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Review

HAT therapy for sepsis: A review of the therapeutic rationale and current clinical evaluation status

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ABSTRACT

Vitamin C-based cluster therapy, which involves the combined application of hydrocortisone, vitamin C, and thiamine (HAT), is a recently proposed new treatment option for sepsis on top of conventional treatment. This therapy has a strong theoretical basis, but its clinical efficacy remains inconclusive. This review summarizes the rationale for HAT therapy for sepsis and describes the evaluation of its efficacy in clinical observational studies and randomized controlled trials, with the aim of providing a reference for the future clinical practice application of HAT therapy in sepsis.

Introduction

Sepsis is a dysregulation of the body's response to infection, resulting in life-threatening organ dysfunction.[1,2] Approximately 1/5 of patients in intensive care units (ICUs) suffer from sepsis, and 1/3 of them die, thus sepsis poses a serious threat to human health.[3] Current clinical treatments of sepsis predominantly include active control of the primary infected lesion, early empirical use of broad-spectrum antibacterial drugs, organ support, and other comprehensive treatment measures. Increasing research on sepsis has revealed that mitochondrial dysfunction plays a key role in the pathophysiology of sepsis, characterized by reduced adenosine triphosphate (ATP) production and enhanced oxidative stress, resulting in oxidative damage to cells and tissues, bioenergetic failure, immune responses, injury, and ultimately organ dysfunction.[4,5] Consequently, modulation of mitochondrial function may be a promising strategy for metabolic resuscitation in sepsis.

In recent years, the combined application of hydrocortisone, vitamin C, and thiamine—in addition to the conventional treatment for sepsis—has been proposed as a triple cocktail therapy (HAT therapy) for sepsis and is essentially metabolic resuscitation. HAT therapy significantly improved in-hospital mortality in a study of patients with severe sepsis and septic shock.[6] However, a series of further studies evaluating the clinical effectiveness of HAT therapy reached mixed conclusions. This review summarizes the existing studies on HAT therapy with a view to providing a reference for the future application of HAT therapy in sepsis.

Vitamin C

Vitamin C has immunomodulatory, antioxidant, and antithrombotic properties, and deficiency of this vitamin can cause abnormal blood coagulation and damage to endothelial function.[7–9] During sepsis, mitochondrial oxidative stress increases and the body is in a hypermetabolic state, resulting in a significant decrease in vitamin C.[10] Vitamin C supplementation in patients with sepsis could directly scavenge excess reactive oxygen species and limit the oxidation of mitochondrial proteins, enzymes, lipoproteins, and cell membranes in pathological states. This antioxidant effect also protects the tight junctions between vascular endothelial cells and epithelial cells, attenuates apoptosis, and ultimately reduces oxidative stress and improves vascular endothelial permeability and microcirculation (Figure 1).[11] Several clinical studies have evaluated the effectiveness of vitamin C on sepsis with mixed findings.[12–19] One influential trial was The LOVIT study,[17] which included a total

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of 872 adult patients with sepsis receiving vasopressors in the ICU and found a higher risk of 28-day mortality or persistent organ dysfunction in the vitamin C-treated group. However, the study included patients with relatively high severity of disease and did not perform a subgroup analysis of the heterogeneity of the included subjects (e.g., whether serum vitamin C levels were reduced, whether the patients were also in a hyperinflammatory state), which may have an impact on the negative conclusions. The latest meta-analysis found that vitamin C reduced the short-term mortality rate and duration of vasopressor, but there was no significant improvement in the sequential organ failure assessment (SOFA) score.[20,21] Overall, considering the varying evidence of clinical efficacy and potential adverse drug reactions (such as nephrotoxicity) of vitamin C, further trials are needed to explore the appropriate patient population and optimal dose and duration of vitamin C use.

Thiamine

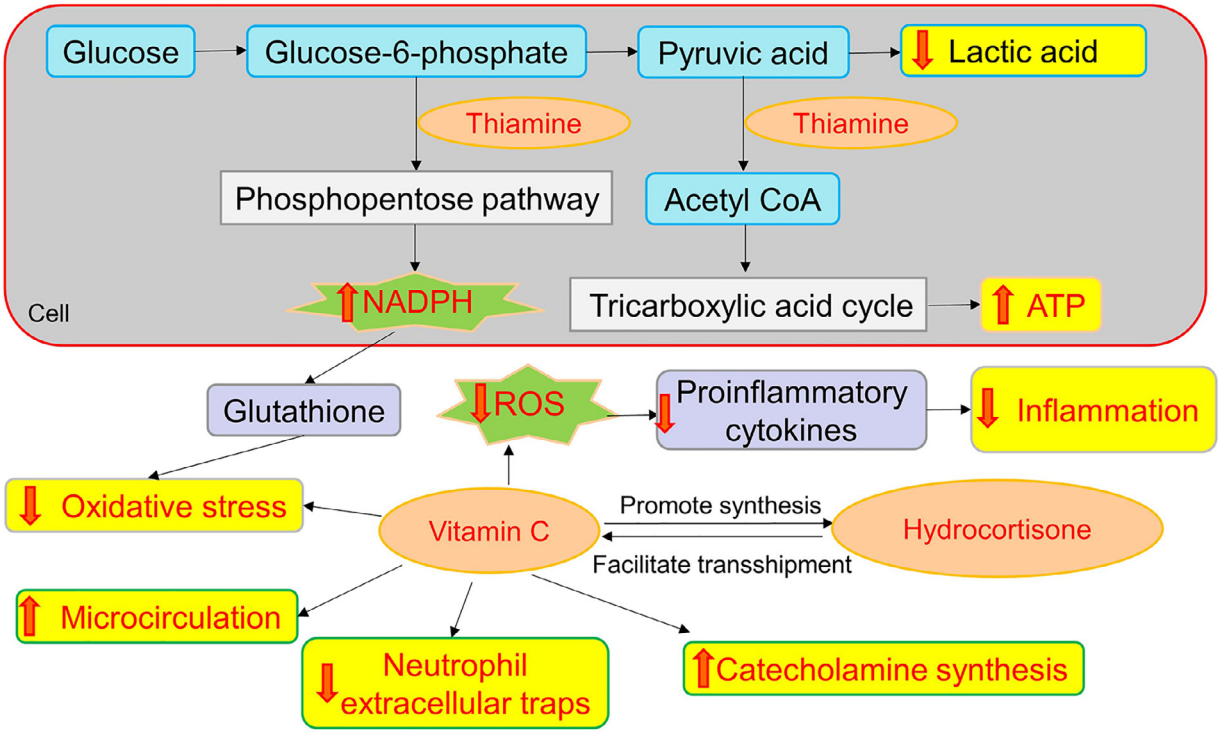
Thiamine is a coenzyme necessary for cellular glucose metabolism, acting in the tricarboxylic acid cycle and the pentose phosphate pathway.[22] Figure 1 shows the specific mechanism of thiamine on cellular metabolism. Thiamine deficiency impairs aerobic cellular respiration and increases the risk of lactic acidosis, hypotension, and even death in critically ill patients.[23,24] Theoretically, thiamine supplementation could reduce lactate clearance levels, attenuate mitochondrial dysfunction, and improve organ dysfunction in sepsis. However, the effectiveness of thiamine in treating patients with sepsis is controversial, although there is no evidence that thiamine supplementation is associated with serious adverse effects.[25–27] Therefore, thiamine is still considered a low-risk and potentially high-reward intervention in critically ill patients, especially those with septic shock who are severely thiamine-deficient.

Hydrocortisone

Corticosteroids have strong immunomodulatory properties and can exert anti-inflammatory effects by inhibiting the differentiation, maturation, proliferation, and migration of various subtypes of leukocytes and producing anti-inflammatory factors,[28] making corticosteroids commonly used in the clinical treatment of sepsis and septic shock.[29] Corticosteroids showed potential to reduce ICU and hospital mortality in some patients with sepsis.[30] However, due to the inhibitory effect of corticosteroids on immune function, long-term use carries the risk of inducing or exacerbating infections. Furthermore, the latest Survival Sepsis Campaign (SSC) guidelines recommend the use of corticosteroids for patients in septic shock (weak recommendation, moderate quality evidence).[31]

Combination of Hydrocortisone, Vitamin C, and Thiamine

Compared with each drug alone, the combination of hydrocortisone, vitamin C, and thiamine appears to have more significant effects on the course of sepsis, which may be related to the synergistic effect of all three agents.[6,8] Figure 1 illustrates the detailed mechanisms by which the three drugs cooperatively regulate cellular metabolism. Thiamin could attenuate cellular oxidative stress together with vitamin C and may protect against possible renal injury caused by high doses of vitamin C by inhibiting oxalate conversion. Vitamin C could cooperate with hydrocortisone to inhibit activation of the nuclear factor (NF)-kB signaling pathway, downregulate the pro-



Figuer 1. Mechanism of metabolic resuscitation by HAT therapy for sepsis.
Acetyl CoA: Acetoacetyl coenzyme A; ATP: Adenosine triphosphate; NADPH: Nicotinamide adenine dinucleotide phosphate oxidase; ROS: Reactive oxygen species.

duction of pro-inflammatory mediators, and maintain vascular endothelial function and microcirculation. In addition, hydrocortisone may promote vitamin C absorption by inducing the expression of ascorbate transporter protein (sodium-vitamin C transporter [SVCT2]), while vitamin C may reduce the oxidation of hydrocortisone receptor and enhance its efficacy. Hydrocortisone combined with vitamin C was shown to synergistically prevent and repair lipopolysaccharide (LPS)-induced damage to human pulmonary microvascular endothelial cells and reverse shock compared with vitamin C or hydrocortisone alone.[32] In addition, the combination of vitamin C and thiamine was associated with lower SOFA scores and a shorter duration of vasopressor use in patients with sepsis and septic shock.[33] In summary, this triple therapy can theoretically interact to synergistically regulate cellular metabolism and function and finally alleviate sepsis-associated organ injury.

Clinical Practice of HAT Therapy for Sepsis in Observational Studies

HAT therapy was first described in a study published in *Chest* in December 2016, which included a total of 94 patients with severe sepsis and septic shock categorized by Sepsis 1.0 criteria.[6] Patients in the treatment group were given intravenous vitamin C (1500 mg every 6 h for 4 days or until ICU discharge), hydrocortisone (50 mg every 6 h for 7 days or until ICU discharge), and thiamine (200 mg every 12 h for 4 days or until ICU discharge) within 24 h of ICU admission, and the control group was treated conventionally. The clinical course and outcomes of patients in both groups were collected before and after treatment. Compared with the control group, the HAT group had a significantly decreased SOFA score at 72 h (4.8 ± 2.4 *vs.* 0.9 ± 2.7, $P<0.001$), significantly reduced in-hospital mortality (8.5% *vs.* 40.4%, adjusted odds ratio [OR]=0.13; 95% confidence interval [CI]: 0.04–0.48; $P=0.002$), and a significantly shorter duration of vasopressor use (18.3 ± 9.8 h *vs.* 54.9 ± 28.4 h, $P<0.001$). These results suggested that HAT therapy was associated with significant reduction in septic organ injury (especially acute kidney injury), time-to-shock reversal, and mortality. However, the study had a limited sample size and a single-center retrospective "before-and-after" design in terms of methodology, that is, the participations were non-concurrent control subjects, and although the baseline characteristics of the two groups were not statistically different, this design did result in an overall average level of evidence for the study. In addition, the optimal dosage and course of treatment of drugs need to be further explored.[6]

After the publication of this study by Marik et al.,[6] the clinical use of HAT therapy increased significantly and immediately. Most observational studies reported similar positive findings to those of Marik et al.,[6] including that HAT therapy was associated with reduction in ICU mortality and SOFA scores or inflammatory markers.[34–37] In contrast, Vail et al.[38] conducted a retrospective cohort study on the clinical data of adult septic shock patients from 379 hospitals in the United States and found that receiving HAT therapy within 2 days of hospitalization was not associated with an improvement in-hospital mortality. However, septic shock in the study was diagnosed according to International Classification of Diseases 10th Revision (ICD-10) criteria, the dose and duration of drugs used were inconsistent across hospitals, and the greater severity of disease in the treatment group may have affected the efficacy of HAT therapy; consequently, the results should be interpreted with caution.[38] A real-world retrospective study found similar negative results, but it was likely that the overall benefit of HAT therapy in that study was markedly reduced by the late administration of drugs and the fact that more than half of the patients in the treatment group did not receive HAT therapy for various reasons.[39]

Clinical Practice of HAT Therapy for Sepsis in Randomized Controlled Trials (RCTs)

As of November 2022, there were 21 registered clinical trials of HAT therapy for sepsis (https://clinicaltrials.gov/) and 11 RCTs had published mixed findings. Among them, a randomized, double-blind, placebo-controlled study by Iglesias et al.[40] explored the efficacy of HAT therapy in sepsis and septic shock patients in terms of metabolic resuscitation. The study found that early application of HAT therapy (vitamin C 1500 mg q6h, thiamine 200 mg q12h, hydrocortisone 50 mg q6h, for up to 4 days, with most starting within 1 h of enrollment) significantly reduced the duration of vasopressin administration (27 ± 22 h *vs.* 53 ± 38 h, $P<0.001$), suggesting the independent reversal of shock with HAT therapy. However, the study did not find an association between HAT therapy and improvement in hospital and ICU mortality, or reduction in SOFA scores in patients with septic shock, which may be due to limitations such as the small study cohort and the homogeneous (predominantly white) study population. Additional monitoring in the study found no serious adverse events associated with the drugs, suggesting the therapy is relatively safe. Four other RCTs reported similar results,[41–44] that is, HAT therapy reduced the duration of vasopressors or time to shock reversal in patients with sepsis and septic shock but did not significantly reduce mortality. However, unlike these studies, a related trial from China found that HAT therapy did not reduce the duration of vasopressor use in patients with sepsis and septic shock but did significantly improve SOFA scores at 72 h (ΔSOFA, 3.5 ± 3.3 and 1.8 ± 3.0; $P=0.02$). Further subgroup analysis in the study suggested a lower mortality rate when the intervention was started within 48 h of sepsis diagnosis, although there was no difference in 28-day all-cause mortality between the two groups. However, the study was a single-center, single-blind design, and most control patients did not actually receive the appropriate placebo (normal saline), which we speculate may have confounded the trial findings and was associated with the increased incidence of hypernatremia—an adverse condition—in the treatment group ($P=0.005$). In addition, a study by Jamshidi et al.[46] showed significant decreases in 72-h SOFA score, mean duration of vasopressor dependency, and in-hospital mortality after HAT treatment ($P<0.05$), but the level of evidence was limited by the small sample size and single-center study design.

In contrast, several clinical trials did not find any significant benefits of HAT therapy for sepsis or septic shock. The RCT by Sevransky et al.[47] revealed that HAT therapy did not reduce the number of days without ventilators and vasopressors in a 30-day period or the 180-day mortality in patients with septic shock. The study was methodologically rigorous and credible but employed an open hydrocortisone strategy (that is participants could be treated with open-label corticosteroids by the clini-

cal team: for daily doses of at least 200 mg of hydrocortisone (or equivalent), hydrocortisone or matching placebo was withheld by the investigational pharmacy) and was terminated early for administrative reasons, which may have affected the conclusion. Another single-center, double-blind, open glucocorticoid therapy RCT likewise did not find any significant improvement in sepsis-related clinical outcomes, including 90-day mortality. However, the patients in this trial were relatively critically ill (a previous study found that mortality benefits were observed only in a subset of patients with lower SOFA scores[42]) and were not monitored for vitamin C and thiamine concentrations, which may explain the observed absence of beneficial effects on clinical outcomes of HAT therapy.[48] Moskowitz et al.[49] conducted a similar multicenter clinical trial that was not open to hydrocortisone treatment, but the findings were still negative. Both studies of Lyu et al.[48] and Moskowitz et al.[49] administered the same dose of HAT therapy as that of Marik et al.,[6] but the median time to receipt of intervention was more than 12 h; however, earlier intervention would likely to improve the outcomes. Fujii et al.[50] conducted a multicenter, open-label RCT across countries to compare the efficacy of HAT therapy with hydrocortisone alone in the relief of septic shock. The study found that HAT therapy did not significantly improve the survival or the duration of vasoactive drug requirements, suggesting that this therapy did not contribute to a more rapid resolution of septic shock. However, the study was limited by the open-label design and lacked a blinded outcome assessment, which may have created ascertainment bias. Notably, none of the above studies reported unexpected serious adverse events associated with the therapy.

The clinical efficacy of HAT therapy for sepsis has been refined through additional original studies in recent years.[51] The most recent meta-analysis found that HAT therapy was not associated with improved long-term mortality in sepsis compared with placebo or conventional therapy, but the study did not separate observational studies from those of RCTs.[52] Another meta-analysis that specifically searched for relevant RCTs revealed that HAT therapy significantly reduced the duration of the need for vasopressors and improved SOFA scores over 72 h.[53] Additionally, HAT therapy appears to have different outcomes for gut-derived sepsis *vs.* pulmonary-derived sepsis. Our preliminary analysis of the included population of published RCTs found that HAT therapy significantly reduced the duration of vasoactive drugs or multi-organ function in studies with a relatively large proportion of patients with pulmonary-derived sepsis and less gut-derived sepsis (at least 30% difference in the proportion).[40,41,45] In contrast, in studies with a relatively large proportion of patients with gut-derived sepsis and less pulmonary-derived sepsis, HAT therapy did not demonstrate any significant benefit.[48,50] Moreover, when there were more patients with pulmonary-derived sepsis than with gut-derived sepsis but the difference in proportion was less than 30%, the conclusions were not consistent.[42,47,49] Unfortunately, there are currently no RCTs evaluating the efficacy of HAT therapy for septic patients with a specific source of infection. Lyu et al.[48] performed a subgroup analysis for the distribution of infection sites and indicated that HAT therapy did not show a better therapeutic effect regardless of whether the patient had abdominal infections or not. Therefore, is the type of infection site the key determinant for the effectiveness of HAT therapy? Future studies are needed to elucidate this issue.

Implications for Future Practice

Considering the contradictory findings of published studies and the limited number of studies the future widespread use of HAT therapy in clinical sepsis patients requires further evidence from high-quality (multicenter, large-scale, prospective, RCTs) clinical trials. From the available data, it appears that although HAT therapy does not significantly reduce mortality, it is beneficial in terms of shortening the duration of vasoactive drug requirements and improving organ function, which is consistent with the pathophysiological mechanisms we described previously. That is, HAT therapy protects the endothelium, promotes endogenous vasoactive drug synthesis, and regulates immunity, which in turn can improve vascular reactivity, maintain hemodynamic stability, reduce oxidative stress and inflammatory responses, and ultimately shorten the duration of exogenous vasoactive drug use and reduce multi-organ functional injury. However, further work is needed to determine why HAT therapy did not benefit the survival rate of patients with sepsis and we speculate that there may be multiple underlying reasons. (1) SOFA scores and time of vasoactive drug use are focused on early recovery of organ function, while mortality endpoints, especially long-term mortality, are influenced by multiple factors and theoretically diluted by many confounding factors that may limit the efficacy evaluation of the therapy for long-term prognosis. (2) Patients with sepsis or septic shock are often associated with multi-organ functional injury and always have complex conditions. Consequently, it is unrealistic to expect that one treatment will save all patients with sepsis or septic shock. (3) Previous clinical trials failed to stratify enrolled subjects by the predominant etiology of sepsis or degree of illness, which may be important to discern the benefits of HAT therapy on mortality. For example, animal experiments by Stolarski et al.[54] found that the inflammatory responses were different in pulmonary sepsis and intra-abdominal sepsis. Furthermore, identical HAT treatment resulted in a significant decrease in oxidative stress and mortality in intestinal sepsis models but not in pulmonary sepsis. In addition, the plasma vitamin C level in pulmonary sepsis was significantly lower compared with that in intra-abdominal sepsis owing to higher consumption during the scavenging of free radicals, suggesting that a larger dose of vitamin C may be required to benefit mortality in patients with pulmonary sepsis.

In terms of the future of HAT therapy, precise treatment may be a breakthrough—that is, HAT therapy for sepsis may benefit specific patient groups but not all patient groups. Whether it is for sepsis or septic shock, the focus of research should not be on confirming whether HAT therapy is effective, but should concentrate on identifying the population that will benefit from the therapy for individualized and precise treatment. The benefit is maximized by finding the right patient at the right time to apply the right dose of HAT treatment. Therefore, we have a number of suggestions for future trial design. (1) Refine the doses of intervention drugs. The doses of HAT therapy in existing studies were predominantly the same as those of Marik et al.[6] However, it is possible that alternative doses may affect the outcome; for example, high doses of vitamin C were associated with a reduction

in mortality in septic patients.[52] (2) Focus on pre-intervention vitamin levels. There may be differences in the distribution of hypovitaminemic patients after the randomization of patients in a trial, and it has yet to be explored whether a certain drug concentration is required to achieve an optimal therapeutic effect. (3) Perform subgroup analysis on patients with different courses of intervention. The characteristics of ICU departments mean some patients did not receive sufficient courses of intervention as planned, and some patients only received one intervention, which may affect the efficacy determination of the drugs. (4) Study the effect of HAT therapy on patients with sepsis or septic shock caused by a site-specific infection, and use subgroup analyses to explore different disease severities and whether patients have combined hyperinflammation, low hypovascular reactivity, and so on, with the aim of identifying the optimal population for HAT therapy. The complexity of clinical practice poses challenges for the implementation of all of the above protocols, but it should be possible to gradually identify the appropriate population for HAT therapy through a series of trials with increasing complexity. For example, our preferred first step is to limit inclusion criteria in our future clinical practice to patients with pulmonary-derived sepsis of low baseline vitamin levels.

Conclusions

Currently, HAT therapy is not considered to significantly improve mortality in patients with sepsis, but it is likely to be beneficial in terms of duration of vasopressor use and relief of shock. Furthermore, most clinical studies have not reported any serious adverse effects of HAT therapy, suggesting this therapy has a good safety profile. Therefore, HAT therapy remains a promising new treatment for the metabolic resuscitation of sepsis.

Author Contributions

All the authors contributed substantially to the work presented in this article. Tongwen Sun conceived of the study. Yali Sun and Yongfang Yang contributed to the relevant literature retrieval. Yali Sun contributed to the writing of the article, and Zhuoyi Ye and Tongwen Sun revised the article.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

[1] Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018;392(10141):75–87. doi:10.1016/S0140-6736(18)30696-2.
[2] Sun T, Wang L, Zhang H. Intestinal microbiota in sepsis. Intensive Care Res 2022;2:1–7. doi:10.1007/s44231-022-00001-8.
[3] Xie J, Wang H, Kang Y, Zhou L, Liu Z, Qin B, et al. The epidemiology of sepsis in Chinese ICUs: a national cross-sectional survey. Crit Care Med 2020;48(3):e209–18. doi:10.1097/CCM.0000000000004155.
[4] Reitsema VA, Star BS, de Jager VD, van Meurs M, Henning RH, Bouma HR. Metabolic resuscitation strategies to prevent organ dysfunction in sepsis. Antioxid Redox Signal 2019;31(2):134–52. doi:10.1089/ars.2018.7537.
[5] Moskowitz A, Andersen LW, Huang DT, Berg KM, Grossestreuer AV, Marik PE, et al. Ascorbic acid, corticosteroids, and thiamine in sepsis: a review of the biologic rationale and the present state of clinical evaluation. Crit Care 2018;22(1):283. doi:10.1186/s13054-018-2217-4.
[6] 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. doi:10.1016/j.chest.2016.11.036.
[7] Marik PE. Vitamin C: an essential “stress hormone” during sepsis. J Thorac Dis 2020;12(Suppl 1):S84–8. doi:10.21037/jtd.2019.12.64.
[8] Fujii T, Fowler R, Vincent JL. Vitamin C and thiamine for sepsis: time to go back to fundamental principles. Intensive Care Med 2020;46(11):2061–3. doi:10.1007/s00134-020-06242-9.
[9] Carr AC, Maggini S. Vitamin C and immune function. Nutrients 2017;9(11):1211. doi:10.3390/nu9111211.
[10] Holford P, Carr AC, Jovic TH, Ali SR, Whitaker IS, Marik PE, et al. Vitamin C-an adjunctive therapy for respiratory infection, sepsis and COVID-19. Nutrients 2020;12(12):3760. doi:10.3390/nu12123760.
[11] Kashiouris MG, L’Heureux M, Cable CA, Fisher BJ, Leichtle SW, Fowler AA. The emerging role of vitamin C as a treatment for sepsis. Nutrients 2020;12(2):292. doi:10.3390/nu12020292.
[12] Fowler AA 3rd, 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;322(13):1261–70. doi:10.1001/jama.2019.11825.
[13] Rosengrave P, Spencer E, Williman J, Mehrtens J, Morgan S, Doyle T, et al. Intravenous vitamin C administration to patients with septic shock: a pilot randomised controlled trial. Crit Care 2022;26(1):26. doi:10.1186/s13054-022-03900-w.
[14] Fowler AA 3rd, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 2014;12:32. doi:10.1186/1479-5876-12-32.
[15] Hudson EP, Collie JT, Fujii T, Luethi N, Udy AA, Doherty S, et al. Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock. Crit Care Resusc 2019;21(4):236–42.
[16] Lavillegrand JR, Raia L, Urbina T, Hariri G, Gabarre P, Bonny V, et al. Vitamin C improves microvascular reactivity and peripheral tissue perfusion in septic shock patients. Crit Care 2022;26(1):25. doi:10.1186/s13054-022-03891-8.
[17] 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):2387–98. doi:10.1056/NEJMoa2200644.
[18] Wacker DA, Burton SL, Berger JP, Hegg AJ, Heisdorffer J, Wang Q, et al. Evaluating vitamin C in septic shock: a randomized controlled trial of vitamin C monotherapy. Crit Care Med 2022;50(5):e458–67. doi:10.1097/CCM.0000000000005427.
[19] Jung SY, Lee MT, Baek MS, Kim WY. Vitamin C for ≥5 days is associated with decreased hospital mortality in sepsis subgroups: a nationwide cohort study. Crit Care 2022;26(1):3. doi:10.1186/s13054-021-03872-3.

[20] Zhu H, Xu X, Zhang K, Ye Q. The effect of intravenous vitamin C on clinical outcomes in patients with sepsis or septic shock: a meta-analysis of randomized controlled trials. Front Nutr 2022;9:964484. doi:10.3389/fnut.2022.964484.
[21] Patel JJ, Ortiz-Reyes A, Dhaliwal R, Clarke J, Hill A, Stoppe C, et al. IV vitamin C in critically Ill patients: a systematic review and meta-analysis. Crit Care Med 2022;50(3):e304–12. doi:10.1097/CCM.0000000000005320.
[22] 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;44(11):1940–4. doi:10.1007/s00134-018-5107-y.
[23] Smith TJ, Johnson CR, Koshy R, Hess SY, Qureshi UA, Mynak ML, et al. Thiamine deficiency disorders: a clinical perspective. Ann N Y Acad Sci 2021;1498(1):9–28. doi:10.1111/nyas.14536.
[24] Heming N, Salah A, Meng P, Sivanandamoorthy S, Bounab R, Chevret S, et al. Thiamine status and lactate concentration in sepsis: a prospective observational study. Medicine 2020;99(7):e18894. doi:10.1097/MD.0000000000018894.
[25] Woolum JA, Abner EL, Kelly A, Thompson Bastin ML, Morris PE, Flannery AH. Effect of thiamine administration on lactate clearance and mortality in patients with septic shock. Crit Care Med 2018;46(11):1747–52. doi:10.1097/CCM.0000000000003311.
[26] Donnino MW, Andersen LW, Chase M, Berg KM, Tidswell M, Giberson T, et al. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. Crit Care Med 2016;44(2):360–7. doi:10.1097/CCM.0000000000001572.
[27] Sedhai YR, Shrestha DB, Budhathoki P, Jha V, Mandal SK, Karki S, et al. Effect of thiamine supplementation in critically ill patients: a systematic review and meta-analysis. J Crit Care 2021;65:104–15. doi:10.1016/j.jcrc.2021.05.016.
[28] Heming N, Sivanandamoorthy S, Meng P, Bounab R, Annane D. Immune effects of corticosteroids in sepsis. Front Immunol 2018;9:1736. doi:10.3389/fimmu.2018.01736.
[29] Lamontagne F, Rochwerg B, Lytvyn L, Guyatt GH, Møller MH, Annane D, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ 2018;362:k3284. doi:10.1136/bmj.k3284.
[30] Liang H, Song H, Zhai R, Song G, Li H, Ding X, et al. Corticosteroids for treating sepsis in adult patients: a systematic review and meta-analysis. Front Immunol 2021;12:709155. doi:10.3389/fimmu.2021.709155.
[31] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181–247. doi:10.1007/s00134-021-06506-y.
[32] 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(5):954–62. doi:10.1016/j.chest.2017.07.014.
[33] Ge Z, Huang J, Liu Y, Xiang J, Gao Y, Walline JH, et al. Thiamine combined with vitamin C in sepsis or septic shock: a systematic review and meta-analysis. Eur J Emerg Med 2021;28(3):189–95. doi:10.1097/MEJ.0000000000000812.
[34] Sadaka F, Grady J, Organti N, Donepudi B, Korobey M, Tannehill D, et al. Ascorbic acid, thiamine, and steroids in septic shock: propensity matched analysis. J Intensive Care Med 2020;35(11):1302–6. doi:10.1177/0885066619864541.
[35] Coloretti I, Biagioni E, Venturelli S, Munari E, Tosi M, Roat E, et al. Adjunctive therapy with vitamin C and thiamine in patients treated with steroids for refractory septic shock: a propensity matched before-after, case-control study. J Crit Care 2020;59:37–41. doi:10.1016/j.jcrc.2020.04.014.
[36] Kim WY, Jo EJ, Eom JS, Mok J, Kim MH, Kim KU, et al. Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: propensity score-based analysis of a before-after cohort study. J Crit Care 2018;47:211–18. doi:10.1016/j.jcrc.2018.07.004.
[37] Kim YO, Yoo KS, Yoon KW, Park HJ, Park CM. Combined hydrocortisone, ascorbic acid, and thiamine therapy for septic shock with complicated intraabdominal infection: before and after cohort study. Ann Surg Treat Res 2021;100(6):356–63. doi:10.4174/astr.2021.100.6.356.
[38] Vail EA, Wunsch H, Pinto R, Bosch NA, Walkey AJ, Lindenauer PK, et al. Use of hydrocortisone, ascorbic acid, and thiamine in adults with septic shock. Am J Respir Crit Care Med 2020;202(11):1531–9. doi:10.1164/rccm.202005-1829OC.
[39] 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. doi:10.3390/jcm8040478.
[40] 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(1):164–73. doi:10.1016/j.chest.2020.02.049.
[41] Wani SJ, Mufti SA, Jan RA, Shah SU, Qadri SM, Khan UH, et al. Combination of vitamin C, thiamine and hydrocortisone added to standard treatment in the management of sepsis: results from an open label randomised controlled clinical trial and a review of the literature. Infect Dis 2020;52(4):271–8. doi:10.1080/23744235.2020.1718200.
[42] Mohamed ZU, Prasannan P, Moni M, Edathadathil F, Prasanna P, Menon A, et al. Vitamin C therapy for routine care in septic shock (ViCTOR) trial: effect of intravenous vitamin C, thiamine, and hydrocortisone administration on inpatient mortality among patients with septic shock. Indian J Crit Care Med 2020;24(8):653–61. doi:10.5005/jp-journals-10071-23517.
[43] Balakrishnan M, Gandhi H, Shah K, Pandya H, Patel R, Keshwani S, et al. Hydrocortisone, vitamin C and thiamine for the treatment of sepsis and septic shock following cardiac surgery. Indian J Anaesth 2018;62(12):934–9. doi:10.4103/ija.IJA_361_18.
[44] 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(9):e14376. doi:10.1111/ijcp.14376.
[45] Chang P, Liao Y, Guan J, Guo Y, Zhao M, Hu J, et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. Chest 2020;158(1):174–82. doi:10.1016/j.chest.2020.02.065.
[46] 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. doi:10.4103/jrms.JRMS_593_19.
[47] Sevransky JE, Rothman RE, Hager DN, Bernard GR, Brown SM, Buchman TG, et 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(8):742–50. doi:10.1001/jama.2020.24505.
[48] Lyu QQ, Zheng RQ, Chen QH, Yu JQ, Shao J, Gu XH. Early administration of hydrocortisone, vitamin C, and thiamine in adult patients with septic shock: a randomized controlled clinical trial. Crit Care 2022;26(1):295. doi:10.1186/s13054-022-04175-x.
[49] Moskowitz A, Huang DT, Hou PC, Gong J, Doshi PB, Grossestreuer AV, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. JAMA 2020;324(7):642–50. doi:10.1001/jama.2020.11946.
[50] Fujii T, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, 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;323(5):423–31. doi:10.1001/jama.2019.22176.
[51] Wu T, Hu C, Huang W, Xu Q, Hu B, Li J. Effect of combined hydrocortisone, ascorbic acid and thiamine for patients with sepsis and septic shock: a systematic review and meta-analysis. Shock 2021;56(6):880–9. doi:10.1097/SHK.0000000000001781.
[52] Fujii T, Salanti G, Belletti A, Bellomo R, Carr A, Furukawa TA, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis. Intensive Care Med 2022;48(1):16–24. doi:10.1007/s00134-021-06558-0.
[53] Assouline B, Faivre A, Verissimo T, Sangla F, Berchtold L, Giraud R, et al. Thiamine, ascorbic acid, and hydrocortisone as a metabolic resuscitation cocktail in sepsis: a meta-analysis of randomized controlled trials with trial sequential analysis. Crit Care Med 2021;49(12):2112–20. doi:10.1097/CCM.0000000000005262.
[54] Stolarski AE, Kim J, Rop K, Wee K, Zhang Q, Remick DG. Machine learning and murine models explain failures of clinical sepsis trials. J Trauma Acute Care Surg 2022;93(2):187–94. doi:10.1097/TA.0000000000003691.