastwood G, Bellomo R. Vitamin C measurement in critical illness: Challenges, methodologies and quality improvements. *Clin Chem Lab Med CCLM* 2020;58(4):460–470. DOI: 10.1515/cclm-2019-0912.
- Rozemeijer S, van der Horst FAL, de Man AME. Measuring vitamin C in critically ill patients: Clinical importance and practical difficulties—Is it time for a surrogate marker? *Crit Care* 2021;25(1):310. DOI: 10.1186/s13054-021-03670-x.