

Letter to the Editor

The revised recommendation for administering vitamin C in septic patients: The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020

To the Editor,

Given the available clinical evidence through the literature search when the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG2020) was creating, J-SSCG2020^{1,2} suggested administering vitamin C to septic patients based on the 11 available randomized control trials (RCT).^{3–13}

Recently, Lamontagne *et al.*¹⁴ conducted a large multicenter RCT, including 872 septic patients, who required vasopressors, to evaluate the effect of high-dose vitamin C. This RCT revealed that the proportion of a composite of death or persistent organ dysfunction at 28 days in the vitamin C group was significantly higher than that in the placebo group. Additionally, several RCTs were published after our meta-analysis on this issue for J-SSCG2020. Therefore, we performed an updated systematic review on 20th June 2022. We identified 12 new RCTs^{14–25} and performed an updated meta-analysis using these 23 RCTs (Table 1 and Appendix S1).

In our updated meta-analysis, the estimated value of the desirable anticipated effect was as follows: the length of ICU stay yielded a mean difference (MD) of 0.25 days shorter (95% Confidence interval (CI): 0.72 days shorter–0.22 days longer) (16 RCTs, $n = 3,534$). Thereby, the desirable anticipated effect was thought to be “trivial.” The estimated values of the effects on mortality were as follows: long-term mortality, namely more than 60 days, yielded a risk difference (RD) of 42 more per 1,000 (95% CI: 8 more–83 more; 6 RCTs, $n = 2,881$), 28 or 30 days mortality yielded an RD of 34 fewer per 1,000 (95% CI: 70 fewer–12 more; 15 RCTs, $n = 3,856$), in-hospital mortality yielded an RD of 20 fewer per 1,000 (95% CI: 80 fewer–53 more; 12 RCTs, $n = 2,344$). Of these three mortalities, long-term mortality was chosen as the effect on mortality since we predetermined that the highest certainty of evidence was adopted. Subsequently, the estimated values of the other undesirable anticipated effects were as follows: the length of hospital stay yielded an MD of 0.24 days longer (95% CI: 0.97 days shorter–1.45 days longer; 12 RCTs, $n = 3,407$), and acute kidney injury yielded an RD of 6 more per 1,000 (95% CI:

20 fewer–38 more; 9 RCTs, $n = 2,230$). Thereby, the undesirable anticipated effects were “moderate.” Thus, we presumed that administering vitamin C was inferior to the placebo or control. Judgment of values, acceptability, and feasibility were not changed, namely, “probably no important uncertainty or variability,” “probably yes,” and “probably yes,” respectively.

Accordingly, we revised our recommendation to “We suggest against administering vitamin C to septic patients (GRADE 2D: certainty of evidence = “very low”).”

DECLARATIONS

ETHICS APPROVAL AND consent to participate: Not applicable.

Consent for publication: Not applicable.

DISCLOSURE

CONFLICTS OF INTEREST (COIs) and members' roles: All financial and non-financial competing interests were declared in the J-SSCG2020.^{1,2}

DATA AVAILABILITY STATEMENT

ALL DATA GENERATED or analyzed during this study are included in this published article and its Appendix S1 files.

Guideline Committee of The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020^{1,2}

¹Japanese Society of Intensive Care Medicine, Tokyo, Japan. Moritoki Egi, Department of Anesthesia, Kyoto University Hospital, Kyoto, Japan. E-mail: moriori@tg8.so-net.ne.jp, and ²Japanese Association for Acute Medicine, Tokyo, Japan. Hiroshi Ogura, Department of Traumatology and Acute Critical Medicine, Osaka University Medical School, Osaka, Japan. E-mail: ogura@hp-emerg.med.osakau.ac.jp

REFERENCES

- 1 Egi M, Ogura H, Yatabe *Tet al.* The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG 2020). *J. Intensive Care*2021; 9: 53.
- 2 Egi M, Ogura H, Yatabe *Tet al.* The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 (J-SSCG 2020). *Acute Med. Surg.*2021; 8: e659.
- 3 Crimi E, Liguori A, Condorelli *Met al.* The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. *Anesth. Analg.*2004; 99: 857–63. <https://doi.org/10.1213/01.ane.0000133144.60584.f6>.
- 4 Ferrón-Celma I, Mansilla A, Hassan *Let al.* Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery. *J. Surg. Res.*2009; 153: 224–30. <https://doi.org/10.1016/j.jss.2008.04.024>.
- 5 Fowler AA3rd, Syed AA, Knowlson *Set al.* Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J. Transl. Med.*2014; 12: 32.
- 6 Fowler AA3rd, Truitt JD, Hite *RDet 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: 1261–70.
- 7 Fujii T, Luethi N, Young *PJet al.* Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the vitamins randomized clinical trial. *JAMA*2020; 323: 423–31.
- 8 Heyland D, Muscedere J, Wischmeyer *PEt al.* A randomized trial of glutamine and antioxidants in critically ill patients. *N. Engl. J. Med.*2013; 368: 1489–97.
- 9 Howe KP, Clochesy JM, Goldstein LS, Owen H. Mechanical ventilation antioxidant trial. *Am. J. Crit. Care*2015; 24: 440–5. <https://doi.org/10.4037/ajcc2015335>.
- 10 Nogueira CR, Borges F, Lameu E, Franca C, Ramalho A. Effects of supplementation of antioxidant vitamins and lipid peroxidation in critically ill patients. *Nutr. Hosp.*2013; 28: 1666–72.
- 11 Porter JM, Ivatury RR, Azimuddin K, Swami R. Antioxidant therapy in the prevention of organ dysfunction syndrome and infectious complications after trauma: early results of a prospective randomized study. *Am. Surg.*1999; 65: 478–83.
- 12 Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch. Surg.*2000; 135: 326–31.
- 13 Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. *J. Res. Pharm. Pract.*2016; 5: 94–100.
- 14 Lamontagne F, Masse MH, Menard *Jet al.* Intravenous vitamin C in adults with sepsis in the intensive care unit. *N. Engl. J. Med.*2022; 386: 2387–98.
- 15 Chang P, Liao Y, Guan *Jet al.* Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. *Chest*2020; 158: 174–82.
- 16 Hussein AA, Sabry NA, Abdalla MS, Farid SF. A prospective, randomised clinical study comparing triple therapy regimen to hydrocortisone monotherapy in reducing mortality in septic shock patients. *Int. J. Clin. Pract.*2021; 75: e14376.
- 17 Hwang SY, Ryoo SM, Park *JEet al.* Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. *Intensive Care Med.*2020; 46: 2015–25.
- 18 Iglesias J, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES trial. *Chest*2020; 158: 164–73.
- 19 Jamshidi MR, Zeraati MR, Forouzanfar B, Tahrekhani M, Motamed N. Effects of triple combination of hydrocortisone, thiamine, and Vitamin C on clinical outcome in patients with septic shock: A single-center randomized controlled trial. *J. Res. Med. Sci.*2021; 26: 47.
- 20 Lv SJ, Zhang GH, Xia JM, Yu H, Zhao F. Early use of high-dose vitamin C is beneficial in treatment of sepsis. *Ir. J. Med. Sci.*2021; 190: 1183–8.
- 21 Mahmoodpoor A, Shadvar K, Sanaie S, Hadipoor MR, Pourmoghaddam MA, Saghaleini SH. Effect of Vitamin C on mortality of critically ill patients with severe pneumonia in intensive care unit: a preliminary study. *BMC Infect. Dis.*2021; 21: 616.
- 22 Moskowitz A, Huang DT, Hou *PCet al.* Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. *JAMA*2020; 324: 642–50.
- 23 Rosengrave P, Spencer E, Williman *Jet al.* Intravenous vitamin C administration to patients with septic shock: a pilot randomised controlled trial. *Crit. Care*2022; 26: 26.
- 24 Sevransky JE, Rothman RE, Hager *DNet al.* Effect of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in patients with sepsis: the VICTAS randomized clinical trial. *JAMA*2021; 325: 742–50.
- 25 Wacker DA, Burton SL, Berger *JPet al.* Evaluating vitamin C in septic shock: a randomized controlled trial of vitamin C monotherapy. *Crit. Care Med.*2022; 50: e458–e67.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. PRISMA flow diagram, risk of bias summary, forest plot, funnel plot, and evidence to decision table.