Journal of Critical Care 59 (2020) 37–41

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Adjunctive therapy with vitamin c and thiamine in patients treated with steroids for refractory septic shock: A propensity matched before-after, case-control study

Irene Coloretti [a], Emanuela Biagioni [a], Sophie Venturelli [a], Elena Munari [a], Martina Tosi [a], Erika Roat [a], Lucio Brugioni [b], Roberta Gelmini [c], Claudia Venturelli [d], Massimo Girardis [a,*]

[a] Department of Anesthesia and Intensive Care, University Hospital of Modena, Modena, Italy
[b] Department of Medicine, University Hospital of Modena, Modena, Italy
[c] Department of Surgery, University Hospital of Modena, Modena, Italy
[d] Laboratory of Microbiology, University Hospital of Modena, Modena, Italy

ARTICLE INFO

Available online xxxx

Keywords:
Sepsis
Steroids
Vitamin C
Thiamine
Septic shock
Mechanical ventilation

ABSTRACT

Purpose: Triple therapy with steroids, vitamin C and thiamine has been recently proposed as a safe and beneficial in patients with sepsis. In 2017, we added the use of intravenous vitamin C and thiamine in septic shock patients receiving low dose hydrocortisone because poorly responsive to vasopressors. Aim of this study is to verify whether triple therapy rather than steroids alone can improve outcome in patients with refractory shock.
Materials and methods: In this before-after retrospective analysis, we compared septic shock patients admitted to our intensive care unit (ICU) who received triple therapy from June 2017 to November 2019 to septic shock patients who received only hydrocortisone from January 2015 to June 2017. Patients of the two study periods were matched 1:1 using a propensity score model.
Results: A final cohort of 56 patients treated with triple therapy were matched to 56 patients treated only with steroids. Triple therapy reduced the length of mechanical ventilation ($p = 0{,}01$) and showed a trend in lowering the 30-day and hospital mortality compared to therapy with only hydrocortisone.
Conclusions: Although with significant limitations, our experience indicated that triple therapy seems to provide an improvement of clinical outcomes in patients with refractory septic shock.

1. Background

Based on their pleiotropic effects at cellular and mitochondrial level, intravenous administration of vitamin C and thiamine, combined with steroids, has been recently promoted as a potential adjunctive therapy in patients with septic shock [1,2]. Vitamin C is an important co-factor for the synthesis of endogenous adrenaline and exerts multifaceted antioxidant activities with a pivotal role in modulating inflammation [1–3]. Besides, a severe deficiency of intracellular vitamin C is common during acute illness, especially in sepsis with endotoxemia [4–6]. Thiamine is a key co-factor in oxidative glucose metabolism for energy production and synthesis of glucose-derived neurotransmitters [7,8]. As vitamin C, thiamine body reserves are also seriously reduced in critically ill patients and, thereby, its supplementation might be reasonable, particularly in the hypermetabolic states. Moreover, thiamine modifies the metabolism of vitamin C reducing the production of oxalate, thereby decreasing the likelihood of oxalate nephropathy [9,10]. Vitamin C has been also suggested to work synergistically with hydrocortisone in modulating inflammatory mediators, stimulating catecholamine synthesis, improving endothelial function and increasing vasopressor sensitivity [11–14].

In the last years, several trials indicated a possible benefit by early administration of vitamin C in critically ill patients, particularly in patients with sepsis [15-21]. In 2014, a double-blind phase I randomized control trial including 24 patients with severe sepsis showed that vitamin C significantly reduced organ dysfunction and levels of pro-inflammatory biomarkers [15]. Two years later, another randomized controlled trial evaluated the effects of high-dose vitamin C infusion (25 mg/kg every 6 h) in 28 surgical patients with septic shock [16]. Mean dose of vasopressors and duration of norepinephrine administration were significantly lower in vitamin C group compared to placebo. Also, 28-day mortality, assessed as a secondary outcome, was significantly lower among treated patients. These findings were further confirmed by the famous Marik's before and after study showing a reduction in the mean duration of vasopressors and reduced in-hospital mortality in septic patients treated with the combination of

* Corresponding author at: Intensive Care Unit, Department of Anaesthesiology and Intensive Care, University Hospital of Modena, Largo del Pozzo 71, 41125 Modena, Italy.
E-mail address: girardis.massimo@unimore.it (M. Girardis).

https://doi.org/10.1016/j.jcrc.2020.04.014
0883-9441/

vitamin C, hydrocortisone, and thiamine [17]. Noteworthy, in the above trials intravenous vitamin C and thiamine at dosages up to 200 mg/Kg/day and 400 mg/day, respectively, resulted to be safe without the occurrence of specific adverse events.

In the second semester of 2017, on the basis of the rationale for use, safety and possible benefit, we decided to introduce in our institutional protocol for the management of septic shock intravenous vitamin C and thiamine in patients receiving low dose hydrocortisone because poorly responsive to vasopressors. This retrospective analysis is aimed to verify whether adjunctive therapy with vitamin C and thiamine can improve outcome in septic shock patients treated with steroids, as reported by a previous similar study [17]. because of refractory septic shock.

2. Subjects and methods

2.1. Study population and treatment protocol

In this before-after case-control study we included consecutive adult patients admitted to the polyvalent ICU of the Modena University Hospital with septic shock and receiving low-dose steroids from January 2015 to November 2019. Patients with do-not-resuscitate orders or end of-life decisions during the ICU stay were excluded from the study. Septic shock was diagnosed according to the Sepsis-3 definitions [22]. Data were prospectively recorded in the electronic case report form provided for the Margherita-PROSAFE protocol [23] and it was approved by our Area Vasta Emilia Nord Ethical Committee (17 October -2016, 120-2016). In the Margherita-PROSAFE study protocol, the written informed consent for data collection from patients or their legal representatives for their clinical records to be used in this study since patient records/information were anonymized prior to analysis [23].

Since 2008, our institutional protocol for the management of septic shock included the use of hydrocortisone at the dosage of 240 mg/day in continuous intravenous infusion in patients requiring noradrenaline dosages >0,3–0,4 μg/kg/min to maintain a mean arterial pressure above 65 mmHg. Treatment with hydrocortisone should be started within 12 h after shock appearance and is continued as long as patient required vasopressor support. In June 2017, as described above, in patients receiving low dose steroids because of high vasopressor requirement we added in the management protocol the use of intravenous vitamin C at the dosage of 1,5 g every 6 h and thiamine at the dosage of 200 mg every 12 h up to discontinuation of vasoactive drugs or steroids. As in the previous period, also after protocol change the high requirement of vasopressors was identified with noradrenaline dosages larger than 0,3–0,4 μg/Kg/min.

Apart vitamin C and thiamine, in the study period the overall management of patients with septic shock remained similar and in agreement with the current sepsis management guidelines [24].

2.2. Data collection and analysis

Two of the authors (CI, RE), who were not involved in the direct management of the patients, verified the data collected in the electronic case report form collected and any uncertain data were reviewed with the attending physician and the clinical charts. The type of admission (medical or surgical), relevant pre-existing diseases, the primary site of infection, the microorganisms isolated with their pattern of resistance, Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) in the first 24 h after shock diagnosis [25,26], the procalcitonin blood concentration at shock diagnosis, the length of vasopressor administration, the length of invasive and non-invasive mechanical ventilation, the use of other adjunctive treatments beyond hydrocortisone, as vitamin C, thiamine and IgM preparation, the need for renal replacement therapy, the ICU and hospital length of stay and the ICU and 30-day mortality rate were collected and analysed for each patient. Infections were considered nosocomial if occurring >48 h after hospital admission and multidrug resistant bacteria was defined in accordance with Magiorakos et al. [27].

To verify the hypothesis of our study, we compared the patients who received triple therapy with low dose hydrocortisone, vitamin C and thiamine from June 2017 to November 2019 (Treatment group) with patients who received only hydrocortisone from January 2015 to June 2017, that is the period before protocol change (Control group). In addition, to rule out possible confounding factors, patients in the Treatment and Control group were matched 1:1 by using a propensity score including as covariates age, sex, SAPS II score, pre-existing diseases, site of infection, pattern of antibiotic resistance of the isolated microorganisms, need for mechanical ventilation and adjunctive therapy with IgM. The 30-day and hospital mortality, the length of vasoactive drug therapy and mechanical ventilation, the need for renal replacement therapy and the ICU length of stay were used as clinical outcome for the comparison.

The differences in baseline characteristics and outcomes between matched patients of the treatment and control groups were estimated by Mann-Whitney U for continuous variables and $\chi 2$ tests for categorical ones. To estimate the association between vitamin C and thiamine adjunctive therapy and the 30-day mortality rate, univariate unadjusted analysis and multivariate logistic regression were used. The multivariate regression model was built including vitamin C and thiamine therapy and variables that differed (i.e. p value <.2) in the univariate analysis. The goodness of fit was assessed by the Hosmer–Lemeshow test. All statistical tests were two-sided with p value <.05 considered significant. SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

3. Results

In the study period, 153 patients with septic shock were treated with hydrocortisone because of high dosages of noradrenaline, 60 of which received also with vitamin C and thiamine. After the exclusion of 21 patients with of end-of life decisions, a final cohort of 56 patients treated with steroids (control group) and 56 treated with triple therapy (treatment) were matched by the propensity score model. The treatment and control groups resulted well balanced for the co-variates considered in the matching. Lung and gram- negative bacteria were the most common site of infection and micro-organisms isolated of which almost 40% resulted to have a multidrug resistant pattern (Table 1). Forty-two (75%) patients in each group received also adjunctive therapy with IgM. Median duration of the triple therapy resulted 3 days (IQR 2–5), with an overall median vitamin C dosage of 18 g per patient (IQR 12–30).

In the matched cohort, the 30-day and hospital mortality showed a trend in favour of patients treated with hydrocortisone, vitamin C and thiamine compared to patients who received only hydrocortisone (absolute risk reduction 7,4% - p 0,45 and 10,7% - p 0,25, respectively) (Fig. 1). Similarly, the length of mechanical ventilation and ICU stay were lower in the treatment group, but only the difference in the length of mechanical ventilation resulted to be significant (Table 1).

The unadjusted regression analysis indicated that SAPS II and SOFA scores, medical admission and pre-existing cirrhosis were associated with 30-day mortality; multivariate adjusted analysis demonstrated that only SAPS II and lung as site of infection were independently related to 30-day mortality. Although not significant ($p = 0,11$), multivariate adjusted analysis showed a trend to a reduced risk of 30-day mortality risk (OR 0,38; 95% IC 0,13-1,13) by using triple therapy (Table 2).

4. Discussion

The results of this before-after, case-control study indicated that adjunctive therapy with vitamin C and thiamine in patients treated with low dose hydrocortisone because of high dosages of noradrenaline

Table 1
Main baseline characteristics and outcomes of patients in the control (only hydrocortisone) and treatment (hydrocortisone, vitamin C and Thiamine) group.

	Control group ($n = 56$)	Treatment group (n = 56)	*P* value
Age (years, median-IQR)	69 (56–77)	69 (56–76)	0,731
Male (*n* - %)	32 (57,1)	37 (66,1)	0,331
SAPS II score (median-IQR)	56 (47–71)	61 (47–72)	0,798
SOFA score (median-IQR)	11 (8–13)	11 (8–12)	0,547
Medical admission (*n* - %)	33 (58,9)	36 (64,3)	0,560
Pre-existing diseases (*n* - %)			0,846
None	21 (37,5)	14 (25)	0,154
Heart failure	9 (16,1)	2 (3,6)	
COPD	3 (5,4)	5 (8,9)	
End Stage Kidney Disease	1 (1,8)	5 (8,9)	
Neoplasia	13 (23,2)	12 (21,4)	
Diabetes	4 (7,1)	4 (7,1)	
Cirrhosis	7 (12,5)	10 (17,9)	
Immunosuppression (*n* - %)	14 (25)	17 (30,3)	0,526
Procalcitonin (ng/dl, median- IQR)	34 (12–104)	49 (8–101)	
Mechanical ventilation (*n* - %)	48 (85,7)	41 (73,2)	0,102
Nosocomial infection (*n* - %)	32 (57,1)	27 (48,2)	0,344
Site of infection (*n* - %)			0,696
Pulmonary	23 (41,1)	27 (48,2)	
Abdominal	20 (35,7)	18 (32,1)	
Bloodstream	10 (17,9)	7 (12,5)	
Other	14 (25)	14 (25)	
Micro-organisms (*n* - %)			0,530
Gram negative	40 (71,4)	37 (66,1)	
Gram positive	11 (19,6)	11 (19,6)	
Fungi	0 (0)	2 (3,6)	
MDR	23 (41,1)	24 (42,9)	
No isolates	5 (8,9)	6 (10,7)	
30-day mortality (*n* - %)	28 (50,0)	24 (42,8)	0,449
Hospital mortality (*n* - %)	34 (60,7)	28 (50,0)	0,254
Vasopressors length (days, median-IQR)	4 (2–7)	3 (2–5)	0,533
Length of Mechanical ventilation (days, median- IQR)	6 (2–15)	3 (0–8)	0,012
Renal replacement therapy (*n* - %)	21 (37,5)	22 (39,2)	0,846
ICU length of stay (days, median- IQR)	9 (5–15)	6 (4–10)	0,092

COPD: chronic obstructive pulmonary disease; MDR: multidrug resistant bacteria, defined in accordance with [27]; ICU: intensive care unit.

appears to be safe and might have beneficial effects on the length of mechanical ventilation and a trend in reducing intensive care stay and the risk of 30 day and hospital mortality,

In the sepsis pathobiology, the combination of vitamin C, thiamine and steroids seems to act synergistically in attenuating oxidative damage, increasing glucocorticoid activity and restoring organ function [1–17]. A recent metanalysis, including 5 small and highly heterogeneous studies with a total of 142 critically ill patients, showed that adjunctive therapy with intravenous vitamin C in patients with sepsis is safe and seems to reduce duration of vasopressor support and mechanical ventilation [18]. On the same line, the recent randomized multicentre CITRIS-ALI trial enrolling adult patients with sepsis and acute respiratory distress syndrome showed that adjunctive treatment with vitamin C seems to be able to improve ICU mortality and ICU free days. Indeed, these outcomes were the secondary outcomes of the study, whereas primary outcomes (i.e. modified SOFA scores at 96 h and plasma biomarker levels at 168 h) did not improve with vitamin C therapy. Noteworthy, in the trial almost 65% of the patients received also steroids [21]. Different from the above positive results, two recent observational trials reported no effects of adjunctive therapy with vitamin C and thiamine in sepsis. A single center retrospective analysis reported no difference in hospital mortality and other outcomes in 47 septic shock patients treated with triple therapy compared to 47 treated only with standard of care [20]. However, the two groups could be not well matched because the decision for triple therapy depended on the physician in charge and specific methods for limiting biases introduced by confounding variables have not been applied. Moreover, only 40% of the patients in the standard of care group received steroids for refractory shock. A large before-after study with a propensity score-based adjustment observed no improvement in survival by very early vitamin C and thiamine administration in septic shock patients treated in emergency department [19], with a possible benefit only in the more severe population with hypoalbuminemia and SOFA score > 10. Noteworthy, in this study patients were treated for only one day and many patients did not receive thiamine. Moreover, only 25% of the patients received a concomitant steroid therapy and the reported hospital mortality of 17–18% appears to be very low considering patients with septic shock. Similarly, the recently published randomized trial VITAMINS, that showed no effects using combination therapy with steroids, vitamin C and thiamine in patients with septic shock admitted to ICU, reported a 28-day mortality of 20% [28]. In our study and in the study by Marik et al. [17] the hospital mortality were at least double, ranging from 40 to 60%. This might be partially explained by the high number of patients with severe comorbidities compared to the patients enrolled in VITAMINS trial [28].

The notable effects of triple therapy reported by Marik et al. [17] in their retrospective before-after study were only partially confirmed by our data. These discrepancies may be due to differences in patients' characteristics and protocols between the two studies. In our study about half of the patients had nosocomial infections with high incidence of multidrug resistant pathogens whereas the population included in the Marik et al. study had only community-acquired infections. In addition, in our study 30% of our patients had abdominal infections requiring surgery compared to only 10% of abdominal infections reported in the Marik el al study [17]. Similarly, also the VITAMINS trial [28] included many patients with surgical sepsis, despite the exact number of medical and surgical patients was not reported. Indeed, adjuvant therapy is likely to have a lesser impact in surgical patients, where the skill of the surgeon and the adequacy of source control are of primary importance. Another difference between the two studies is the varied delay between shock onset and triple therapy administration that in our trial was not initiated immediately after shock diagnosis but a few hours later (within 12 h). As in VITAMINS trial [28], this delay might have underpowered the effects of HAT therapy.

Our study has several limitations, mainly due to study design and the small sample size. Although the use of propensity score model for matching is considered an effective method in non-randomized trials, the two groups appear to be well matched for baseline characteristics and during the study period the management protocol for septic shock patients did not change, except vitamin C and thiamine, a selection bias in treated and controls could not be excluded in our before-after study. The sample size of 112 patients would have been able to detect, with a power of 80% and hospital mortality rate of 60% in the control group, an absolute difference between the 2 study groups in hospital mortality of about 25%, that was lower than the difference observed in the trial from Marik et al. that included only 94 patients [17]. Unfortunately, the difference observed was only 10% and, thus, the hypothesis of beneficial effects by vitamin C and thiamine addition to steroids could not be confirmed by our results. Nevertheless, despite due to chance, the difference in hospital mortality observed in our trial, associated with the low probability of related adverse events, should be considered in the clinical decision for an eventual adjunctive therapy with vitamin C and thiamine, upon new evidences will be available.

In conclusion and waiting for the future incoming trials that will better define the patient who could benefit the most and the appropriate time for administration, the rational for use combined with evidences available so far and the results of our study, even though with significant limitations and only a trend in favour of outcomes improvement, suggest that intravenous vitamin C and thiamine may be considered a possible adjuvant therapy in patients with septic shock receiving low dose steroids because of refractory shock.

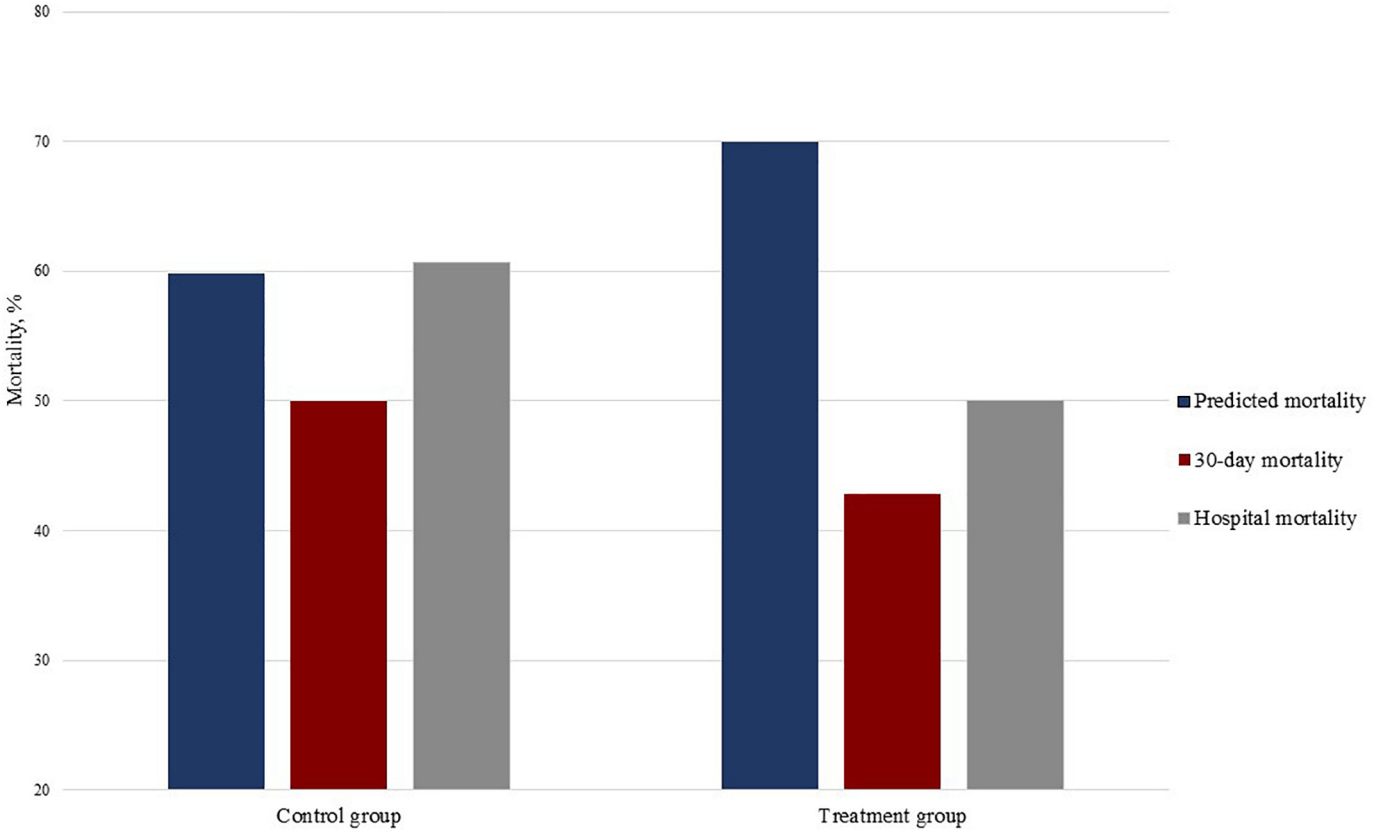

Fig. 1. Comparison between predicted mortality (white bars) calculated by SAPS II score at admission and actual mortality rates (30-day, black bars; hospital, grey bars) in the control (only steroids) and treatment (triple therapy) groups.

Table 2
Odds ratios and confidence interval obtained by unadjusted univariate and adjusted multivariate logistic regression analysis for 30-day mortality. Data for survived and no survived at 30 day are also reported.

	Survived ($n = 60$)	No Survived ($n = 52$)	Unadjusted OR (95% CI); p value	Adjusted * OR (95% CI); p value
Age (median; IQR)	67 (51–75)	70 (61–77)	1,02 (0,99-1,05) **0,100**	1,02 (0,98-1,06) **0,381**
SAPS II score (median; IQR)	48 (41–59)	70 (57–78)	1,08 (1,05-1,11) **<0,001**	1,07 (1,03-1,12) **<0,001**
SOFA (median; IQR)	9 (7,5–11)	12 (10–15)	1,30 (1,14-1,45) **<0,001**	1,05 (0,87-1,26) **0,575**
Medical admission, (n; %)	30 (50)	39 (75)	1,61 (1,15-2,24) **0,007**	1,74 (0,56-4,40) **0,339**
Cirrhosis (n; %)	4 (6,7)	13 (25)	2,51 (1,05-6,00) **0,007**	4,07 (0,74-21,27) **0,111**
Immunosuppression (n; %)	13 (21,7)	18 (34,6)	1,38 (0,88-2,18) **0,127**	3,41 (0,82-14,24) **0,092**
Nosocomial infection, (n; %)	28 (46,7)	31 (59,6)	1,27 (0,90-1,80) **0,171**	2,31 (0,70-7,59) **0,169**
Pulmonary site (n; %)	22 (36,7)	28 (53,8)	1,39 (0,96-2,02) **0,068**	2,84 (0,99-8,04) **0,050**
Gram negative (n; %)	46 (76,7)	31 (59,6)	0,67 (0,43-1,05) **0,052**	0,44 (0,14-2,06) **0,160**
Renal replacement therapy, n (%)	16 (26,7)	27 (51,9)	1,71 (1,12-2,63) **0,006**	1,87 (0,64-5,65) **0,223**
Vitamin C and Thiamine n (%)	32 (53,3)	24 (46,2)	0,88 (0,62-1,24) **0,449**	0,38 (0,13-1,13) **0,11**

* Hosmer–Lemeshow goodness of fit: $p = 0,78$.

Funding

Research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author statement

Coloretti Irene, Biagioni Emanuela, Girardis Massimo: formulation of research goals and aims, writing the initial draft.

Venturelli Sophie, Munari Elena, Martina Tosi, Roat Erika, Venturelli Claudia: performing data collection and analysis.

Brugioni Lucio, Gelmini Roberta: revision of the initial draft.

Acknowledgements

No acknowledgments.

References

[1] Oudemans-van Straaten HM, Spoelstra-de Man AM, de Waard MC. Vitamin C revisited. Crit Care 2014 Aug 6;18(4):460. https://doi.org/10.1186/s13054-014-0460-x.

[2] Tyml K. Vitamin C and Microvascular Dysfunction in Systemic Inflammation. Antioxidants (Basel) 2017 Jun 29;6(3):49. https://doi.org/10.3390/antiox6030049.

[3] May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. Antioxid Redox Signal 2013 Dec 10;19(17):2068–83. https://doi.org/10.1089/ars.2013.5205.

[4] Borrelli E, Roux-Lombard P, Grau GE, Girardin E, Ricou B, Dayer J, 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 Mar;24(3):392–7. https://doi.org/10.1097/00003246-199603000-00006.

[5] Evans-Olders R, Eintracht S, Hoffer LJ. Metabolic origin of hypovitaminosis C in acutely hospitalized patients. Nutrition 2010;26(11−12):1070–4. https://doi.org/10.1016/j.nut.2009.08.015.

[6] Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care 2017;21(1):300 Published 2017 Dec 11 https://doi.org/10.1186/s13054-017-1891-y.

[7] Donnino MW, Carney E, Cocchi MN, Barbash I, Chase M, Joyce N, et al. Thiamine deficiency in critically ill patients with sepsis. J Crit Care 2010 Dec;25(4):576–81. https://doi.org/10.1016/j.jcrc.2010.03.003.

[8] 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. https://doi.org/10.1097/MCO.0000000000000148.

[9] Leite HP, de Lima LF. Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic? J Thorac Dis 2016;8(7):E552–7. https://doi.org/10.21037/jtd.2016.05.37.

[10] Donnino MW, Andersen LW, Chase M, Berg KM, Tidswell M, Giberson T, et al. Center for Resuscitation Science Research Group. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. Crit Care Med 2016 Feb;44(2):360–7. https://doi.org/10.1097/CCM.0000000000001572.

[11] Langley RJ, Tsalik EL, van Velkinburgh JC, Glickman SW, Rice BJ, Wang C, et al. An integrated clinico-metabolomic model improves prediction of death in sepsis. Sci Transl Med 2013 Jul 24;5(195). https://doi.org/10.1126/scitranslmed.3005893 195ra95.

[12] Langley RJ, Tipper JL, Bruse S, Baron RM, Tsalik EL, Huntley J, et al. Integrative "omic" analysis of experimental bacteremia identifies a metabolic signature that distinguishes human sepsis from systemic inflammatory response syndromes. Am J Respir Crit Care Med 2014 Aug 15;190(4):445–55. https://doi.org/10.1164/rccm.201404-0624OC.

[13] 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 Published 2015 Nov 27 https://doi.org/10.1186/s13054-015-1131-2.

[14] Kim SR, Ha YM, Kim YM, Park EJ, Kim JW, Park SW, et al. 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 Jun 15;95(4):279–89. https://doi.org/10.1016/j.bcp.2015.04.007.

[15] Fowler 3rd AA, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, et al. Medical Respiratory Intensive Care Unit Nursing, Fisher BJ, Natarajan R. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 2014 Jan 31;12:32. https://doi.org/10.1186/1479-5876-12-32.

[16] 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(2):94–100. https://doi.org/10.4103/2279-042X.179569.

[17] 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):1229–38. https://doi.org/10.1016/j.chest.2016.11.036.

[18] Zhang M, Jativa DF. Vitamin C supplementation in the critically ill: A systematic review and meta-analysis. SAGE Open Med 2018;6. https://doi.org/10.1177/2050312118807615 2050312118807615. Published 2018 Oct 19.

[19] Shin TG, Kim YJ, Ryoo SM, Hwang SY, Jo IJ, Chung SP, et al. Early vitamin C and thiamine administration to patients with septic shock in emergency departments: propensity score-based analysis of a before-and-after cohort study. J Clin Med 2019 Jan 16;8(1):102. https://doi.org/10.3390/jcm8010102.

[20] Litwak JJ, Cho N, Nguyen HB, Moussavi K, Bushell T. Vitamin C, hydrocortisone, and thiamine for the treatment of severe sepsis and septic shock: a retrospective analysis of real-world application. J Clin Med 2019;8(4):478 Published 2019 Apr 9 https://doi.org/10.3390/jcm8040478.

[21] Fowler AA, Truwit 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 Oct 1;322(13):1261–70. https://doi.org/10.1001/jama.2019.11825.

[22] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA 2016 Feb 23;315(8):801–10. https://doi.org/10.1001/jama.2016.0287.

[23] Committee GiViTI Steering, Bertolini G, Nattino G, Tascini C, Poole D, Viaggi B, et al. Mortality attributable to different Klebsiella susceptibility patterns and to the coverage of empirical antibiotic therapy: a cohort study on patients admitted to the ICU with infection. Intensive Care Med 2018 Oct;44(10):1709–19. https://doi.org/10.1007/s00134-018-5360-0.

[24] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017 Mar;43(3):304–77. https://doi.org/10.1007/s00134-017-4683-6.

[25] Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/north American multicenter study. JAMA 1993;270(24):2957–63. https://doi.org/10.1001/jama.270.24.2957.

[26] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996 Jul;22(7):707–10. https://doi.org/10.1007/bf01709751.

[27] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012 Mar;18(3):268–81. https://doi.org/10.1111/j.1469-0691.2011.03570.x.

[28] Fujii T, Luethi N, Young PJ, et 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. https://doi.org/10.1001/jama.2019.22176.