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Systematic Review: Impact of Vitamin C, Hydrocortisone, and Thiamine Therapy on Sepsis and Septic Shock Patients

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ABSTRACT

Systematic Inflammatory Response Syndrome and Sepsis are inflammatory responses to many health manifestations. Sepsis mortality is high despite global treatment standards, with metabolic resuscitation being a novel approach for managing Sepsis. The purpose of this systematic review is to assess the effectiveness of the critical care combination comprising hydrocortisone, Vitamin C, and thiamine in potentially mitigating Sepsis, reducing mortality associated with septic shock, and alleviating organ failure. In order to execute this scoping review, recent research based on the effect of vitamin C, hydrocortisone, and thiamine therapy in Sepsis and Septic Shock was identified. Data was gathered from Google Scholar, PubMed, NCBI, Hindawi, Scirp, Journal of Immunology, and Critical Care Medicine. Studies selected from different years ranging between 2017 to 2023 using keywords 'Severe Sepsis,' 'Septic Shock,' 'Effect of Vitamin C on Sepsis,' 'Effect of Thiamine on Sepsis Treatment,' 'Hydrocortisone Therapy in Sepsis,' 'SIRS,' 'Septic Shock Criteria.' Access was made to the whole texts of the articles that were found. This review could provide fundamental strategic plans dealing with specific risk factors and managing accordingly. The systemic review has been completed according to the guidelines regulated by Preferred Reporting Items for Systemic Research and Meta-Analysis. The initial search for publications on vitamin C, hydrocortisone, and thiamine in Sepsis and septic shock retrieved 1710 papers, from which 265 were selected. The reviews' articles were further evaluated to assess vitamin C, hydrocortisone, and thiamine's effects on Sepsis. Over 80 references were considered for their potential use in medical diagnosis and therapy. This review has included ten recent articles for the last seven years. Intravenous vitamin C, corticosteroids, hydrocortisone, and thiamine prevent organ failure, reduce vasopressor use, and decrease mortality in severe Sepsis and septic shock patients.

INTRODUCTION

Systematic Inflammatory Response Syndrome (SIRS) is an inflammatory response to various clinical disorders. (Davies & Hagen, 1997) The intensity of SIRS impacts the host's susceptibility to infection through the innate immune system. (Robertson & Coopersmith, 2006; J. Wang *et al.*, 2023) The innate immune response can be defined as the first line of defense against a microbial intruder and characterized as a non-specific response that takes only a few minutes to activate. Pathogen-Associated Molecular Patterns (PAMPS) were recognized via Pattern Recognition Receptors (PRRs) prevalent in innate cell types, including neutrophils and macrophages. (Beutler *et al.*, 2004) The adaptive immune system is more effective than the innate immune system in protecting the host from various microorganisms. (Davies & Hagen, 1997) Similarly, Systematic inflammatory response syndrome is a body's defence response to a noxious stressor (infection, trauma, surgery, acute inflammation, ischemia or reperfusion, or malignancy) (Chakraborty & Burns, 2019; Nyström, 1998) to localize and then eliminate the exogenous and endogenous source of insult. (Chakraborty & Burns, 2019) Furthermore, SIRS can be diagnosed by observing abnormalities such as heart rate,

temperature, respiratory rate, and white blood cell (WBC) count. (Davies & Hagen, 1997)

Moreover, SIRS is a multifaceted condition, classified into two primary categories: Sepsis and non-infectious inflammation. (Davies & Hagen, 1997) SIRS, when associated with infection, can progress to Sepsis. The term 'Sepsis' encompasses a range of conditions (Lever & Mackenzie, 2007), all stemming from the intrusion of microbial agents from a local infectious source into the bloodstream. (Henriquez-Camacho & Losa, 2014) These conditions can manifest with mild signs and symptoms of systemic infection, including traditional indicators like fever, tachycardia, tachypnea, and leukocytosis. (Nyström, 1998) In more severe cases, they can lead to shock and organ dysfunction. (Henriquez-Camacho & Losa, 2014; Lever & Mackenzie, 2007) In addition, the pathophysiology of Sepsis primarily results from the host's innate immune system response (Lever & Mackenzie, 2007), and SIRS occurs at an exceptionally elevated rate.

Numerous research indicated that one-third of patients admitted to ICU (Intensive Care Unit) suffer from SIRS. (Brun-Buisson, 2000) Hemodynamic instability despite intravascular volume resuscitation is referred to

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as Septic shock, while severe Sepsis is defined as Sepsis accompanied by one or more instances of end-organ failure. (Chakraborty & Burns, 2019) These conditions illustrate a physiological continuum marked by an imbalance between the body's pro and anti-inflammatory responses. Consequently, for immune-compromised septic patients meeting two or more Sequential Organ Failure Assessment (SOFA) SIRS criteria, the term

Multiple Organ Dysfunction (MOD) is applied, signifying altered organ function. (Kaukonen *et al.*, 2015; Nyström, 1998) This definition was established during a sepsis definitions consensus conference sponsored by the American College of Chest Physicians and the Society of Critical Care Medicine. (Chakraborty & Burns, 2019; Suárez-de-la-Rica *et al.*, 2023)

The execution of any two of the following conditions

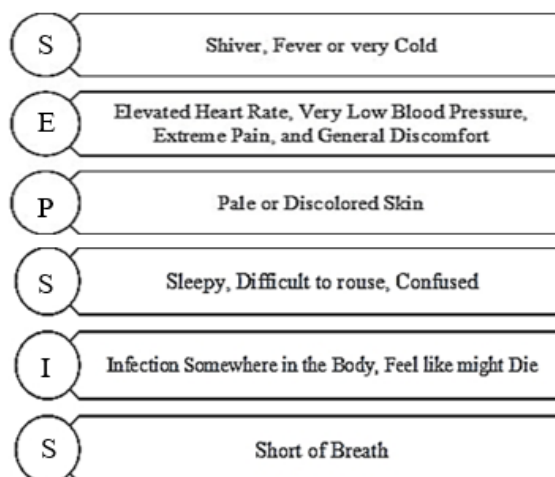


Figure 1: Showing the symptoms of Sepsis

SIRS	Systemic Inflammatory Response Syndrome
• Response to infection	
SEPSIS - 1	The presence of infection as well as systematic inflammatory response characterizes a diagnosable disorder
• Culture documented infection • Severe Sepsis: Sepsis plus organ dysfunction • Septic Shock: Despite fluid volume resuscitation and the prevalence of perfusion anomalies, sepsis-induced hypotension apparently prevailed.	
SEPSIS - 2	Sepsis associated with organ dysfunction
• Oliguria • Severe Sepsis: Sepsis plus hypotension, hypoperfusion, including but not limited to lactic acidosis, acute mental status changes • Septic Shock: Arterial hypotension that persists and is unrelated to other conditions indicates a state of acute circulatory failure	
SEPSIS - 3	Fluid resuscitation
*Hypotension and hypoperfusion *Sepsis: organ dysfunction that poses a life-threatening risk due to a moderate to severe host response to infection *Septic Shock: A subset of sepsis where the underlying cellular, metabolic, and/or circulatory abnormalities are severe enough to significantly raise mortality	

Figure 2: Showing the stages of Sepsis

constitutes the objective measurement of SIRS (Chakraborty & Burns, 2019) SIRS with a source of infection:

- Above 38 or below 36 degrees Celsius for body temperature.
- Heart beats per minute greater than 90.
- Respiration more than 20 times per minute or Partial CO₂ pressure under 32 mmHg.
- Over 10% immature forms or bands, Leukocyte Count/White Blood Cells (WBC) greater than 12000, or

fewer than 4000/microliter. (Chakraborty & Burns, 2019)

Severe sepsis criteria (Hypotension, Hypo perfusion, and Organ Dysfunction): (Herzum & Renz, 2008; B. Liang *et al.*, 2023)

- Lactic acidosis, SBP greater than 90 or SBP lesser than or equal to 40 mmHg of normal.

Septic Shock Criteria

- Hypotension with severe Sepsis despite receiving enough fluid support.

MODS Criteria

- Indications of less than or equal to two organ failures. (Herzum & Renz, 2008)

The level of organ system damage can be measured using a variety of measures. (Chakraborty & Burns, 2019) A few examples include the Multiple Organ Dysfunction (MOD) (Chakraborty & Burns, 2019) scores, Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) score versions II and III, and Logistic Organ Dysfunction (LOD) score. (Chakraborty & Burns, 2019)

LITERATURE REVIEW

Epidemiology of Septic Syndrome

Sepsis is a significant public health concern, with Septic syndrome being the leading cause of mortality in the United States. (Giamarellos-Bourboulis, 2008) Globally, it affects many individuals annually, with estimates ranging from 15 to 19 million cases. (Litwak *et al.*, 2019; Marik *et al.*, 2017; K. Wang *et al.*, 2023)

Treatment Options for SIRS, Severe Sepsis, and Septic Shock

SIRS, Severe Sepsis, and Septic Shock are severe disease states that require effective treatment strategies. One therapeutic approach involves the administration of Vitamin C, Hydrocortisone, and Thiamine (Vitamin B1). (Sprung *et al.*, 2008) Studies have suggested a regimen of these agents administered every six to twelve hours for patients with severe Sepsis and septic shock, demonstrating potential mortality benefits. (Litwak *et al.*, 2019; Marik *et al.*, 2017)

Depletion of Vitamin C in Sepsis

Research has indicated that Sepsis can lead to a depletion of Vitamin C, an essential cofactor for producing catecholamines and cortisol, hormones critical for shock survival. (Balakrishnan *et al.*, 2018) Studies have explored the safety and efficacy of Vitamin C supplementation to counteract this depletion, with doses as high as 6g reported to be safe and without adverse side effects. (Balakrishnan *et al.*, 2018)

Metabolic Resuscitation as an Effective Treatment Option

To mitigate the adverse effects of high-dose Vitamin C intake, intravenous thiamine has been administered alongside hydrocortisone to enhance endogenous catecholamine synthesis. (Balakrishnan *et al.*, 2018) This combination of metabolic resuscitation has been investigated and found to be an effective adjuvant treatment for septic shock and Sepsis (Fujii *et al.*, 2022), emerging as a viable therapeutic option. (Kuhn *et al.*, 2018; Shi & Tie, 2020).

Immunomodulatory Therapies for Sepsis: Efficacy and Mechanisms

Patients with Sepsis treated with high doses of vitamin

C, hydrocortisone, and thiamine discovered a substantial reduction in mortality and improved disease prevention. (Balakrishnan *et al.*, 2018; Mohamed *et al.*, 2023; Shi & Tie, 2020) Ascorbic acid, or vitamin C, is an anti-inflammatory and cellular anti-oxidant. (Fujii *et al.*, 2019) Water-soluble vitamin C produces cortisol, catecholamines, and vasopressin, essential disease-process mediators. Because of its antioxidant characteristics, vitamin C also helps reduce inflammation. Emerging findings support the use of vitamin C in addition to standard therapy for patients with Sepsis and septic shock to decrease inflammation and improve hemodynamic stability (Teng *et al.*, 2018). Another study (Sprung *et al.*, 2008) demonstrated that patients with septic shock frequently utilize hydrocortisone (Sprung *et al.*, 2008), which decreases infection resistance by reducing inflammation. (Suffredini, 2018).

Additionally, having anti-endo-toxic and antipyretic properties, corticosteroids and hydrocortisone have been demonstrated to affect vascular reactivity in a way that may be advantageous to the infected person. (Suffredini, 2018) Moreover, another study stated the beneficial effect of thiamine as therapy for Sepsis. (Moskowitz & Donnino, 2020) The study estimated the correlation between thiamine, rapid lactate clearance, and lower mortality. (Moskowitz & Donnino, 2020) Nevertheless, these immunomodulatory therapies showed significance for Sepsis, effectively lowering the mortality risk and treating this infection's symptoms. (Vincent *et al.*, 2002)

This scoping review aims to assess the association between Vitamin C, Thiamin, and Hydrocortisone effect as a therapy for Sepsis and Septic Shock. This unique association has not been addressed earlier in the scientific literature. It suggests a novel approach to metabolic resuscitation, potentially adding value to medical sciences and diagnostic research. This approach will add value and new insights to the medical sciences and diagnostic research field.

METHODOLOGY

Search Strategy

In order to execute this scoping review, recent research and review articles/publications are based on the effect of vitamin C, hydrocortisone, and thiamine therapy in Sepsis and Septic Shock were identified.

Study Selection and Eligibility

The databases used to collect articles include Google Scholar, PubMed, Web of Science, NCBI, Hindawi, Scirp, Journal of Immunology, Critical Care Medicine, PLoS ONE, Journal of Sepsis and Blood Infection, National Library of Medicine, Frontiers in Medicine, ResearchGate, Internal Medicine Journal, Journal of Medical Internet Research, MEDLINE, EMBASE database, and BioMed.

For this study, we searched through the literature to find articles that addressed the role of vitamin C, hydrocortisone, and thiamine in treating Sepsis and septic shock. Search strategy based on the use of MeSH

terminologies which were related to the topic, studies were selected from different years ranging between 2017 to 2023 using keywords 'Sepsis,' 'Severe Sepsis,' 'Septic Shock,' 'Effect of Vitamin C on Sepsis,' 'Effect of Vitamin C in Septic Shock Treatment,' 'Vitamin C in Sepsis,' 'Effect of Thiamine on Sepsis Treatment,' 'Hydrocortisone Therapy in Sepsis,' 'SIRS,' 'Septic Shock Criteria,' 'Response Syndrome Septic Shock,' 'Patients with Septic Shock,' 'Epidemiology of Sepsis,' 'Markers of Sepsis,' 'Inflammatory Markers of Septic Shock,' 'Systematic Inflammatory Response Syndrome,' 'Sepsis

Response to Infection,' 'Innate Immunity in Sepsis,' 'Adaptive Immune Response in Sepsis,' 'Sepsis Diagnosis,' 'Immunity in Sepsis Mechanism,' 'Anti-inflammatory Therapy in Sepsis,' 'Sepsis Immunomodulatory Therapy,' 'Antioxidant Therapy Severe Sepsis,' 'Review on Sepsis Therapy,' 'Correlation between Vitamin C Therapy and Sepsis.' Access was made to the whole texts of the articles that were found. Furthermore, the systemic review has been completed according to the guidelines regulated by Preferred Reporting Items for Systemic Research and Meta-Analysis (PRISMA).

Table 1: Data selection strategy

Years	Search Engines	Keywords
2017- 2023	Google Scholar	Sepsis
	PubMed	Severe Sepsis
	NCBI	Septic Shock
	Hindawi	Correlation between Vitamin C Therapy and Sepsis
	Scirp	Epidemiology of Sepsis
	Frontiers in Medicine	Sepsis Immunomodulatory Therapy
	BioMed	Hydrocortisone Therapy in Sepsis
	Journal of Immunology	
	PLoS ONE	
	Journal of Sepsis and Blood Infection	

Inclusion Criteria

The following addition and omission criteria were used to filter the titles rather than study relevance. We only selected those studies submitted to peer-reviewed journals for approval that were already published. These studies were taken into consideration to understand the research criteria better.

- Papers in English and articles published in recent years were preferred.
- Studies describing Sepsis and its types were included.
- Studies related to Sepsis diagnostics and treatments were included.
- Studies related to the effect of vitamin C on Sepsis were also considered.
- Studies of the correlation between antioxidants, anti-inflammatory therapy, and Sepsis were also considered.
- Roadmap report on Sepsis was included in this review.
- Reviews of recent developments in Sepsis diagnostic systems.

- The role of Vitamin C, Hydrocortisone, and Thiamin in the therapy of Sepsis, Severe Sepsis, *Septic Shock, and
- MODS was also reviewed.

Exclusion Criteria

The exclusion criteria involve;

- Papers written in languages other than English were excluded.
- Studies focusing solely on the impact of Sepsis on Cardio-logical health were excluded.
- Studies on Sepsis-associated hyperlactatemia were excluded.
- Papers not aimed at Sepsis and the advancement of its treatment were excluded from the review. The objective was not related to Sepsis and its diagnosis.
- Papers related to Sepsis but whose main objective was not related to the effect of Vitamin C and its therapy in Sepsis and Septic Shock were excluded from the review.
- Duplicate studies were excluded.

Table 2: Indicating the Inclusion and Exclusion Criteria of Studies

Included Articles	Excluded Articles
Articles in the English language	Articles were written other than in the English language
Articles of recent years	Studies that focused on the impact of Sepsis on Cardio-logical health
Relevant to Sepsis and types	Studies related to Sepsis-associated hyperlactatemia
Relevant to Sepsis diagnostics and treatments	Not aimed at the therapy of Sepsis, advancement, and scopes in its diagnostics
Roadmap Report on Sepsis	The objective was not related to Sepsis and its treatment
Reviews of recent developments in Sepsis diagnostic systems	Not aimed at the effect of Vitamin C in Sepsis and Septic Shock treatment

• Studies lacking predefined findings' supporting data. Among the 1710 research, 265 were retrieved, and 1445 papers were eliminated due to their no direct relevance to the study's main goal and were written primarily in languages other than English, most commonly Arabic, French, Spanish, and Dutch.

Data Extraction and Risk of Bias

Using Microsoft Excel, the researcher extracted and sorted the sample size, study type, duplicates, full-text articles, and empirical studies, making the systematic review approach practicable. The two authors reviewed and decided to include all reviews independently based on the eligibility criteria. Information of variables includes the author, year of publication, and number of studies. The two reviewers assessed the methodological qualities by using the 7-item scale of risk of bias developed by the Cochrane Bias Methods Group. This review used the PRISMA guideline and flow diagram to lower the risk of bias. The sources of bias assessed included outcomes, population, study selection process, incompleteness of data, and time frame and setting.

Quality of Systematic Reviews

The expert team members assessed the quality of the systematic reviews, including questions regarding the degree to which the systematic reviewers had evaluated the risk of bias in individual studies. Systematic reviews with major limitations were excluded. The Authors have assessed the methodological quality of studies in Sepsis

and septic shock based on the review authors' assessments of risk of bias in the primary studies they had included.

Summary Measures and Synthesis of Results

The authors analyzed the data collected by the members of the expert team. Due to the expected heterogeneity of studies regarding participants, interventions, outcomes and study designs, a quantitative summary measure of the results was not planned. We did a qualitative and narrative summary of the results of the systematic reviews. The literature review results were presented and discussed in two workshops intending to validate results.

RESULTS

The initial search for publications concerning the significance of vitamin C, hydrocortisone, and thiamine in treating Sepsis and septic shock yielded 1710 papers, from which 265 were selected. The reviews' articles were further analyzed to ensure they were pertinent to assessing the impact of vitamin C, hydrocortisone, and thiamine in sepsis treatment. Around 80 references were examined for their potential applicability to the medical field as a treatment. A total of 10 articles were included, with preference given to those published during the last seven years. Figure 3 illustrates the Preferred Reporting Items for Systemic Research and Meta-Analysis guidelines (PRISMA) flowchart of article identification, displaying the many stages of the systematic review applied in identifying studies.

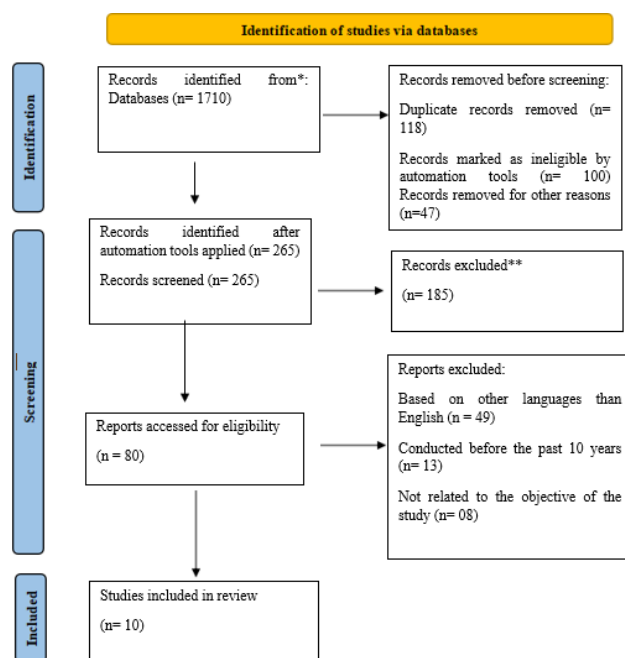


Figure 3: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

DISCUSSION

Effectiveness of Vitamin C, Hydrocortisone, and Thiamine in Sepsis and Septic Shock Treatment

Numerous studies have explored the efficacy of immunomodulatory therapies as a potential treatment for

Sepsis and Septic shock, yielding a range of findings and perspectives. This systematic review aims to consolidate and analyze the research in this field, highlighting areas of agreement and divergence among various studies. An unrestrained immune reaction to the microorganisms

is one of the defining characteristics of blood infection, often known as Sepsis. As a result, inflammation develops throughout the body. Sepsis is a potentially life-threatening condition that can develop when an infection is not properly diagnosed and treated promptly. A widely acknowledged notion is that the hydrocortisone, vitamin C, and Thiamine (HVT) combination could help restore the imbalanced immune response, correct oxidative mitochondrial function, and enhance energy production. However, current clinical practice has an ongoing debate regarding using the HVT strategy (Sun *et al.*, 2023). In addition to the potential combined benefits, the rationale for employing HVT includes its minimal risk, affordability, and easy availability. Any minor clinical side effects, like hydrocortisone-induced hyperglycemia, hypertension, or hypernatremia, may occur but are generally inconsequential and can be effectively managed in the intensive care unit. (Briegel *et al.*, 2018; Marik, 2018; Shi & Tie, 2020; J. Wang *et al.*, 2023)

Vitamin C as an Anti-Inflammatory Agent

Studies such as (Lv *et al.*, 2021), (Wei *et al.*, 2020), and (Fujii *et al.*, 2019) have all suggested the potential benefits of vitamin C in the treatment of Sepsis (Marik *et al.*, 2017). Moreover, it was examined that Sepsis patients have shown benefits from vitamin C in addition to conventional treatment (Marik *et al.*, 2017). According to the Surviving Sepsis Guidelines, the same therapy was administered to every patient in this trial. (Lv *et al.*, 2021) The vitamin C group began using vitamin C on the day they entered the intensive care unit, and patients received IV injections of 3.0 g of vitamin C dissolved in 5% dextrose (100 ml each time, twice a day) until they were released from the hospital. In contrast, intravenous 5% dextrose (100 ml/time, twice a day) was given to the control group as a placebo. A significant vitamin C deficiency typically results in an overactive inflammatory response. (Lv *et al.*, 2021) Vitamin C has multiple roles in treating patients with severe Sepsis and septic shock due to its anti-inflammatory properties, anti-oxidation properties, inhibition of nitric oxide synthesis, cortisol retention effect, and increased catecholamine synthesis in the brain and adrenal medulla. (Long, Du, Ouyang, Zhong, & Zeng, 2023; Lv *et al.*, 2021)

Combination Therapy: Role in Treating Sepsis

In addition, another study (Wei *et al.*, 2020) showed that a potential cure for Sepsis would be exogenous vitamin C supplementation. Li (2018) conducted a meta-analysis that showed vitamin C use could dramatically lower sepsis-related mortality (Yao *et al.*, 2021a). The study's findings determined that a vitamin C infusion could shorten the time that vasopressors were administered. Catecholamines were also synthesized with the assistance of vitamin C (Wei *et al.*, 2020). Furthermore, another study by (Fujii *et al.*, 2019) stated that vitamin C is an anti-inflammatory and cellular antioxidant. It was undetermined whether hydrocortisone, thiamine, and vitamin C combination

therapy in septic shock lower vasopressor reliance. (Fujii *et al.*, 2019) The Vitamins trial would assess whether combination therapy consisting of vitamin C, thiamine, and hydrocortisone, when compared with hydrocortisone alone, boosts the amount of vasopressor-free hours in critically sick patients suffering from septic shock. (Fujii *et al.*, 2022; Fujii *et al.*, 2019)

Moreover, in another study (Mohamed *et al.*, 2020), researchers investigated the combination therapy of vitamin C, thiamine, and hydrocortisone. It was evaluated that administering a combination of hydrocortisone, thiamine, and ascorbic acid did not lower all-cause in-hospital mortality in patients suffering from septic shock within six hours of receiving a diagnosis of septic shock. Patients diagnosed with septic shock who were given intravenous vitamin C, thiamine, and hydrocortisone at the dose and for the duration prescribed had no impact on the hospital mortality rate. The treatment with vitamin C appeared to be risk-free. There was evidence to suggest that the inflammatory process had been mitigated. (Mohamed *et al.*, 2020)

Furthermore, in other research conducted at Zhujiang Hospital of Southern Medical University in Guangdong Province, China, a single-centre, single-blind, randomized, parallel, controlled trial was undertaken. The study found that combining hydrocortisone, vitamin C, and thiamine did not significantly reduce mortality among Sepsis and Septic shock patients. This outcome aligns with a prior retrospective study conducted by Litwak *et al.*, 2019. (Chang *et al.*, 2020; Litwak *et al.*, 2019)

Combination Therapy and Mortality Rate

Furthermore, according to the findings of another meta-analysis conducted by (Yao *et al.*, 2021b), a significant decrease in SOFA score and vasopressor duration among patients with Sepsis and septic shock was associated with vitamin C and thiamine, either alone or in conjunction with hydrocortisone administration; however, it did not affect short-term mortality (Mitchell *et al.*, 2020). In the meantime, the findings demonstrated that combination therapy did not impact death rates in intensive care units or hospitals. (Yao *et al.*, 2021b) It was further described that a deficit in vitamins C and B1 could lead to several disorders with pathophysiological features similar to those of Sepsis. These features include peripheral vasodilation, coagulation problems, cardiac and endothelial dysfunction, and hypoxia. Hence, vitamin C and thiamine are recommended for organ function restoration in Sepsis and septic shock. (Yao *et al.*, 2021b) Pyruvate dehydrogenase requires phosphorylated thiamine to maintain aerobic respiration. Insufficient thiamine may cause anaerobic pathway shift and lactate accumulation. Meanwhile, intravenous vitamin C treatment was safe even at very large dosages, and the dosage was relatively consistent across all studies. (Yao *et al.*, 2021b)

Metabolic Resuscitation

Another study (Fujii *et al.*, 2022) summarized that

“Metabolic resuscitation” had drawn great interest as a complementary treatment for septic shock and Sepsis. Usually, vitamin C, glucocorticoids, and vitamin B1 or one of its components were mixed while executing such metabolic resuscitation. (Fujii *et al.*, 2022) Prior research showed hydrocortisone, vitamin C, and thiamine (HVT) as potential adjuvant therapy for Sepsis and septic shock, with lower mortality and improved disease cure. (Shi & Tie, 2020)

Positive Impact of Combination and Immunomodulatory Therapy

Consequently, another study by Marik *et al.*, 2017 showed that the natural progression of patients with severe Sepsis and septic shock appeared to be significantly changed by the intravenous administration of vitamin C, hydrocortisone, and thiamine in moderate dosage. (Marik *et al.*, 2017) The findings of this study were supported by several experimental and clinical studies that have demonstrated the efficacy and prospective utility of moderate-dose hydrocortisone, intravenous vitamin C, and thiamine in critically ill patients. (Marik *et al.*, 2017) However, this was the initial study to examine the relationship between thiamine and intravenous vitamin C hydrocortisone, which works synergistically to reverse the

pathophysiologic alterations of Sepsis. (Marik *et al.*, 2017)

Mixed Findings and Perspectives

The study by (Chang *et al.*, 2020) demonstrated the combination therapy of vitamin C, hydrocortisone, and thiamine. Chang *et al.*, 2020 did not find substantial improvement for patients diagnosed with Sepsis with combination therapy, and it did not appear to improve the mortality rate. In contrast, another study by Long *et al.*, 2023 supported the positive effect of vitamin C and hydrocortisone in treating Septic shock. (Long, Du, Ouyang, Zhong, & Ye, 2023). Hydrocortisone showed antitoxic effects, and the combination of hydrocortisone with vitamin C and thiamine showed significant effects in refractory Sepsis and Septic shock. (H. Liang *et al.*, 2023; Long, Du, Ouyang, Zhong, & Ye, 2023)

This systematic review summarizes the findings based on the effect of Vitamin C, Hydrocortisone, and Thiamine in Sepsis and Septic shock treatment and provides a comprehensive overview of the research findings related to immunomodulatory therapy. In comparison, some studies suggest potential benefits, while others present mixed results, underscoring the complexity of this therapeutic approach and the need for further investigation.

Table 3: The lists of studies discussed in this review are relevant to the effect of Vitamin C, Hydrocortisone, and Thiamine in treating Sepsis and Septic Shock

No	Title	Author	Year	Conclusion	Reference No.
01	Retracted Article: Early use of high-dose vitamin C is beneficial in the treatment of Sepsis	Ly, S. J., Zhang, G. H., Xia, J. M., Yu, H., & Zhao, F.	2021	The early treatment of Sepsis with intravenous high-dose vitamin C in combination with standard therapy showed a beneficial effect on Sepsis in terms of reduced 28-day mortality, decreased SOFA score, and increased clearance rate of procalcitonin.	Ly, S.-J., <i>et al.</i> , (2021)
02	Efficacy of vitamin C in patients with Sepsis: An updated meta-analysis.	Wei, X. B., Wang, Z. H., Liao, X. L., Guo, W. X., Wen, J. Y., Qin, T. H., & Wang, S. H.	2020	In conclusion, including the recently published retrospective studies in our meta-analysis could not reveal the beneficial effect of vitamin C on patients with Sepsis. The value of vitamin C in Sepsis needs to be clarified through more high-quality randomized controlled trials in the future.	Wei, X.-b., <i>et al.</i> , (2020)
03	Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock (VITAMINS) trial: study protocol and statistical analysis plan.	Fujii, T., Udy, A. A., Deane, A. M., Luethi, N., Bailey, M., Eastwood, G. M., & Bellomo, R.	2019	Septic shock is associated with poor outcomes. Vitamin C (ascorbic acid) is a cellular antioxidant with anti-inflammatory properties. Whether the combination therapy of vitamin C, thiamine, and hydrocortisone reduces vasopressor dependency in septic shock is unclear.	Fujii, T., <i>et al.</i> , (2019)

04	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.	Mohamed, Z. U., Prasannan, P., Moni, M., Edathadathil, F., Prasanna, P., Menon, A., & Menon, V.	2020	We conclude that intravenous vitamin C, thiamine, and hydrocortisone in the dose and duration used did not affect the hospital mortality in patients with septic shock. Vitamin C therapy seems to be safe. There is evidence of a reduction in the inflammatory process	Mohamed, Z.U., <i>et al.</i> , (2020)
05	Combination therapy of thiamine, vitamin C and hydrocortisone in treating patients with Sepsis and septic shock: a meta-analysis and trial sequential analysis.	Yao, R., Zhu, Y., Yu, Y., Li, Z., Wang, L., Zheng, L., & Yao, Y.	2021	In the current meta-analysis, the combination therapy of vitamin C and thiamine, with or without hydrocortisone, had no impact on short-term mortality compared with placebo but was associated with a significant reduction in SOFA score among patients with Sepsis and septic shock.	Yao, R., <i>et al.</i> , (2021)
06	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.	Fujii, T., Salanti, G., Belletti, A., Bellomo, R., Carr, A., Furukawa, T. A., & Young, P. J.	2022	On NMA, metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs was not proven to reduce longer-term mortality. However, NMA and component NMA suggested an association between high dose and very high dose vitamin C and decreased mortality with low certainty. Glucocorticoid therapy was associated with a decreased duration of vasopressor support and ICU therapy. Further RCTs evaluating very high doses of intravenous vitamin C therapy appear justified.	Fujii, T., <i>et al.</i> , (2022)
07	Benefit of hydrocortisone, thiamine, and vitamin C for patients with Sepsis or septic shock? Too early to conclude.	Shi, R., & Tie, H.	2020	In conclusion, the beneficial findings of our study support that HVT remains an attractive choice for Sepsis and septic shock, while results from large-scale RCTs are still expected before a definite conclusion, especially regarding the timing of HVT and the severity of Sepsis.	Shi, R., & Tie, H., (2020)
08	Hydrocortisone, vitamin C, and thiamine for the treatment of severe Sepsis and septic shock: a retrospective before-after study.	Marik, P. E., Khangoora, V., Rivera, R., Hooper, M. H., & Catravas, J.	2017	Our results suggest that the early use of intravenous vitamin C, corticosteroids, and thiamine effectively prevents progressive organ dysfunction, including acute kidney injury, and reduces the mortality of patients with severe Sepsis and septic shock. Additional studies are required to confirm these preliminary findings.	Marik, P.E., <i>et al.</i> , (2017)

09	Combined treatment with hydrocortisone, vitamin C, and thiamine for Sepsis and septic shock: a randomized controlled trial.	Chang, P., Liao, Y., Guan, J., Guo, Y., Zhao, M., Hu, J., & Liu, Z.	2020	In conclusion, hydrocortisone, vitamin C, and thiamine did not appear to reduce the 28-day mortality compared with a placebo in patients with Sepsis or septic shock. Moreover, we must consider side effects, such as severe hyponatremia. However, a larger sample and multi-centre, randomized controlled trials are required to validate the effectiveness and timing of this treatment.	Chang, P., <i>et al.</i> , (2020)
10	Research Progress on Therapeutic Effect and Mechanism of Hydrocortisone on Sepsis	Yicen Long Xiaoqiang Du Zhi Ouyang Jian Zhong Zeng Ye	2023	Sepsis has remained a high mortality rate worldwide. Hydrocortisone has potent immunological and antitoxic effects, and thus, it is frequently used in treating septic shock. In recent years, the combination of hydrocortisone and other drugs, such as vitamin C and thiamine, has achieved promising outcomes in refractory septic shock. The present review focuses on the therapeutic effects of hydrocortisone in Sepsis and summarizes the mechanisms by which hydrocortisone acts on vascular endothelial cells. We highlighted the effect of hydrocortisone on anti-inflammation, anti-apoptosis, improvement of vascular functions, and anti-oxidative stress.	Long, Y., <i>et al.</i> , (2023)

CONCLUSION

An uncontrolled immunological response to the microorganisms characterizes blood infection or Sepsis. This causes inflammation throughout the body. Sepsis is typically brought on by a delay in the infection's detection and treatment. Contrarily, intravenous vitamin C, corticosteroids, hydrocortisone, and thiamine successfully prevent organ dysfunction progression and lower the need for vasopressors and the mortality of patients with severe Sepsis and septic shock. Moreover, severe Sepsis and septic shock patients may benefit from vitamin C, corticosteroids, and thiamine combination. These therapies were medically proven and showed significance in treating Sepsis, lowering its symptoms' effects, and preventing organ malfunctioning. However, it should be chosen for the proper type of septic shock, the suitable patient who would benefit, and the right dosage and duration when treating Sepsis. Triple therapy remains considered to be a promising technique in this regard.

RECOMMENDATIONS

Researchers are encouraged to explore various avenues

in treating Sepsis, including patient stratification, dosage, duration optimization, subtype specificity, long-term effects, and combination therapies. Precision medicine is crucial for optimizing treatment outcomes. Further refinement of dosages and duration is necessary to balance efficacy and safety. Subtype specificity is also crucial, as a tailored approach may be required for each. Long-term effects of immunomodulatory therapies in Sepsis survivors and combining therapies can further enhance their efficacy.

Further recommendations include clinical trials, precision medicine approach, pharmacokinetic and pharmacodynamics studies, long-term follow-up studies, and combination therapies. It also encourages data sharing and collaboration among researchers, healthcare institutions, and pharmaceutical companies to accelerate research. Public awareness about early Sepsis symptoms is crucial for early detection and treatment. Policy advocacy for evidence-based immunomodulatory therapies in Sepsis treatment protocols is encouraged, prioritizing patient outcomes and safety. Moreover, international collaboration in Sepsis research and treatment is

encouraged to foster global cooperation. These recommendations aim to advance the understanding of Sepsis, improve management, and enhance the quality of care for Sepsis patients.

LIMITATIONS

- The majority of the screened articles were not in English, and the majority of the articles were unreachable. The limitations of the study were these considerations.
- Publication bias, language bias, timeframe, and quality of included studies are common limitations in systematic reviews. Acknowledging these biases and assessing individual studies' quality is crucial for evaluating the strength of evidence.

Strengths

- The review utilized a comprehensive search strategy, focusing on recent research published within the last seven years.
- It followed clear inclusion and exclusion criteria, enhancing its credibility.
- The discussion section effectively highlighted conflicting findings, demonstrating a balanced analysis.
- The review integrated findings from various studies, including supportive and contradictory evidence, providing a holistic understanding of the topic.
- The review also discussed potential clinical implications, valuable for healthcare professionals and researchers in Sepsis and Septic shock treatment.

Novelty of Research

The review focuses on the combination therapy of vitamin C, Hydrocortisone, and Thiamine in treating Sepsis and Septic shock. It synthesizes recent studies to examine the potential synergic effects and clinical benefits of administering them together. The review includes studies from 7 recent years, providing a contemporary perspective. The research evaluates diverse perspectives, highlighting the complexity of Sepsis and Septic Shock treatment. It provides clear and actionable recommendations for future research and clinical practice, offering guidance on refining treatment protocols, patient selection criteria, and developing clinical guidelines. The research emphasizes a multidisciplinary approach involving various medical specialties and healthcare providers to address the multifaceted nature of Sepsis and Septic shock. The novelty of the research lies in its systematic and contemporary analysis, consideration of diverse research perspectives, and practical recommendations for future research and clinical practice.

Contribution to Knowledge

This review has made significant contributions to critical care medicine and immunomodulatory therapies. It synthesizes existing research, strengthens the evidence base for this therapy, and offers insights into strategies to improve patient care, reduce mortality rates, and

alleviate symptoms. The research also provides valuable information for developing clinical guidelines and protocols for Sepsis and Septic shock treatment. It acknowledges the knowledge gap and emphasizes a multidisciplinary approach, recognizing the complexity of these conditions. Future research directions include patient selection criteria, dosages, and treatment duration.

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