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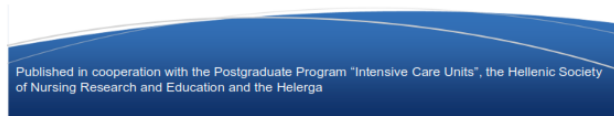
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ADMINISTRATION OF ASCORBIC ACID IN THE TREATMENT OF SEPTIC SHOCK



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### Administration of ascorbic acid in the treatment of septic shock

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## SYSTEMATIC REVIEW

## ADMINISTRATION OF ASCORBIC ACID IN THE TREATMENT OF SEPTIC SHOCK

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**Abstract**

**Introduction:** Septic shock is a common condition encountered in the intensive care unit. Sepsis is the leading cause of death with mortality ranging from 35-50%. Several factors are involved in the increasing incidence of sepsis including age, immunosuppression and antibiotic resistance. Gram+ or Gram- infections are considered leading causes of sepsis. Septic shock prognosis is significantly affected by early treatment. The hospitalization of the patient in the intensive care unit is particularly important as it is essential to support vital functions due to the complications of the shock.

**Aim:** To investigate the action of ascorbic acid in the treatment of septic shock and the benefits of its administration.

**Method-Material:** Randomized trials were searched in CENTRAL, EMBASE and PubMed databases. The total number of studies included was 6. The Cochrane Risk of Bias Tool Review Manager Revman 5.3 was used to control the studies. The criteria for the inclusion of patients were: age more specifically over 18 years old, patients accepted to intensive care unit with septic shock, patients with septic shock who received ascorbic acid randomized studies and cohort studies and articles in English with a time limit from 2008 to the first semester of 2020.

**Results:** The results of the studies showed that patients with septicemia and septic shock have shown beneficial effects of ascorbic acid alone or in combination with corticosteroids and thiamine in the prevention of progressive organ dysfunction and in the reduction in mortality and severity of severe sepsis. Also, there was a reduced inflammatory response observed in septic shock and attenuated levels of circulatory injury biomarker.

**Conclusions:** Ascorbic acid has beneficial properties in septic shock and various studies have highlighted the importance of the combination of ascorbic acid and other vitamins and trace elements.

**Keywords:** Sepsis, septic shock, ascorbic acid.

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## INTRODUCTION

Septic shock is a common condition encountered in the intensive care unit. Sepsis is the leading cause of death with mortality ranging from 35-50%. Several factors are involved in the increasing incidence of sepsis including age, immunosuppression and antibiotic resistance. Gram+ or Gram- infection are considered leading causes of sepsis. Septic shock prognosis is significantly affected by early treatment. The hospitalization of the patient in the intensive care unit is particularly important as it is essential to support vital functions due to the complications of the shock. It is known that gram + and gram - microorganisms can cause the onset of septic shock syndrome. The endotoxin secreted by the cell wall of gram-microbes, is responsible for mobilizing the cascade of sepsis. The severity of the induced septic shock is proportional to the level of endotoxin in the patient's blood. In septic shock from gram + microorganisms is blamed more than one substance eg exotoxin peptidoglycans and their relationship with the severity of symptoms is not analogous. Regardless of the responsible substance, the response of the organism is similar, is the same quality disorders are observed but there are differences in the size of each. Sepsis is the body's systematic response to severe infection and is characterized by a multitude of clinical, hemodynamic, hematological, immunological and biochemical symptoms. These are the body's effort to deal with the microbial invasion. Although sepsis is triggered by a microbial infection, the cascade of various mediators is secreted, many times it can continue even if the microbial agent has been controlled. The mediators modify the reaction of certain receptors in the various organic systems, which in turn respond with organic or other secretions. Thus, they feed back this reaction creating a vicious circle. What causes death due to sepsis is not so much microgranulation as the body's reaction to it, a reaction that ultimately affects the functioning of all organic systems. The best treatment for sepsis and septic shock is prevention, and if this is not possible, timely and correct therapeutic intervention can modify the body's response to sepsis for the benefit of the patient. Supporting vital functions and choosing the right

treatment should be done without delay, even on suspicion of sepsis.<sup>1</sup>

Septic shock syndrome has been known since antiquity. It is a severe disease since it occurs in the community and in hospitalized patients and exhibits a high mortality rate (30-45%). The scientific community has published international guidelines, such as the "Surviving Sepsis Campaign" in 2012 that aim to aid the proper diagnostic and therapeutic treatment of patients with sepsis.<sup>2</sup> It is important to stabilize the patient on the basis of specific guidelines and to administer appropriate medication (mainly antimicrobial) in a timely manner. Compliance with these guidelines has significantly reduced the mortality rate of sepsis patients in recent years.<sup>3</sup>

William Osler (1849-1919) was the first to identify the role of the host's immune response in sepsis. He has stated the following: "With the exception of some cases, patients die because of their body's response to infection and not because of infection." This discovery was a milestone in understanding the role of the host's immune response to an infection.<sup>4</sup>

In recent years, several research groups have focused on identifying compounds that can contribute to the treatment of septic shock. One of these compounds is ascorbic acid.

## AIM

The aim of the present study was to assess the role of ascorbic acid in the treatment of septic shock and the benefits of its administration.

## METHODOLOGY

A bibliographical review was carried out in the CENTRAL, EMBASE, PubMed databases with language restriction. The selection included articles in English with a time limit from 2008 to the first semester of 2020. The selection was limited to the type of studies (use of randomized and Cohort studies). The total number of studies included using the Preferred Reporting Items of Systemic Reviews and Meta-analysis tool was 6. The Review Manager – RevMan 5.3 risk of Bias Tool was used to assess these studies.

### Keywords

The keywords that were used to search for the studies were the following: Septic shock AND ascorbic acid, OR sepsis AND ascorbic acid, OR ascorbic acid AND shock.

### Inclusion criteria

The criteria for the inclusion of patients were: age more specifically over 18 years old, patients accepted to intensive care unit with septic shock, patients with septic shock who received ascorbic acid randomized studies and cohort studies and articles in English with a time limit from 2008 to the first semester of 2020.

### Exclusion criteria

The exclusion criteria were: patient under 18 years, studies that were in a language other than English, studies prior to 2008, small number of participants and the dose of ascorbic acid or the description of the control group was not reported.

The flow diagram 1 depicts the flow of information through the different phases of a systematic review. It maps out the number of records identified, included and excluded, and the reasons of exclusion.

## RESULTS

Vitamin C is considered particularly important, as L-ascorbic acid plays a major role in the health of animal organisms. The human body cannot synthesize vitamin C due to the absence of an enzyme. The lack of vitamin C is known to cause scurvy, a disease that primarily manifests itself in bleeding. To date, it has been shown that the adjustment of the diet and the inclusion of fruits and vegetables can reduce the incidence of the disease. It has been also reported that the administration of L-ascorbic acid is beneficial in patients with septic shock and sepsis.<sup>5</sup>

In particular, in their research Carr et al studied a sample of 44 patients with critical disease, of which 24 had septic shock, 17 had no sepsis, while 3 had not been classified. The data indicated that 40% of patients with septic shock developed vitamin C deficiency compared to 25% of non-septic patients. The baseline vitamin C status was  $17.8 \pm 8.7 \mu\text{mol/L}$ ; of these, 68%

were classified as hypovitaminosis C (i.e.,  $< 23 \mu\text{mol/L}$ ), and 32% were deficient in vitamin C (i.e.,  $< 11 \mu\text{mol/L}$ ). Concentrations of plasma vitamin C were significantly lower in septic shock patients than in the nonseptic patients ( $P = 0.03$ ). Of the septic shock patients, 88% were in the hypovitaminosis C category, compared with 50% in the non-septic patients, and 38% of the septic shock patients were deficient in vitamin C, compared with 25% of the non-septic patients. Concluded that this was likely to occur due to an increase in metabolism as a result of the increased inflammatory response observed in septic shock.<sup>6</sup>

In their study, Fowler et al.,<sup>7</sup> randomized 24 patients with severe sepsis into three groups, at a ratio of 1:1:1. The first group received intravenous infusions of ascorbic acid every six hours for four days: (Lo-Asca, 50 mg/kg/24 h n=8), the second Hi-Asca 200 mg/kg/24 h (n=8) and the third group placebo 5% dextrose/water (n=8). Patients treated with ascorbic acid experienced immediate reductions in the SOFA score, while patients treated with placebo did not show such a decrease. Ascorbic acid significantly reduced the levels of the pro-inflammatory biomarkers C-reactive protein and procalcitonin. Unlike patients treated with placebo, thrombomodulin infusion into patients receiving ascorbic acid did not cause a significant increase in induction of inflammation, indicating a weakening of vascular endothelial damage.

In a previous study, Marik et al.,<sup>8</sup> treated 94 patients in the ascorbic acid therapy group (n=47) (intravenous vitamin C (1.5 g every 6 h for 4 days or until ICU discharge), hydrocortisone (50 mg every 6 h for 7 days or until ICU discharge followed by a taper over 3 days), as well as intravenous thiamine (200 mg every 12 h for 4 days or until ICU discharge). The vitamin C was administered as an infusion over 30 to 60 Intravenous thiamine was given as a piggyback in 50 mL of either D5W or normal saline and was administered as a 30-min infusion and mixed in a 100- mL solution of either dextrose 5% in water (D5W) or normal saline and the control group (n=47). Their results demonstrated that hospital mortality was estimated to 8.5% (4 out of 47) in the ascorbic acid treatment group compared with

40.4% (19 out of 47) noted in the control group. Natarajan et al.,<sup>9</sup> divided 24 patients into three groups: 1) Placebo: 5% dextrose and water; 2) Low dose ascorbic acid (Lo): 50 mg/kg/24 hours; and 3) High dose ascorbic acid (Hi): 200 mg/kg/24 hours. It appeared that cfDNA values were higher and remained elevated for 96 h. mtDNA values were increased in the placebo group, whereas they decreased in the treatment group. Red cell distribution width (RDW) increased significantly only in the placebo group, while the expression of antimicrobial proteins increased significantly only in the treatment group. Their findings concluded that ascorbic acid administration could improve the effects of sepsis by reducing the levels of cfDNA and mtDNA, while causing an increase in endogenous antimicrobial proteins and the maintenance of RDW.

A recent study by Sadaka et al.,<sup>10</sup> included 62 patients and demonstrated that the combination of ascorbic acid, thiamine and hydrocortisone. The exact doses of each medicine were: ascorbic acid [1.5 g every 6 hours for 4 days], hydrocortisone [50 mg every 6 hours for 7 days], and thiamine [200 mg every 12 hours for 4 days]. They concluded that ATS compared with the NO ATS group had longer duration of vasopressors ( $P=0.001$ ), lower intensive care unit mortality ( $P=0.004$ )

Shin et al.,<sup>11</sup> reported in a study of 1,144 people that early administration of vitamin C and thiamine in patients with septic shock did not improve survival, whereas administration could benefit the patients in more severe conditions, such as hypoalbuminemia or severe organ failure. In particular, mortality rates did not differ between treatment and control groups (18.3 vs. 17.5%).

## CONCLUSIONS

On the basis of the investigations, it emerged that the majority of the studies indicated that ascorbic acid has beneficial properties in sepsis and septic shock such as lower duration on mechanical ventilation, decreased intensive care unit mortality and reductions on the SOFA score. Several studies stress the importance of the combined administration of ascorbic acid and other vitamins and trace elements to the patient.

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## ANNEX



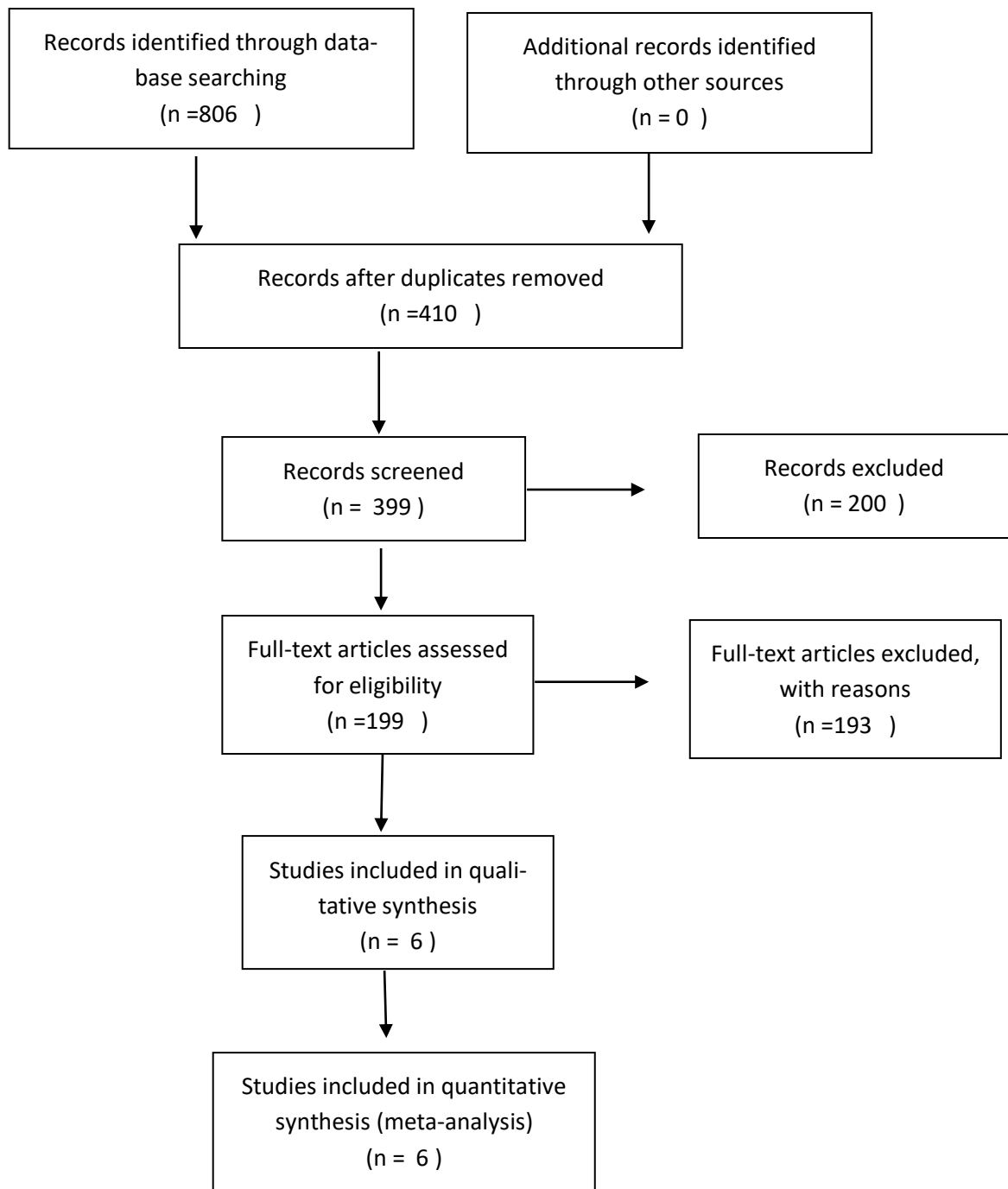
## PRISMA 2009 Flow Diagram

Identification

Screening

Eligibility

Included



**Table 1.** Summary table presenting the characteristics of the study

AYTHOR	STUDY DESIGN	POPULATION	FINDINGS	CONCLUSIONS
<b>Carr et al, 2017</b>	Observational study	44 patients with critical disease (24 with septic shock, 17 non-septic, 3 unclassified)	Nearly 40% of patients with septic shock were deficient in vitamin C, compared to 25% of non-septic patients.	Septic shock patients have significantly depleted vitamin C levels compared with non-septic patients due to the enhanced inflammatory response observed in septic shock.
<b>Fowler et al, 2014</b>	Randomized double blind controlled placebo	24 patients with severe sepsis were randomized 1:1:1 to receive intravenous infusions every six hours for four days of ascorbic acid: Lo-Asca (n=8) or Hi-Asca (n=8), placebo (n=8).	Patients treated with ascorbic acid experienced immediate reductions in SOFA while placebo patients showed no such reduction. Ascorbic acid significantly reduced pro-inflammatory biomarkers C-reactive protein and procalcitonin. Unlike patients treated with placebo, thrombomodulin infusion into patients receiving ascorbic acid did not show a significant increase, indicating a weakening of vascular endothelial damage.	Pharmacologic ascorbic acid repletion reduces the extent of multiple organ failure and attenuates circulating injury biomarker levels.
<b>Mariket al, 2017</b>	Retrospective study after a clinical trial	94 patients were divided into the treatment group (n=47) and the control group (n=47)	Hospital mortality was 8.5% (4 out of 47) in the treatment group compared to 40.4% (19 out of 47) in the control group. The adjusted mortality forecast in patients treated with vitamin C was 0.13	The early use of intravenous vitamin C, together with moderate-dose hydrocortisone and thiamine, may prove to be effective in preventing progressive organ dysfunction, including acute kidney injury, and reducing the mortality of patients with severe sepsis and septic shock
<b>Natarajan et al, 2014</b>	Retrospective study of a phase I trial, randomised, double-blind, placebo-controlled and intravenous ascorbic acid in severe sepsis	24 patients	cfDNA values were higher and remained elevated for 96 hours. mtDNA values increased in the placebo group, but decreased in treatment groups without achieving statistical significance. <b>RDW</b> increased significantly only in the placebo group, while the expression of antimicrobial proteins increased significantly only in treatment groups	Pharmacologic ascorbic acid repletion reduces the extent of multiple organ failure and attenuates mortality by multiple mechanisms involving potential reductions in circulating cf-DNA and mtDNA levels, augmentation of endogenous antimicrobial proteins such as $\alpha$ 4D and BPI as well as preservation of RDW. Infusion of ascorbic acid in pharmacological dosages to critically ill patients with sepsis may provide adjunctive therapy in the treatment of severe sepsis.



<b>Sadaka et al, 2019</b>	Retrospective cohort study	62 patients	The <b>ATS</b> team had a longer <b>VP</b> duration (Corresponding <b>RRT</b> for <b>AKI</b> (26 vs. 29%), similar days without <b>MV</b> (9.6 vs. 42%), and a trend towards lower hospital mortality (29 vs. 45%) compared to <b>NO ATS</b>	Patients with <b>SS</b> who were treated with ascorbic acid, thiamine, and hydrocortisone had a reduced ICU mortality compared with patients with <b>SS</b> with similar acuity who were not treated with ascorbic acid, thiamine, and hydrocortisone. Complications did not differ between the groups.
<b>Shin et al, 2019</b>	Retrospective cohort study	229 patients treated with intravenous treatment of Vitamin C and thiamine after shock recognition from July to December 2017 (n=229) and 915 patients in the control group from October 2015 to June 2017 (n=915)	In 28 days (18.3 vs. 17.5%, p=0.76) in hospital (16.6 vs. 18.3%, r=0.55), mortality rates did not differ between treatment and control groups; neither did 28-day mortality rates (18.5 vs. 17.5%, p=0.84) and in hospital (16.7 vs. 18.4%, p=0.54) after the mapping. In the subgroup analysis, treatment was associated with lower inpatient mortality patients with albumin <3.0 mg/dL	Intravenous vitamin C and thiamine infusion during the initial resuscitation period in patients with septic shock was not associated with improved survival. Considering the individual variability of patients with sepsis, its use could be beneficial in a subgroup of patients, such as those with hypoalbuminemia or severe organ failure