Intravenous Vitamin C Decreasing Mortality of ICU Patients with Septic Shock

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Abstract

**Background:** Sepsis is the leading cause of death in critically ill patients worldwide, with over a 30-50% mortality rate. The inflammatory response that occurs in sepsis is known to cause multi-system organ failure, followed quickly by death. The current mainstay for treatment of sepsis is intravenous fluid resuscitation to maintain hemodynamic stability, antibiotics to combat infection, and the use of vasopressors, or vasoconstrictors for refractory hypotension. Since sepsis causes such an inflammatory response, and most critically ill patients present with hypovitaminosis C due to oxidative stress from infection, the thought of adding vitamin C to the sepsis bundle has been recently studied. Vitamin C is easily accessible, affordable and safe for those patients suffering from sepsis. Its own antioxidant and anti-inflammatory properties, along with its connection to synthesizing endogenous norepinephrine and vasopressin, make it an exciting new possibility to decrease global mortality.

**Methods:** An exhaustive search of online literature was conducted using MEDLINE, CINAHL, Google Scholar, and Web of Science. Keywords used in the search included sepsis, septic shock, vitamin C and ascorbic acid. These results were screened for eligibility, and articles that assessed the mortality of septic shock patients in the ICU were included. These studies were then appraised and assessed for quality of evidence by GRADE.

**Results:** Two studies met the inclusion criteria, studied the same primary outcome of mortality, and were included in this systemic review. One RCT took 28 patients in the ICU and found a significant decrease in hospital mortality, along with a decreased dose and duration needed for vasopressors when vitamin C was administered in the treatment group versus the control group. A retrospective observational study of 94 patients, (n=47) in both the treatment and control group who used a combination of steroids, thiamine and vitamin C found a propensity adjusted odds ratio of mortality in those treated with the vitamin C protocol to be 0.13.

**Conclusion:** The addition of vitamin C may prove to be an added benefit to the sepsis bundles in the ICU. Further research needs to be done with larger patient populations in order to accurately confirm Vitamin C's effect on improving septic patients' mortality outcomes.

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Megan DeMarco

A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Patrick Boyle, MD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography
Megan DeMarco is originally from the East Coast and spent her entire life growing up on stage and entertaining those around her. She spent years with a performing arts group based out in California teaching children singing and dancing and showing communities how important music is in education. Realizing that she wanted to continue making a difference, she looked to medicine, and was a medical assistant in a cardiology office for 3 years. She received her Bachelor of Health Sciences from Philadelphia University, and always knew that her number one dream PA school was Pacific University. She is incredibly grateful for the opportunity to have learned from such a dedicated faculty, and looks forward to a future as a competent, passionate clinician in critical care medicine.
Abstract

Background: Sepsis is the leading cause of death in critically ill patients worldwide, with over a 30-50% mortality rate. The inflammatory response that occurs in sepsis is known to cause multi-system organ failure, followed quickly by death. The current mainstay for treatment of sepsis is intravenous fluid resuscitation to maintain hemodynamic stability, antibiotics to combat infection, and the use of vasopressors, or vasoconstrictors for refractory hypotension. Since sepsis causes such an inflammatory response, and most critically ill patients present with hypovitaminosis C due to oxidative stress from infection, the thought of adding vitamin C to the sepsis bundle has been recently studied. Vitamin C is easily accessible, affordable and safe for those patients suffering from sepsis. Its own antioxidant and anti-inflammatory properties, along with its connection to synthesizing endogenous norepinephrine and vasopressin, make it an exciting new possibility to decrease global mortality.

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Results: Two studies met the inclusion criteria, studied the same primary outcome of mortality, and were included in this systemic review. One RCT took 28 patients in the ICU and found a significant decrease in hospital mortality, along with a decreased dose and duration needed for vasopressors when vitamin C was administered in the treatment group versus the control group. A retrospective observational study of 94 patients, (n=47) in both the treatment and control group who used a combination of steroids, thiamine and vitamin C found a propensity adjusted odds ratio of mortality in those treated with the vitamin C protocol to be 0.13.

Conclusion: The addition of vitamin C may prove to be an added benefit to the sepsis bundles in the ICU. Further research needs to be done with larger patient populations in order to accurately confirm Vitamin C’s effect on improving septic patients’ mortality outcomes.

Keywords: Sepsis, septic shock, vitamin C
Acknowledgements

To my parents-Thank you for your never-ending support throughout everything I have ever done. You are the reason I am here today, and you have stood next to me through it all. I am so glad you can be here to celebrate with me. I am forever grateful for your continuous love and care.
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Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

ICU Intensive Care Unit
SSC Surviving Sepsis Campaign
SIRS Systemic Inflammatory Response Syndrome
SOFA Sequential Organ Failure Assessment
APACHE Acute Physiology and Chronic Health Evaluation
MAP Mean Arterial Pressure
RCT Randomized Clinical Trial
Intravenous Vitamin C Decreasing Mortality of ICU Patients with Septic Shock

BACKGROUND

Sepsis is a life-threatening inflammatory response that is the leading cause of death in critically ill patients.\textsuperscript{1} It is responsible for 26 million lives taken worldwide annually, and accounts for one-third of all hospital deaths.\textsuperscript{2} This inflammatory response can result in multi-system organ failure, as well as refractory hypotension. Currently the mainstay treatment for the management of severe sepsis is fluid resuscitation to maintain hemodynamic stability, controlling the ongoing infection with broad-spectrum antibiotics, and respiratory and central nervous system support. Since septic shock alters the cardiovascular system and has an inappropriate degree of vasodilation, resulting in refractory hypotension, a vasopressor such as norepinephrine is required for further vasoconstriction to increase the systolic blood pressure.\textsuperscript{3} Septic patients are the sickest of the sick in the intensive care unit (ICU) and early recognition and intervention to improve morbidity and mortality for such patients is the most crucial step healthcare providers can take to manage and control this condition.

In 2002, the Surviving Sepsis Campaign (SSC)\textsuperscript{4} was created to increase awareness, improve diagnosis and treatment, and have a worldwide evidence-based approach to sepsis. The SSC updates their guidelines every 4 years, with the most recent update in 2016 bringing about a new definition of Sepsis-3.\textsuperscript{5} In the previous and more well-known definition of Sepsis-2, the
systemic inflammatory response syndrome (SIRS) criteria was how most medical professionals know sepsis to be defined, where at least 2 of 4 requirements needed to be met: tachycardia, increased respiratory rate (> 20), a fever proving systemic infection and either an increased white blood cell (WBC) count or a significantly diminished one (>12,000 or <4,000 cells/mL). Along with this new definition, a new scoring system known as Sequential Organ Failure Assessment (SOFA) was recommended. The SOFA is a way to assess ICU mortality based on lab values such as bilirubin and creatinine, and other clinical data. The newly modified version of the SOFA known as the “quick sofa” or qSOFA gives a more rapid evaluation of whether the patient in question is at risk of dying from sepsis and only looks at 3 components, receiving 1 point each if present. Those 3 components include a respiratory rate of >22/min, a change in mental status, and a systolic blood pressure <100 mmHg. If someone were to receive a score >2, this would prove the patient to be in end organ damage.  

Another scoring system that has evolved over time in the ICU is the Acute Physiology and Chronic Health Evaluation (APACHE), which is currently the APACHE IV. Similarly to the SOFA, this looks at the possibility of mortality of admitted patients based on a list of certain lab values and clinical findings.

Critically ill patients have considerably low protective antioxidant levels, particularly vitamin C. The addition of such an accessible antioxidant could be a strong new possible intervention. The potential benefits in the use of vitamin C to help treat sepsis are looked at from 3 main properties. These properties include the anti-oxidant effect of vitamin C, assisting as an anti-
inflammatory, and the idea that ascorbic acid helps boost the host’s own immune defense by improving T cell and leukocyte function assisting in chemotaxis and killing of bacteria.\textsuperscript{9} The most interesting role that vitamin C plays is being a cofactor for various biosynthetic pathways to increase endogenous synthesis of norepinephrine, and other catecholamines.\textsuperscript{10,11} With the production of increased catecholamines by the host’s own body, the duration of vasopressor use and vasopressor doses could certainly be decreased. Potential harms related to extended duration of vasopressor usage include lethal tachyarrhythmias and severe vasoconstriction which could cause limb ischemia.\textsuperscript{10}

In patients with septic shock, increased oxidative stress and ongoing infection increases their inflammatory response, which in turn decreases their endogenous circulating ascorbate. The purpose of this research is to explore whether the addition of intravenous vitamin C to sepsis and septic shock management could help improve mortality in ICU patients worldwide.

**METHODS**

An exhaustive online literature search was conducted using MEDLINE-PubMed, CINAHL, Google Scholar, and Web of Science. Keywords used in the search included sepsis, septic shock, vitamin C and ascorbic acid. The search was narrowed to only include English language articles and only reports of testing on human subjects. Bibliographies of chosen articles were evaluated for further resources. Articles that assessed the mortality of septic shock patients in the ICU were included. The quality of relevant articles was
assessed using the Grading, Recommendations, Assessment, Development and Evaluation. (GRADE).  

**RESULTS**

The initial search yielded 261 results. After careful review and screening for relevancy, duplicates were excluded from the search leaving 27 articles to be further evaluated. After investigation and screening of the abstracts, 2 articles\(^\text{13,14}\) met the inclusion criteria and answered the clinical question. One study was a randomized clinical trial,\(^\text{13}\) and the other was a retrospective observational study.\(^\text{14}\) A single study was found as a clinical trial testing the safety of intravenous vitamin C in patients with sepsis,\(^\text{15}\) but was excluded as it did not test the primary outcome of mortality (See Table 1).

**Zabet et al**

This randomized clinical trial\(^\text{13}\) evaluated the effects of ascorbic acid in critically ill patients diagnosed with septic shock. The trial took place in an ICU in Tehran, Iran and the recruitment for patients’ eligible ran from September 2015 to January 2016. Eligible participants were between 18-65 years old, who needed a vasopressor to maintain a MAP (mean arterial pressure) >65 mmHg, despite aggressive intravenous fluid resuscitation. Those requiring the vasopressor to help with hemodynamic stability either received 25 mg/kg IV ascorbic acid every 6 hour or a matching placebo for 72 hours. The dose and duration of the vasopressor needed for each patient as well as the 28-day mortality were the outcomes measured after the 3-day
study. The researchers, ICU nurses, and the physicians were blinded and the intervention (ascorbic acid or placebo) was prepared by the Pharmacy Department. The patients were randomized according to permuted block randomization. There were 7 blocks and each block contained 4 patients in complete random order. The patients’ demographic data and lab results were removed from the charts, and their Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were calculated at the time of recruitment, showing relatively comparable numbers between both groups. Twenty-eight patients (14 in each group) were recruited for the study, with no statistically significant difference detected between the two groups demographics or clinical characteristics.\textsuperscript{13}

Septic shock was defined based on the Surviving Sepsis Campaign and patients needed to have either the presence of a systemic inflammatory response (fever, leukocytosis or leukopenia), a suspected or proven infection, and/or signs and symptoms of sepsis induced end organ damage. Any contraindications for ascorbic acid therapy such as chronic hemodialysis, hemochromatosis, and G6PD deficiency were excluded. Fluid resuscitation was the mainstay treatment in the ICU for all patients with septic shock, and once patients had MAP <65 mmHg, despite fluid administration of 6 hours, a vasopressor, norepinephrine, was started. Each patient requiring norepinephrine started with a dose of 5 mcg/min and was slowly titrated up based on the patient’s hemodynamic status, not to exceed 30 mcg/min. Those in the ascorbic acid group received 25 mg/kg IV ascorbic acid which
was diluted in 50 mL of dextrose 5% solution and was administered over 30 min, while those in the placebo group received dextrose 5% solution over 30 min as a continuous IV infusion. Changes in the MAP, heart rate, respiratory rate, fluid intake and renal function during the study were compared between both groups. Adverse effects to intravenous ascorbic acid was also followed, but none were reported.\textsuperscript{13}

The study showed the mean dose of norepinephrine throughout the 3 days, as well as just the first 24 hours and the duration of required vasopressors were significantly lower in the ascorbic acid than the placebo group. The 28-day mortality was found to be significantly lower in the ascorbic acid (14.28\%) than the placebo group (64.28\%; P= 0.009).\textsuperscript{13}

\textbf{Marik et al}

This retrospective observational study\textsuperscript{14} compared the clinical outcomes and hospital survival of consecutive septic patients treated with intravenous vitamin C, hydrocortisone, and thiamine during a 7-month period, compared to a control group who only received standard sepsis therapy. The study was conducted at Sentara Norfolk Hospital in Virginia between January 2016 and July 2016. Throughout those 7 months, patients admitted to the ICU with severe sepsis or septic shock and a procalcitonin level >2 ng/mL were treated with the triple intervention within 24 hours of admission. The elevated procalcitonin level was evaluated to increase the certainty that the patient was suffering from severe sepsis, and likely at risk of developing end organ dysfunction or damage. Patients under the age of 18
years and those who were pregnant were excluded from the study. The control group consisted of similar patients admitted to the ICU between June 2015 and December 2015, using the same inclusion and exclusion criteria. There were 47 patients in each group, and at the time of recruitment there were no significant differences in demographic data or baseline characteristics between both groups.14

The APACHE II and APACHE IV scores7,13,14 predicting hospital mortality were recorded for both the treatment and control groups. The SOFA6,13,14 score was calculated 24 hours after admission to the ICU, and daily thereafter. The overall treatment of patients with sepsis or septic shock during the study was similar, besides the administration of the 3 added interventions for the treatment group. Each group received broad-spectrum antibiotics, intravenous fluids, and vasopressors to target a MAP >65 mmHg. During the treatment period, those that were diagnosed with sepsis and met the elevated procalcitonin level requirement were treated with intravenous vitamin C (1.5 g every 6 hours for 7 days or until discharge), hydrocortisone (50 mg every 6 hour for 7 days or until discharge followed by a taper over 3 days), along with intravenous thiamine (200 mg every 12 hour for 4 days or until discharge from the ICU). The vitamin C was infused over 30 to 60 minutes and mixed in a 100 mL solution of either dextrose 5% in water (D5W) or normal saline (NS). The vitamin C level of the patient was determined before the first administered dose, none of which were found to be at a normal level.14
In order to adjust for any differences or queries of the baseline characteristics between the treatment and control group a propensity score was generated to show the likelihood of a patient receiving the new vitamin C protocol. Some factors included in generating this score were age, sex, APACHE IV score, WBC count at presentation, and presenting procalcitonin level. This propensity score adjustment along with statistical binary logistic regression was performed to assess the odds ratio for mortality. The mortality of those in the treatment group was 8.5% (4 of 47 patients), and 40.4% (19 or 47) in the control. The propensity adjusted odds ratio of mortality who were administered vitamin C was 0.13 (95% CI, 0.04-0.48; P=0.002). None of those in the treatment group suffered sepsis related deaths, but instead passed due to their own underlying diseases.\textsuperscript{14}

**DISCUSSION**

After careful consideration and research of these 2 small studies\textsuperscript{13,14} the use of intravenous vitamin C was shown to be beneficial in reducing the mortality of those patients suffering from sepsis and septic shock. While the evidence and findings were statistically significant in both studies,\textsuperscript{13,14} greater research needs to be performed to fully understand the benefit of this new therapy. Proving no adverse side effects in either study, as well as a single safety trial that was excluded in this systematic review due to not measuring the primary outcome of mortality,\textsuperscript{13-15} vitamin C is an easy, affordable, safe and accessible addition to septic treatment that could soon be utilized worldwide in the ICU.
The important limitations of both these studies\textsuperscript{13,14} included the small sample size, with the largest study only including 94 people. In the RCT study\textsuperscript{13} most of the participants in both the treatment and control groups were male, where the retrospective observational study\textsuperscript{14} had a much more even split between male and female participants. While the inclusion criteria for each study required participants to be over the age of 18, the average age in both studies was 55-65. The only group of patients that were studied in the RCT\textsuperscript{13} were post-surgical patients, which is just a minor subset of those that present with septic shock. A retrospective observational study\textsuperscript{14} is difficult due to the study being performed at different times. They provide useful evidence of the effectiveness of an intervention but make it more difficult to truly test the efficacy. Both studies\textsuperscript{13,14} used different doses and duration of intravenous vitamin C, which makes it difficult to recognize which dosing would be the most beneficial as an addition to the current implemented sepsis bundle.

The main limitation in the Marik et al study\textsuperscript{14} was the prognosis of the patients regardless of being in the treatment or the control group was different because certain confounders were added along with ascorbic acid. Vitamin C is known to be a precursor to oxalate, which is responsible for nephrolithiasis. By adding thiamine, which is a coenzyme to prevent oxalate formation, the chances of developing nephrolithiasis were decreased\textsuperscript{14}. More than half the control group received the steroid hydrocortisone to help reduce inflammation on top of regular sepsis ICU standard of care. Hydrocortisone is frequently utilized for septic shock with associated refractory hypotension.
This made it particularly difficult to determine which part of the treatment was responsible for the primary outcome measured. The retrospective study\textsuperscript{14} began with a “low” quality of evidence compared to the RCT,\textsuperscript{13} and with the limitations of a small sample size, while failing to control for all confounders downgraded the quality of evidence of the outcome to “very low”, meaning the estimate of the effect is uncertain. The RCT study had a limitation of a small sample size, and shortened duration of therapy and was found to have a moderate quality of evidence when assessed by GRADE which can be seen in Table 1.

The early use of intravenous vitamin C is of interest, yet somewhat controversial ever since the Marik et al study\textsuperscript{14} was published. Further studies should concentrate on what dose of vitamin C would be the most effective, how long the duration of treatment would be, or when ascorbic acid should be administrated to obtain the greatest outcome. While searching articles for this review, new multiple clinical trials were shown on the NIH website. The largest of which is the VICTAS trial\textsuperscript{16} a multi-center, randomized, double blinded study being conducted at large academic universities and hospitals worldwide. They have more than 2000 patients enrolled, and are again using the combination of vitamin C, steroids, and thiamine to determine if mortality of septic patients can be decreased with this triple therapy. Several sites in Minnesota are also performing an RCT study\textsuperscript{17} using intravenous vitamin C alone and evaluating its effectiveness in those with septic shock. These results will not be available for some time. As one can imagine, it is hard to
find subjects willing to be a part of a such a study that could potentially be the difference between life and death.

CONCLUSION

The addition of intravenous vitamin C to the treatment of septic shock may prove to be beneficial, as it has great potential to act on multiple body systems affected by septic shock. Both studies performed showed statistically significant benefit in mortality of septic ICU patients, and the need for a shorter duration along with a decreased dose of vasopressors when vitamin C is added to standard septic treatment. However, small sample sizes and the lack of randomized clinical trials makes it hard to say if this same data would be meaningful in a different population. With additional larger studies, the benefit of this treatment can be better evaluated.

A treatment as simple as vitamin C could be utilized worldwide, as it is low cost and readily available. There are many ICUs across the country that have begun implementing intravenous vitamin C for their septic shock patients, despite the lack of true evidence. The diagnosis of septic shock is a daunting one, and any improvements in outcomes due to effective therapies would be beneficial for patients, providers and health care systems. The use of vitamin C should continuously be studied, as it could reduce the global mortality from sepsis.
References


9. Carr AC, Maggini S. Vitamin C and immune function. *Nutrients* 2017; 9:


# Table 1: GRADE Criteria

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^a small sample size  
^b failure to control for all confounders  
^c Study had an amazing OR of 0.13, but was not upgraded due to high risk of bias.